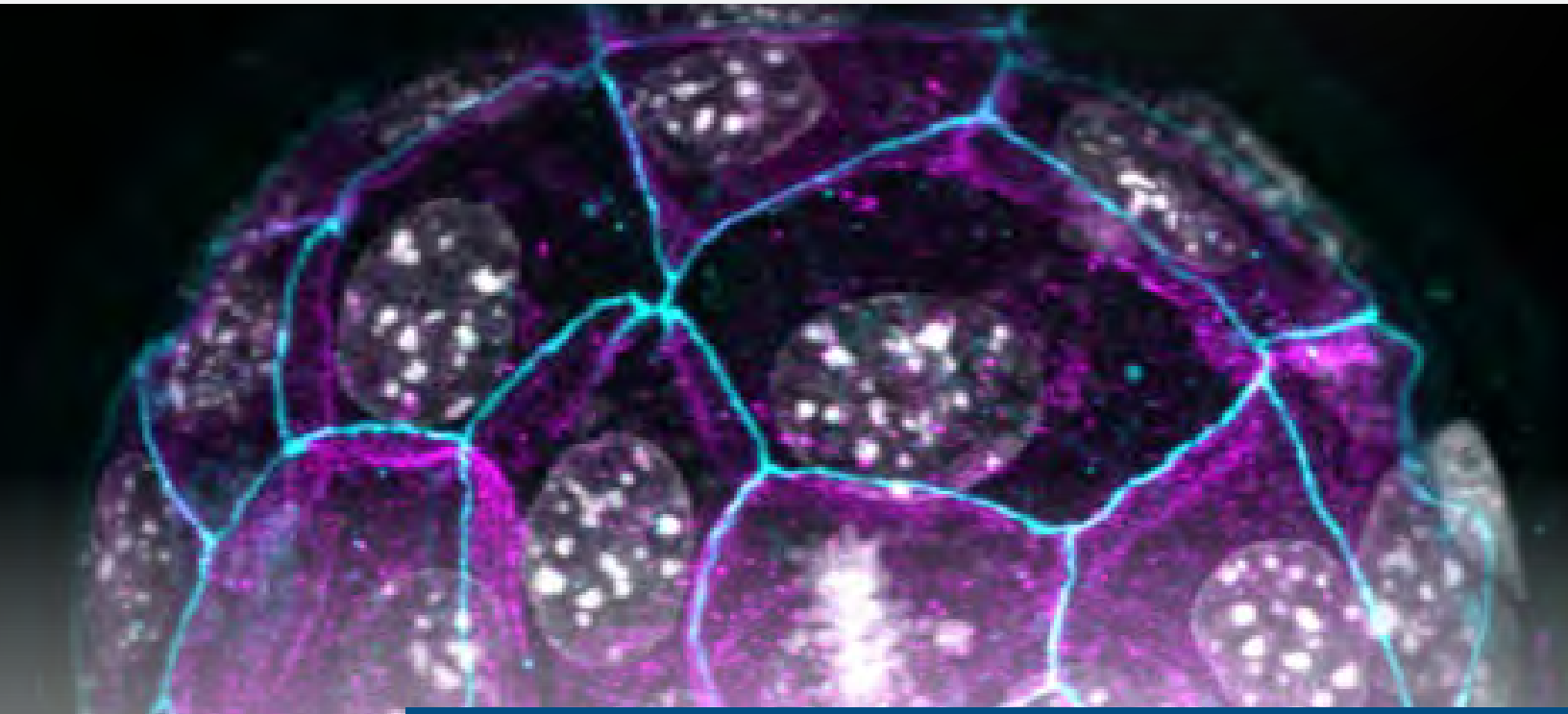

Biology and Physics Confront Cell-Cell Adhesion

October 14–17, 2019 | Aussois, France

Biophysical Society

Biophysical *Journal*

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Organizing Committee

Sandrine Etienne-Manneville, Institut Pasteur, France

Jean-Leon Maître, Curie Institute, France

Virgile Viasnoff, National University of Singapore, Singapore

Alpha Yap, University of Queensland, Australia

Thank You to Our Sponsors

October 2019

Dear Colleagues,

We would like to welcome you to the Biophysical Society Thematic Meeting on ***Biology and Physics Confront Cell-Cell Adhesion***. The purpose of the meeting is to bring together physicists who work on topics such as adhesion, fracture and friction with biologists who work on cell-cell contacts. These are communities that typically do not talk to each other very much, but which have much to mutually offer. Physicists bring major insights into the physical properties of adhesion without perhaps caring as much about molecular/cellular details whereas many biologists are rather the opposite. One interesting challenge is for each community to understand where the other is coming from, as we differ so much in the concepts that we use (and even the meaning of the words that we use).

We think that this meeting will be an interesting opportunity to begin a dialogue between our two communities. In particular, we would really want this meeting to foster conversation that highlights the current parts that are NOT understood in soft matter or in cell-cell adhesion. To this end we have organized round table to stimulate cross conversation about the still-to-be discovered aspect of adhesion.

We have tried to prepare a program of talks that cover many different aspects of cell-cell adhesion. We hope that the nice Alpine setting of Aussois will inspire many conversations and insights.

Wishing you a wonderful and fruitful workshop.

Sincerely yours,

Sandrine Etienne-Manneville — Institut Pasteur, France
Jean-Leon Maître — Curie Institute, France
Virgile Viasnoff — National University of Singapore, Singapore
Alpha Yap — University of Queensland, Australia

Biophysical Society Code of Conduct Anti-Harassment Policy

Adopted by BPS Council November 2015

The Biophysical Society (BPS) is committed to providing an environment that encourages the free expression and exchange of scientific ideas. As a global, professional Society, the BPS is committed to the philosophy of equal opportunity and respectful treatment for all regardless of national or ethnic origin, religion or religious belief, gender, gender identity or expression, race, color, age, marital status, sexual orientation, disabilities, veteran status, or any other reason not related to scientific merit. All BPS meetings and BPS-sponsored activities promote a working environment that is free of inappropriate behavior and harassment by or toward all attendees of Society meetings and Society-sponsored activities, including scientists, students, guests, exhibitors, staff, vendors, and other suppliers.

This global policy applies to all locations and situations where BPS business is conducted and to all BPS-sponsored activities and events. This policy does not replace the specific staff policies for situations in which only staff are involved.

Reported or suspected occurrences of harassment will be promptly and thoroughly investigated. Following an investigation, BPS will immediately take any necessary and appropriate action. BPS will not permit or condone any acts of retaliation against anyone who files harassment complaints or cooperates in the investigation of same.

Definition of Harassment
The term "harassment" includes but is not limited to epithets, unwelcome slurs, jokes, or verbal, graphic or physical conduct relating to an individual's race, color, religious creed, sex, national origin, ancestry, citizenship status, age, gender or sexual orientation that denigrate or show hostility or aversion toward an individual or group.

Sexual harassment refers to unwelcome sexual advances, requests for sexual favors, and other verbal or physical conduct of a sexual nature. Behavior and language that are welcome/ acceptable to one person may be unwelcome/offensive to another. Consequently, individuals must use discretion to ensure that their words and actions communicate respect for others. This is especially important for those in positions of authority since individuals with lower rank or status may be reluctant to express their objections or discomfort regarding unwelcome behavior. It does not refer to occasional compliments of a socially acceptable nature. It refers to behavior that is not welcome, is personally offensive, debilitates morale, and therefore, interferes with work effectiveness. The following are examples of behavior that, when unwelcome, may constitute sexual harassment: sexual flirtations, advances, or propositions; verbal comments or physical actions of a sexual nature; sexually degrading words used to describe an individual; a display of sexually suggestive objects or pictures; sexually explicit jokes; unnecessary touching.

Investigative Process
Anyone who feels harassed is encouraged to immediately inform the alleged harasser that the behavior is unwelcome. In many instances, the person is unaware that their conduct is offensive and when so advised can easily and willingly correct the conduct so that it does not reoccur. Anyone who feels harassed IS NOT required to address the person believed guilty of inappropriate treatment. If the informal discussion with the alleged harasser is unsuccessful in remedying the problem or if complainant does not feel comfortable with such an approach, he/she should contact BPS's Executive Director or the Society President, or any BPS Officer. All complaints will be promptly and thoroughly investigated.

All reports of harassment or sexual harassment will be treated seriously. However, absolute confidentiality cannot be promised nor can it be assured. BPS will conduct an investigation of any complaint of harassment or sexual harassment, which may require limited disclosure of pertinent information to certain parties, including the alleged harasser.
No retaliation will be taken against any employee, member, volunteer, exhibitor, or supplier because he or she reports a problem concerning possible acts of harassment. Employees, members, volunteers, exhibitors, or suppliers can raise concerns and make reports without fear of reprisal.

Investigative Procedure
Once a complaint of harassment or sexual harassment is received, BPS will begin a prompt and thorough investigation.

- An impartial investigative committee, consisting of the Past-President, current President, and President-Elect will be established.
- The committee will interview the complainant and review the written complaint. If no written complaint exists, one will be requested.
- The committee will speak to the alleged offender and present the complaint.
- The alleged offender will be given the opportunity to address the complaint, with sufficient time to respond to the evidence and bring his/her own evidence.
- If the facts are in dispute, the investigative team may need to interview anyone named as witnesses.
- The investigative committee may seek BPS Counsel’s advice.
- Once the investigation is complete, the committee will report their findings and make recommendations to the Society Officers.

Disciplinary Actions
Individuals engaging in behavior prohibited by this policy as well as those making allegations of harassment in bad faith will be subject to disciplinary action. Such actions range from a verbal warning to ejection from the meeting or activity in question without refund of registration fees and the reporting of their behavior to their employer. Repeat offenders may be subject to further disciplinary action, such as being banned from participating in future Society meetings or Society-sponsored activities. In the event that the individual is dissatisfied with the results of the investigation, he or she may appeal to the President of the Society. Any questions regarding this policy should be directed to the BPS Executive Officer or other Society Officer.

BPS Management Responsibility
Every officer, director, supervisor, and manager is responsible for ensuring that BPS provides an environment free of harassment and inappropriate behavior and that complaints are handled promptly and effectively. The BPS Society Office and Officers must inform the Society membership and all vendors and suppliers about this policy, promptly investigate allegations of harassment, take appropriate disciplinary action, and take steps to assure retaliation is prohibited

Table of Contents

GENERAL INFORMATION

Registration/Information Location and Hours

On Sunday, Monday, Tuesday, Wednesday, and Thursday, registration will be located in the lobby near the La Parrachée Room of the Centre Paul Langevin. Registration hours are as follows:

Sunday, October 13	15:00 – 18:00
Monday, October 14	8:30 – 19:35
Tuesday, October 15	8:30 – 19:35
Wednesday, October 16	8:30 – 19:35
Thursday, October 17	8:30 – 12:35

Instructions for Presentations

(1) Presentation Facilities:

A data projector will be available in the La Parrachée Room. Speakers are required to bring their own laptops and adaptors. It is recommended to have a backup of the presentation on a USB drive in case of any unforeseen circumstances. Speakers are advised to preview their final presentations before the start of each session.

(2) Poster Session:

1) All poster sessions will be held in the mezzanine of the Centre Paul Langevin.

2) A display board measuring 120 cm wide x 85 cm high (3.9 feet wide x 2.8 feet high) will be provided for each poster. Poster boards are numbered according to the same numbering scheme as listed in the e-book.

3) Posters should be set up the morning of, Monday, October 14 and removed by noon Thursday, October 17. All posters are available for viewing during all poster sessions; however, there will be formal poster presentations at the following times:

Monday, October 14	16:35 – 17:22	Odd-numbered poster boards
Monday, October 14	17:22 – 18:00	Even-numbered poster boards
Tuesday, October 15	16:35 – 17:22	Odd-numbered poster boards
Tuesday, October 15	17:22 – 18:00	Even-numbered poster boards

4) During the assigned poster presentation sessions, presenters are requested to remain in front of their poster boards to meet with attendees.

5) All posters left uncollected at the end of the meeting will be disposed.

Meals and Coffee Breaks

There will be an Opening Dinner on Sunday evening from 18:30 – 20:00. Dinner will be held in the Restaurant.

Coffee Breaks (Monday, Tuesday, Wednesday, and Thursday) will be served in the Mezzanine.

Breakfast (Monday, Tuesday, Wednesday, and Thursday) will be available from 7:30 – 9:00 in the Restaurant.

Lunches (Monday, Tuesday, Wednesday, and Thursday) and Dinners (Sunday, Monday, Tuesday, and Wednesday) will be served family-style in the Restaurant.

Reception will be held prior to dinner on Monday in the Bar.

Smoking

Please be advised that smoking is not permitted at the Centre Paul Langevin.

Name Badges

Name badges are required to enter all scientific sessions, poster sessions, and social functions. Please wear your badge throughout the conference.

Internet

WiFi will be provided at the venue. Attendees will receive the access code upon check-in to the Centre Paul Langevin.

Contact

If you have any further requirements during the meeting, please contact the meeting staff at the registration desk from October 13 – 17 during registration hours.

In case of emergency, you may contact the following:

Christa Balzar, Centre Paul Langevin
Cell: +33 047 920 4205
Email: christa.balzer@caes.cnrs.fr

Virgile Viasnoff, Aussois Program Organizer
Cell: +33 950 06 717
Email: virgile.viasnoff@espci.fr

Jennifer Fraser, BPS Staff
Email: jfraser@biophysics.org

Biology and Physics Confront Cell-Cell Adhesion

Aussois, France
October 14 – 17, 2019

PROGRAM

All scientific sessions will be held in the La Parrachée Room

Sunday, October 13, 2019

15:00 – 18:00	**Registration/Information**	**Lobby**
18:30 – 20:00	**Opening Dinner**	**Restaurant**

Monday, October 14, 2019

8:30 – 19:35	**Registration/Information**	**Lobby**
9:00 – 9:10	Virgile Viasnoff, National University of Singapore, Singapore **Welcome & Opening Remarks**	
Session I	Virgile Viasnoff, National University of Singapore, Singapore, Chair	
9:10 – 9:45	Alpha Yap, University of Queensland, Australia ***Cell-Cell Adhesion: Known Knowns and Known Unknowns***	
9:45 – 10:20	Francoise Brochard-Wyart, Curie Institute, France ***Hybrid Active Matter: Particles and Cellular Aggregates***	
10:20 – 10:30	General Discussion	
10:35 – 11:00	**Coffee Break**	**Mezzanine**
Session II	Alpha Yap, University of Queensland, Australia, Chair	
11:00 – 11:35	Carl-Philipp Heisenberg, IST Austria, Austria ***Tension-Dependent Stabilization of E-Cadherin Limits Cell-Cell Contact Expansion***	
11:35 – 12:00	Qilin Yu, University of Melbourne Biomedical Engineering, Australia* ***A Computational Model Coupling E-Cadherin Dynamics and Actomyosin Network Illustrates the Cell-Cell Contact Maturation***	
12:00 – 12:35	**Costantino Creton,** ESPCI ParisTech, France ***Adhesion and Stickiness of Soft Matter***	
12:35 – 13:30	**Lunch**	**Restaurant**
Session III	Carl-Philipp Heisenberg, IST Austria, Austria, Chair	
13:30 – 15:00	Roundtable	
15:00 – 15:35	Virgile Viasnoff, National University of Singapore, Singapore ***Overview of the Biophysical Aspects of Cell-Cell Adhesion***	

15:35 – 16:00	Julia Eckert, Leiden University - Leiden Institute of Physics, The Netherlands* ***Tensile Strength vs. Shear Stress – An Approach to Measure Internal Tensions Between Cell-Cell Junctions***	
16:00 – 16:35	Vania Braga, Imperial College London, England ***Intrinsic Cell Contraction Is Essential for Junction Configuration and Stabilization***	
16:35 – 18:00	**Coffee Break / Poster Session I**	**Mezzanine**
Session IV	Virgile Viasnoff, National University of Singapore, Singapore, Chair	
18:00 – 18:35	William Weis, Stanford University, USA ***Vinculin Allosterically Enhances Force-Dependent Binding of Alpha-E-Catenin to F-Actin***	
18:35 – 19:00	Lèa Pinon, Institut Pierre Gilles de Gennes, France* ***Oil-in-Water Emulsion Droplets and Microfluidic Tools to Study B Cells Polarization and Mechanics of Immunological Synapse***	
19:00 – 19:35	Ana-Suncana Smith, FAU Erlangen-Nurnberg, Germany ***Physical Effects Catalyzing Cell Adhesion: From Mimetic Systems to Tissues***	
19:35 – 20:00	**Reception**	**The Bar**
20:00 – 21:00	**Dinner**	**Restaurant**

Tuesday, October 15, 2019

8:30 – 19:35	**Registration/Information**	**Lobby**
Session V	William Weis, Stanford University, USA, Chair	
9:00 – 9:35	Laurent Cortè, MINES ParisTech, France ***Creating Adhesion at Hydrogel-Tissue Interfaces***	
9:35 – 10:00	Shaobo Zhang, Mechanobiology Institute, Singapore* ***Mechanical Proofreading by Myosin II Oscillation & Filopodia Adhesion Regulates Robust Cell Matching***	
10:00 – 10:35	Frank Jülicher, Max Planck Institute, Germany ***Biophysics of Epithelia***	
10:35 – 11:00	**Coffee Break**	**Mezzanine**
Session VI	Laurent Cortè, MINES ParisTech, France, Chair	
11:00 – 11:35	Jean-Leon Maître, Curie Institute, France ***Hydraulic Fracturing and Active Coarsening Position the Lumen of the Mouse Blastocyst***	
11:35 – 12:00	Christian Cammarota, University of Rochester, USA* ***Biological and Physical Basis for Epithelial Cell Reintegration***	

12:00 – 12:35	Joelle Frechette, Johns Hopkins University, USA ***Soft, Wet, and Sticky: Viscous Forces and Elasticity in Wet Adhesion***	
12:35 – 13:30	**Lunch**	**Restaurant**
Session VII	Jean-Leon Maître, Curie Institute, France, Chair	
13:30 – 15:00	Roundtable	
15:00 – 15:35	Pierre-François Lenne, Aix Marseille University, CNRS, IBDM, Marseille, France ***Shaping Cell Contacts during Tissue Morphogenesis***	
15:35 – 16:00	Willem-Jan Pannekoek, UMC Utrecht, The Netherlands* ***Mechanical Regulation of Paracrine Growth Factor Signaling***	
16:00 – 16:35	Alex Dunn, Stanford University, USA ***A Geometry-Based Model Describes Lumen Stability in Epithelial Cells***	
16:35 – 18:00	**Coffee Break / Poster Session II**	**Mezzanine**
Session VIII	Pierre-François Lenne, Aix Marseille University, CNRS, IBDM, Marseille, France, Chair	
18:00 – 18:35	Andrew Kowalczyk, Emory University, USA* ***VE-Cadherin Endocytosis Regulates Cell Polarity, Collective Cell Migration and Angiogenesis***	
18:35 – 19:10	Sanjeevi Sivasankar, University of California, USA* ***Inside-Out Regulation of Cadherin Adhesion***	
19:10 – 19:35	Tamara Bidone, University of Utah, USA* ***Computational Model of Cell Adhesions Mechanobiology***	
19:35 – 20:30	**Dinner**	**Restaurant**

Wednesday, October 16, 2019

8:30 – 19:35	**Registration/Information**	**Lobby**
Session IX	Andrew Kowalczyk, Emory University, USA, Chair	
9:00 – 9:25	Feyza Nur Arslan, IST Austria, Austria* ***Function of Blebs in Cell-Cell Adhesion Studied on Supported Lipid Bilayers***	
9:25 – 9:50	Kabir Biswas, Hamad Bin Khalifa University, Qatar* ***Kinetic Nucleation-Dependent E-Cadherin Clustering Regulates Alpha-Catenin Conformational Activation***	
9:50 – 10:15	Aditya Arora, National University of Singapore, Singapore * ***Cortical Contractility Overrides the Influence of Binding Energy of Trans Interactions during Adherens Junction Formation***	
10:15 – 10:40	Mateusz Sikora, Max Planck Institute, Germany* ***Truss-Like Arrangement of Cadherins Is Responsible for Desmosome Strength***	
10:40 – 11:05	**Coffee Break**	**Mezzanine**

Session X	Feyza Nur Arslan, IST Austria, Austria, Chair	
11:05 – 11:40	Sandrine Etienne-Manneville, Institute Pasteur, France ***PTEN Functions in Collective Migration***	
11:40 – 12:05	Sara Stahley, Princeton University, USA* ***Planar Cell Polarity-Disrupting Mutation Alters Celsr1-Mediated Cell Adhesion and Dynamics***	
12:05 – 12:40	Margarita Staykova, Durham University, United Kingdom ***Hydraulic Fracture of Membrane Adhesion Contacts***	
12:40 – 13:30	**Lunch**	**Restaurant**
13:30 – 17:30	**Free Time**	
Session XI	Sandrine Etienne-Manneville, Institut Pasteur, France, Chair	
18:00 – 18:35	Nicolas Borghi, Jacques Monod Institute, CRNS, France ***Force Transmission at Cell***	
18:35 – 19:00	Stéphane Verger, Swedish University of Agricultural Sciences, Sweden ***Mechanics and Dynamics of Cell-Cell Adhesion in Plants***	
19:00 – 19:35	Thomas Magin, TRM Universitat Leipzig, Germany ***Keratin Isotypes Regulate Desmosome Protein Composition and Adhesive Strength***	
19:35 – 20:30	**Dinner**	**Restaurant**

Thursday, October 17, 2019

8:30 – 12:35	**Registration/Information**	**Lobby**
Session XII	Nicolas Borghi, Jacques Monod Institute, CRNS, France, Chair	
9:00 – 9:35	Sandra Citi, University of Geneva, Switzerland ***Tight Junction Mechanics and Signaling***	
9:35 – 10:00	Markus Körbel, University of Cambridge, United Kingdom* ***Shining Light on Topology in Early T-Cell Activation - A Novel Bilayer System***	
10:00 – 10:35	Jasna Brujic, New York University, USA ***Cadherin-Coated Emulsions as Biomimetic Tissues***	
10:35 – 11:00	**Coffee Break**	**Mezzanine**
Session XIII	Sandra Citi, University of Geneva, Switzerland, Chair	
11:00 – 11:35	Deborah Leckband, University of Illinois, Urbana, USA ***Molecular Force Transduction at Intercellular Adhesions***	

11:35 – 12:10	Jay Groves, University of California, Berkeley, USA ***Phosphotyrosine-Driving Protein Condensation Phase Transitions and the Mechanics of Signaling Through the T-Cell Receptor***	
12:10 – 12:35	**Closing Remarks and *Biophysical Journal* Poster Awards**	
12:35	**Lunch & Departure**	**Restaurant**

**Short talks selected from among submitted abstracts*

SPEAKER ABSTRACTS

CELL-CELL ADHESION: KNOWN KNOWNS AND KNOWN UNKNOWNS

Alpha Yap[1];
[1]University of Queensland, Institute for Molecular Bioscience, Brisbane, Australia

Cell-cell adhesion is a fundamental determinant of metazoan development and tissue homeostasis. A major advance in elucidating this problem came in the late 1970s, with the independent discovery of cadherin cell-cell adhesion receptors by Masatoshi Takeichi and Rolf Kemler. Since then, we have made major progress in characterizing the molecular mechanisms of cadherin adhesion. In particular, we have come to appreciate that cadherins function as dynamic composites with the cortical cytoskeleton, which are conditioned by cell signaling, the plasma membrane itself, and membrane traffic. In contrast, the physical biology of cadherins and cell-cell adhesion has been relatively neglected until now. A goal of this conference is to ask how understanding the physics of adhesion can guide, and be constrained, by the biology of cadherin adhesion. And, conversely, how our knowledge of the biology of cell-cell adhesion can provide new challenges for physics. To set the scene for our discussion, I will: a) Provide an overview of the cell biology of cadherin adhesion; and b) Outline some outstanding biological problems that we have yet to resolve.

HYBRID ACTIVE MATTER: PARTICLES AND CELLULAR AGGREGATES

Francoise Brochard-Wyart; Françoise Brochard Wyart[1];
[1]Institut Curie, Physico Chimie Curie, Paris Cedex 05, France
[2]Sorbonne Université, Paris, France

We first investigate the collective migration of cell on adhesive gels, using 3D cellular aggregates as a model system. Aggregates spread by expanding outwards a cell monolayer, which may partially dewet, causing the aggregates to move as "Giant Keratocytes", where the lamellipodium is a cell monolayer that expands at the front and retracts at the back. We characterize the diverse modes of collective migration by quantifying the flows and force field responsible of the bipedal stick-slip motion. We propose two mechanisms: i) chemical modification of the substrate in analogy to reactive droplets. We show that it is possible to mimic the croissant shape of keratocyte fragments with a droplet of oil containing a surfactant and ii) symmetry-breaking arising from cell polarization in analogy to active droplets.

We then describe mixture of dead and living matter and how microparticles play with cells. The size of the particles is varied from nanometers to few microns. Nanoparticles (size 20nm) can be used as a glue "nanostickers" to enable the formation of self-assembled aggregates by promoting cell–cell interactions and have important applications for cellular therapy and cancer treatment. Micro-particles MiPs (size ≈ micron) are used to study the spreading of cell aggregates deposited on a substrates decorated with MiPs. A cell monolayer expands around the aggregate. The cells at the periphery uptake the microparticles "gluttonous cells" by phagocytosis, clearing the substrate and forming an aureole of cells full of particles. As the size of the particles increases, macro-particles MaPs (size ≈10 microns), they become to big to be eaten and they are put into motion" dancing" For hybrid cells-MaPs aggregate, mixture of active-passive matter, we observe a phase separation, predicted by simulations for a mixture of particles with different level of activity.

TENSION-DEPENDENT STABILIZATION OF E-CADHERIN LIMITS CELL-CELL CONTACT EXPANSION

Carl-Philipp Heisenberg[1];
[1]IST Austria, Heisenberg lab, Klosterneuburg, Austria

Tension of the actomyosin cell cortex plays a key role in determining cell-cell contact growth and size. The level of cortical tension outside of the cell-cell contact, pulling at the contact edge, is generally thought to scale with the total size to which a cell-cell contact can grow[1,2]. Here we have used primary germ layer progenitor cells from zebrafish to show that this relationship only applies to a narrow range of cortical tensions, and that above a critical threshold level of cortical tension, tension inversely scales with contact size. This switch from cortical tension increasing to decreasing progenitor cell-cell contact size is caused by cortical tension promoting E-cadherin anchoring to the actomyosin cytoskeleton, thereby increasing clustering and stability of E-cadherin at the contact. Once tension-mediated E-cadherin stabilization at the contact exceeds a critical threshold level, the rate by which the contact expands in response to pulling forces from the cortex sharply drops, leading to smaller contacts at physiologically relevant timescales of contact formation. Thus, the activity of cortical tension in expanding cell-cell contact size is limited by tension stabilizing E-cadherin-actomyosin complexes at the contact.

A COMPUTATIONAL MODEL COUPLING E-CADHERIN DYNAMICS AND ACTOMYOSIN NETWORK ILLUSTRATES THE CELL-CELL CONTACT MATURATION

Qilin Yu[1]; Rodney Luwor[2,3]; William Holmes[4]; Vijay Rajagopal[1];
[1]University of Melbourne, Department of Biomedical Engineering, Parkville, Australia
[2]University of Melbourne, Department of Surgery (RMH), Parkville, Australia
[3]University of Melbourne, Department of Microbiology & Immunology, Parkville, Australia
[4]Vanderbilt University, Department of Physics and Astronomy, Nashville, TN, USA

E-cadherin based intercellular adhesion plays a fundamental role in many biological processes including tissue development, wound healing, tissue integrity and cancer metastasis. Previous studies have demonstrated that cell-cell contact formation is regulated by a variety of biochemical pathways that modulate the actomyosin cytoskeleton and the cadherin-catenin-complex – two key players in the intercellular junction formation. Furthermore, micropipette-based cell-cell doublet experiments have shown that mechanical forces experienced by the cells also play an important role in the formation of the intercellular junction. However, a quantitative understanding of the complex interplay between these mechanical forces and the biochemical pathways remains to be resolved.

In this study, we present a new computational model of intercellular junction maturation in a cell doublet. The model couples a 2D lattice-based model of E-cadherin dynamics with a continuum, reaction-diffusion model of the reorganizing actomyosin network and it's regulation by Rho signaling at the intercellular junction. In the model, the force balance around the cell-cell contact evolves as a result of interactions between E-cadherins and the actomyosin network. These forces feedback to the intercellular junction through force sensitive molecules, such as myosin and α-catenin. The model can recapitulate the asymmetric distribution of E-cadherins and related molecules on the rim of the cell doublet contact due to the asymmetric forces along the contact. These results demonstrate how the interplay between mechanical forces and chemical signaling lead to changes during the contact maturation.

ADHESION AND STICKINESS OF SOFT MATTER

Costantino Creton[1,2];
[1]PSL University, Paris, France
[2]ESPCI Paris, Laboratoire SIMM, Paris, France

One of the reasons to hold this workshop is the cross-fertilization of ideas between the community interested in adhesion in the life sciences and the soft matter community interested in adhesion of soft materials. Our group has been working for the last twenty years on a comprehensive description of what makes materials sticky. The key concept that we are going to address here is the coupling between the actual chemical/physical interactions that occur at the interface, and the deformability of the environment. Although these ideas have been developed with experiments on macroscopic polymer-based adhesives, they are broadly applicable at all scales. In particular we are going to show how short range viscous forces and long range elastic forces couple and the crucial role played by strain stiffening in the transmission of forces in materials. The other important concept coming from macroscopic mechanics is the spatial (and often temporal) heterogeneity of stresses due to long range elastic forces, which leads to localized failure as opposed to flow. We hope to start the discussion and point out some analogies with adhesion in life sciences.

OVERVIEW OF THE BIOPHYSICAL ASPECTS OF CELL-CELL ADHESION

Virgile Viasnoff
National University of Singapore, Singapore

In this talk I will summarize some of the key challenges that have to be resolved to understand cell-cell adhesion, mediated by adherens junction, from a biophysical point of view. I will bridge these aspects with other problems in soft matter. Lastly, I will highlight how the approaches we developed lately in the lab can help dissect the contribution of the different biophysical parameters driving cell-cell contact in the case of suspended doublets and 2-celll lumens.

TENSILE STRENGTH VS. SHEAR STRESS – AN APPROACH TO MEASURE INTERNAL TENSIONS BETWEEN CELL-CELL JUNCTIONS

Julia Eckert[1]; Luca Giomi[1]; Thomas Schmidt[1];
[1]Physics of Life Processes, Leiden Institute of Physics, Leiden University, Leiden, The Netherlands

Cell-cell junctions and cell-extracellular-matrix adhesions are important for communication and coordination within tissues. Thereby, cells sense and apply different mechanical types of stress, for example during migration of cell clusters, tissue expansion or tissue compression. During all these cues, internal tensions act at the interface, of cell-matrix and of cell-cell junctions. Where stress at the cellmatrix interface have been extensively studied, cellular stress and forces at the cell-cell junctions in tissue are less well characterized.

We have developed a methodology to measure both the external stress of cells towards the matrix and the internal stress between cells. Our methodology allows us to distinguish and to compare tensile vs shear stress on cell-cell junctions. Based on micropillar arrays for cell traction force measurements, we produced PDMS micropillar array-blocks, of size resembling that of individual cells, separated by micrometer-spacings. Cells adhere to individual blocks and are allowed to connect over the spacings. A controlled stretch allows us to change either the distance or the parallel position of the blocks with respect to each other. Thereby we are able to apply pure tensile or pure shear stress on the cell-cell junctions up to the point where they break.

Our new methodology opens the way to study the influence of mechanical stress on cell-cell adhesions and to measure directly the internal tension between involved junctions of different types of cells.

INTRINSIC CELL CONTRACTION IS ESSENTIAL FOR JUNCTION CONFIGURATION AND STABILIZATION

Vania M Braga[1];
[1]Imperial College London, Faculty of Medicine, London, United Kingdom

Cell-cell adhesion plays an essential role in the determination of cell shape and function during development and adult life, including tissue integrity, morphogenesis and homeostasis. Dynamic regulation of cadherin-dependent cell-cell adhesion modulates important cellular processes such as contractility, distribution of different polarity markers and specific localization of signalling platforms. Conversely, tumour de-differentiation in epithelial tissues is accompanied by disruption of cell-cell contacts and re-writing of signalling to drive uncontrolled proliferation and migration. Here I discuss the interplay between intrinsic cellular contraction and the shape and strength of cadherin contacts, and how this cross-talk impact on the disruption of junctions and epithelial architecture by oncogenic stimulation

VINCULIN ALLOSTERICALLY ENHANCES FORCE-DEPENDENT BINDING OF ALPHA-E-CATENIN TO F-ACTIN

William Weis[1]; Nicholas Bax[1]; Derek Huang[1]; Alexander Dunn[1];
[1]Stanford University, Stanford, CA, USA

The connection of cadherin-based intercellular adhesions and the actomyosin cytoskeleton is a fundamental feature of metazoan tissues. alphaE-catenin, which links the cadherin/beta-catenin complex to F-actin, displays catch bond behavior, such that force applied to the ternary cadherin/beta-catenin/alphaE-catenin complex enhances its lifetime on actin. Mechanical tension also promotes binding of the actin-binding protein vinculin to alphaE-catenin, which is thought to reinforce the cadherin-catenin/actin linkage. Here, we examined the effect of vinculin on binding of the ternary cadherin/beta-catenin/alphaE-catenin complex to actin. Although the actin-binding activity of vinculin likely contributes to junctional strengthening, we find that a vinculin construct lacking its actin-binding domain enhances the lifetime of the cadherin/catenin complex on actin, in a force-dependent manner. Computational modeling suggests that this force-dependent strengthening of individual alphaE-catenin/F-actin bonds results in adhesions with increased resilience to fluctuating loads and higher energetic efficiency in force transmission at cell-cell junctions. Our results demonstrate a form of force-dependent allosteric regulation that may enhance the ability of cells to form robust connections and sense mechanical cues at cell-cell contacts.

OIL-IN-WATER EMULSION DROPLETS AND MICROFLUIDIC TOOLS TO STUDY B CELLS POLARIZATION AND MECHANICS OF IMMUNOLOGICAL SYNAPSE

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Right after a pathogen invasion, organism deploys two lines of defense: the innate and adaptive immunities. The first one is a short-term response providing pathogen destruction then antigen presentation promoted by Antigen Presenting Cells (APC). The latest ensures an important long-term response mostly thanks to B lymphocytes which promote high-affinity antibodies secretion and memory B cells differentiation. B cells either catch soluble antigens in the plasma or extract them onto the APC membrane. In the latest case, APC and B cells ensure the antigen transfer via a highly organized contact: the immunological synapse.

To precisely understand the physicochemical mechanics involved in this synapse, we first model cell-cell contact by creating new APC-like substrates respecting crucial properties. Emulsion droplets properly mimic antigen mobility at the oil/water interface as observed on the cellular membrane; and due to low and controllable surface tension, droplets are as deformable as real APC. We determine the visco-elastic modulus of droplets and B cells thanks to glass microplates experiment. We so optimize emulsion properties to observe the cellular response of B lymphocytes. We also use microfluidic-trap devices to ease the observation of several isolated synapses simultaneously and follow their formation over time. Consequently, we temporally and spatially control the APC-like droplet/B cell synapse. By combining emulsion and microfluidic tools, the kinetic of lysosomes moving to the synapse area and the stress applied by the cell on the droplet are quantified.

As preliminary results, we find the lysosomal recruitment only occurs during the synapse with stiff droplets: mechanical force is not enough to extract antigen. Moreover, we quantify the force applied by B cells on soft droplets. We here point out the role of APC rigidity during the immune synapse and show how droplets and microfluidic traps are promising tools to study the physicochemical parameters of cell-cell contact.

PHYSICAL EFFECTS CATALYZING CELL ADHESION: FROM MIMETIC SYSTEMS TO TISSUES

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A number of cell functions rely on the formation of macromolecular adhesive platforms in the plasma membrane. While the functional role of these assemblies has been intensively investigated over the years, little is known about the mechanisms underlying their formation. In this presentation, several possible physical pathways will be explored by studying adhesion of mimetic vesicles, cells and epithelial tissue. Focusing on the formation of adhesion domains, the role of membrane elasticity, composition fluctuations, and the interactions with the cytoskeleton will be discussed. Furthermore, cooperative attachments of proteins with different length, flexibility and affinities will be analyzed, allowing the development of a hypothesis regarding the simultaneous repellent and catalytic roles of the glycocalyx in adhesion. In the closing, the relation between cell adhesion and mechanoresponse in cellular aggregates will be examined.

CREATING ADHESION AT HYDROGEL-TISSUE INTERFACES

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The fixation of hydrogels to soft biological tissues is of outmost interest for numbers of biomedical applications but it is a highly challenging task due to the fragile and wet nature of both hydrogels and tissues. Here, we explore how physical mechanisms occurring at hydrogel-tissue interfaces can be exploited to design bioadhesive hydrogels that are relevant for clinical applications. For that, ex vivo and in vivo experiments were devised to measure the adhesion between model polyethylene glycol hydrogel films and the surface of porcine livers. In a first study, we find that a transition from a lubricated contact to an adhesive contact is governed by the transport of liquid across the tissue-hydrogel interface. We show that this transition corresponds to a draining of the interface, which is well described by a simple model taking into account the microanatomy of tissues. This interfacial wetting effect explains the strong decrease in adhesion observed between ex vivo and in vivo conditions and suggests a new route to improve adhesion using superabsorbent hydrogel meshes.

In a second study inspired by the pioneering works by Leibler and coworkers, we investigate how tissue-hydrogel adhesion can be created using particles that bridge the interface by adsorbing on both gels and tissues. Ex vivo peeling experiments show how adhesion energy depends on the contact parameters and coating properties (nanoparticle size, surface chemistry and aggregation). As an example, for a 5 min contact on liver tissues, a 3 to 4 fold increase in adhesion energy was obtained by coating dry PEG membranes with silica or iron-oxide nanoparticles. These results and methods shed a new light on the design of predictive bioadhesion tests and on the strategies to control the fixation and biointegration of hydrogel based-devices.

MECHANICAL PROOFREADING BY MYOSIN II OSCILLATION & FILOPODIA ADHESION REGULATES ROBUST CELL MATCHING;

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It has been an age-old question about the embryo development: how the cells find their partners correctly in a complicated as well as dynamic cellular environment? In the past, studies from neurogenesis have found various molecules being important in this cell matching process. However, the underlying mechanisms, especially the dynamics, remain elusive. Here, we explored this by applying the cardiogenesis in the Drosophila embryo as a simplified matching system. The formation of the Drosophila heart involves a long range of cell migration but results in robustly formed cell-partner connections. By fast in vivo live imaging, we found that cell matching is particularly robust at boundaries between cardioblast (CB) subtypes of which their filopodia show distinct binding affinities. Through genetic screening, we identified the adhesion molecules Fas3 and Ten-m, both of which also regulate synaptic targeting, as having complementary expression patterns in CBs. Altering Fas3 or Ten-m expression changes differential filopodia adhesion and leads to CB mismatch.

Further, focusing on Myosin II, showing ‘wave’ like dynamics within the CBs, we found that coordination between Myosin II oscillations within CBs and differential filopodia connectivity between CBs is essential in ensuring robust cell matching. By using genetic manipulations and laser ablation, we have found that the CB filopodia activity is highly Myosin II dependent. It appears that the Myosin II oscillation acts as a “mechanical proof-reader” of cell-cell connections, whereby weak connections are broken and strong ones reinforced. Altering Myosin II activity – either by over- activation or inhibition of Myosin II – results in perturbed cell matching. Additionally, changing the Myosin II oscillation pattern also leads to misaligned CBs. Combined, these results suggest that the mechanical properties of cells are precisely tuned to provide a ‘proofreading’ machinery to ensure robust cell matching.

BIOPHYSICS OF EPITHELIA

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A fundamental question in Biology is to understand the collective organisation of many cells during morphogenesis. Morphogenesis often involves the dynamic remodeling of tissues involving cell rearrangements, cell divisions and cell flows. The fly wing is an important model system for the study of multicellular dynamics during morphogenesis. The growth of the wing imaginal disk is governed by characteristic patterns of cell rear-rangements and cell shape changes. During pupal stages, the early fly wing undergoes a spectacular dynamic reorganization which generates the final shape of the wing. We characterize tissue remodeling by quantifying the contributions of specific cellular processes such as cell shape changes, cell neighbor exchanges, cell division and cell extrusion to the macroscopic tissue shear. Based on this approach, we discuss tissue mechanics and dynamics with a focus on the active and passive mechanics of T1 transitions by which cells change their neighbors.

HYDRAULIC FRACTURING AND ACTIVE COARSENING POSITION THE LUMEN OF THE MOUSE BLASTOCYST

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During mouse preimplantation development, the formation of the blastocoel, a fluid-filled lumen, breaks the radial symmetry of the blastocyst. What controls the formation and positioning of this basolateral lumen remains obscure. We find that accumulation of pressurized fluid fractures cell-cell contacts into hundreds of micron-size lumens. Microlumens eventually discharge their volumes into a single dominant lumen, which we model as a process akin to Ostwald ripening, underlying the coarsening of foams. Using chimeric mutant embryos, we tune the hydraulic fracturing of cell-cell contacts and steer the coarsening of microlumens, allowing us to successfully manipulate the final position of the lumen. We conclude that hydraulic fracturing of cell-cell contacts followed by contractility-directed coarsening of microlumens sets the first axis of symmetry of the mouse embryo.

BIOLOGICAL AND PHYSICAL BASIS FOR EPITHELIAL CELL REINTEGRATION

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Proliferating epithelia face a challenge: dividing cells must increase in size despite spatial constraints presented by their neighbors. Mitotic epithelial cells often move apically, likely as a way to escape epithelial confinement by extending into the third dimension. The resulting daughter cells must subsequently reintegrate into the tissue so that proper tissue architecture is maintained. Reintegration is a poorly understood process, and we are using the Drosophila follicular epithelium to investigate the physical and biological driving forces behind it. A suite of lateral Ig-superfamily adhesion proteins, named Neuroglian, Fasciclin 2, and Fasciclin 3 in the fly, are integral to reintegration. We have determined that these Ig-superfamily adhesion proteins work in parallel rather than as steps in a linear pathway, suggesting that reintegration is an effect of total cell-cell adhesion. Intracellular binding of these proteins also plays a key role in reintegration, likely by allowing force transmission to the cytoskeleton. We propose that the function of these proteins is to build an anchored track that reintegrating cells can adhere to. This adhesion provides the force necessary to reinsert an apically positioned daughter cell into the tissue. Furthermore, our work in non-fly models suggests that this set of proteins and their role in reintegration may be conserved throughout proliferative epithelia.

SOFT, WET, AND STICKY: VISCOUS FORCES AND ELASTICITY IN WET ADHESION

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Understanding and harnessing the coupling between lubrication pressure, elasticity, and surface interactions provides materials design strategies for applications such as adhesives, coatings, microsensors, and biomaterials. This presentation will discuss our efforts to understand how soft materials make contact and adhere under dynamic conditions in fluid environments. Measurements of interactions between soft surfaces will show how elastic films deform due to viscous forces and influence adhesion and show practical implications for adhesives on skin.

SHAPING CELL CONTACTS DURING TISSUE MORPHOGENESIS

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During animal morphogenesis cell contacts are constantly remodeled. This stems from active contractile forces that work against adhesive forces at cell contacts. Using physical approaches including super-resolution imaging, optical manipulation and modeling, we study the mechanics and the supramolecular organization of cell contacts during morphogenesis. In the first part of my talk, I will show how active contractile forces interact with adhesive forces to remodel cell contacts in the Drosophila embryo. In the second part, I will describe the supramolecular organization of the zonula adherens with super-resolution imaging and show that nectin rather than E-cadherin anchors the actin belt within simple columnar epithelia.

MECHANICAL REGULATION OF PARACRINE GROWTH FACTOR SIGNALING

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Epithelial cells exert tensile forces on each other that are transduced by adherens junctions (AJs) to control cell proliferation, differentiation, migration and metabolism. Despite our growing knowledge on force-sensitive cellular processes, the underlying signal transduction pathways that are regulated by fluctuations in tension on AJs remain largely elusive. Here, we uncover tension-sensitive signal transduction pathways using proteome-wide analysis of phosphorylation changes in epithelial monolayers subjected to mechanical stretch. This reveals stretch-induced activation of the MAP kinases ERK1 and ERK2, which we show to require force transduction by AJs. Mechanical stretch induces the entire EGFR/Ras/MEK/ERK pathway, in a manner dependent on ligand binding to EGFR. To elucidate how force transduction by AJs enhances EGFR activity, we performed APEX2-mediated proximity labeling of the core AJ component E-cadherin. This identifies the spatial vicinity of AJs and the metalloproteinase ADAM17, which cleaves the ectodomain of transmembrane EGFR ligands to enable paracrine activation of EGFR. We identify an inhibitory phosphorylation site on ADAM17 that is downregulated upon mechanical stretch, and demonstrate that chemical inhibition of ADAM17 attenuates stretch-induced EGFR and ERK activation. These data uncover a novel mechanism of force-dependent control of cell signaling, comprising AJ-mediated paracrine activation of the EGFR/ERK pathway via ADAM17.

A GEOMETRY-BASED MODEL DESCRIBES LUMEN STABILITY IN EPITHELIAL CELLS

Alex Dunn
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No Abstract

VE-CADHERIN ENDOCYTOSIS REGULATES CELL POLARITY, COLLECTIVE CELL MIGRATION AND ANGIOGENESIS

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Vascular morphogenesis is thought to require fine tuning of endothelial cell-cell adhesion, but the cellular mechanisms that govern the plasticity of adhesion are poorly understood. We hypothesized that endocytosis of vascular endothelial cadherin (VE-cad) is a key modulator of adherens junction plasticity, and that unbalancing this regulation would alter both angiogenesis and vascular permeability. VE-cad endocytosis is mediated by an internalization motif (DEE) within the p120-catenin binding domain of the VE-cad cytoplasmic tail. We used CRISPR/CAS9 to generate a series of mouse mutants with VE-cad point mutations that specifically disrupt endocytosis (VE-cadDEE) and/or p120 binding (VE-cadGGG). We found that mutating conserved GGG residues to uncouple p120 from VE-cad caused decreased VE-cad levels, microvascular hemorrhaging, and impaired postnatal survival. Thus, p120-binding is essential for VE-cad stability and vascular integrity in vivo.

By contrast, mice lacking the DEE endocytic residues had normal vascular permeability. Furthermore, the VE-cadDEE mutation rescued the lethality observed in mice lacking endothelial p120, demonstrating that p120 is dispensable if cadherin is stabilized. However, VE-cadDEE animals displayed striking defects in microvascular patterning in the embryonic yolk sac, postnatal retina, and in ex vivo aortic ring explants. These defects included decreased microvascular density and reduced branching. In vitro, we found that VE-cad endocytosis is required for establishment of polarity during collective cell migration. These migration defects in the DEE mutant cells were alleviated by additional mutations in VE-cad that abrogated actin associations, suggesting that DEE-mediated endocytosis coordinates cell polarity and migration by regulating the dynamics of the actin cytoskeleton. These findings indicate that that p120 binding to VE-cad is essential for normal vascular integrity, while VE-cad endocytosis is required for endothelial cells to polarize and undergo directed collective cell migration during neovascularization.

INSIDE-OUT REGULATION OF CADHERIN ADHESION

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During morphogenesis and wound healing, cellular migration and rearrangements rely on tightly regulated changes in cadherin adhesion. However, the molecular mechanisms by which cadherin adhesion is regulated remains poorly understood. To addresses this critical gap, we integrated biophysical measurements of cadherin structure-function with cell biological manipulations of cadherin-cytoskeleton interactions. Our data demonstrates, for the first time, that changes in E-cadherin (Ecad) ectodomain structure and adhesion are regulated from the inside-out by Ecad linkage to the actin cytoskeleton. Ecad ectodomains bind in two load bearing adhesive conformations: strand-swap dimers and X-dimers. We have previously used ultrasensitive, single molecule Atomic Force Microscopy (AFM) to show that X-dimers and strand-swap dimers have different adhesive properties [1-3]. Here we use high resolution, live cell AFM to correlate the structure and adhesion of Ecad ectodomains to their cytoskeletal linked states in parental, α-catenin knockout, and vinculin knockout MDCK cells. We demonstrate that in MDCK cells, only a third of non-junctional Ecad robustly bind to the actin cytoskeleton; the remaining Ecad only transiently associate with cortical actin. Robust linkage of Ecad to the cytoskeleton requires both α-catenin and vinculin.

Strikingly, we show that while the ectodomains of cytoskeleton bound Ecads adopt an strand-swap dimer conformation, Ecad in the α-catenin and vinculin knockout cells only form X-dimers. Finally, we show that collective migration of epithelial cells is disrupted when α-catenin or vinculin are knocked-out. Our data directly demonstrates ‘inside-out’ regulation of cadherin ectodomain conformation by cytoplasmic proteins and connects these structural changes to collective cell migration.1. Rakshit et al., Proc. Natl. Acad. Sci. U.S.A., 2012,109 (46) : p. 18815-188202. Manibog et al., Nat. Commun., 2014, 5 (3941)3. Manibog et al., Proc. Natl. Acad. Sci. U.S.A., 2016, 113 (39): p. E5711-E5720

COMPUTATIONAL MODEL OF CELL ADHESIONS MECHANOBIOLOGY

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Cell-cell junctions and cell-substrate adhesions are specialized regions of the plasma membrane that couple the contractile cytoskeleton network to the extracellular environment. They are critical in several cell and tissue activities, including tissue morphogenesis, cell migration and wound healing. Central elements of adhesions are transmembrane receptors: cadherins mediate cell-cell junctions and integrins form cell-substrate adhesions. Cadherin and integrin sense, resist and transmit cytoskeletal contractility. In particular, adhesion resistance to contractility makes cadherin and integrin cell mechanosensors, that have specific responses to mechanical signals.

Unfortunately, the biophysical mechanisms by which adhesions reinforce in response to stress are not fully understood. In this study, we developed a computational model based on Brownian Dynamics in order to study mechanisms of adhesion reinforcement via two biophysical mechanisms: catch-bond kinetics and clustering. Our model shows that a dynamic interplay between the two biophysical mechanisms can promote adhesions stabilization. Moreover, combination of catch-bond kinetics with receptor clustering allow identifying different regimes of adhesion tension, that are necessary to transmit stresses via variations in junctional tension and cell-substrate interactions. These results provide important insights into the biophysical principles and mechanisms of adhesion mechanosensing, with functional consequences on both cell and tissue physiology.

FUNCTION OF BLEBS IN CELL-CELL ADHESION STUDIED ON SUPPORTED LIPID BILAYERS

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Bleb-like protrusions are thought to contribute to locomotion of various cell types in development and disease. In zebrafish embryos, morphologically distinct blebs that travel around the cell periphery are commonly observed in intact as well as dissociated embryos, and have been implicated in progenitor cell migration. Yet, whether blebs have also other functions during the course of development, in particular in cell-cell adhesion, remains to be elucidated. Here, we have devised a biomimetic system consisting of supported lipid bilayers (SLBs) functionalized with zebrafish E-cadherin ectodomain (E-cad-ECD) as a cell-surface model. This system enables us to control bilayer composition and perform high spatiotemporal resolution imaging on cell-bilayer contacts of seeded zebrafish progenitor cells. We found that blebs frequently form and retract at the edge of cell-substrate contacts and trigger a temporary local enrichment of actin and E-cadherin at the contact edge during retraction. This local enrichment is followed by enhanced clustering and immobilization of E-cadherin at the contact, which again modulates contact growth. To determine the potential role of blebs in cell-cell contact formation, we are currently studying contact dynamics under conditions where we manipulate bleb formation by changing membrane-to-cortex attachment or actomyosin contractility.

KINETIC NUCLEATION-DEPENDENT E-CADHERIN CLUSTERING REGULATES ALPHA-CATENIN CONFORMATIONAL ACTIVATION

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E-cadherin-based cell-cell adhesion (E-cadherin adhesion) is essential for organogenesis and maintenance of the epithelial tissue, and a loss of cell-cell adhesion has been suggested to contribute to cancer development. In addition to performing its adhesive function through the extracellular domain-mediated homotypic interaction, E-cadherin adhesion enables cells to sense mechanical tension in the tissue through the adaptor protein, alpha-catenin. This has been proposed to be mediated through, in part, a conformational change in alpha-catenin upon increase in the actomyosin tension on E-cadherin adhesion resulting in the availability of cryptic binding sites in alpha-catenin leading to an enhancement in its interaction with vinculin, an adaptor protein that is homologous to alpha-catenin, and the actin cytoskeleton. Reconstitution of E-cadherin adhesion in a hybrid format wherein a live cell interacts with a synthetic, supported lipid bilayer functionalized with the extracellular domain of E-cadherin showed that cells utilize filopodia to cluster E-cadherin. Importantly, E-cadherin clustering requires a reduced diffusive mobility of the protein on the membrane indicating the presence of a step of kinetic nucleation in the process. Further, experiments with nanopatterned supported lipid bilayer substrates revealed that the size of E-cadherin clusters regulate the conformational activation of alpha-catenin. Once activated, however, alpha-catenin is sustained in the active conformation even when actomyosin tension in the cell is reduced pharmacologically. Thus, membrane diffusion-regulated E-cadherin clustering impacts alpha-catenin conformational activation and mechanical signaling.

CORTICAL CONTRACTILITY OVERRIDES THE INFLUENCE OF BINDING ENERGY OF TRANS INTERACTIONS DURING ADHERENS JUNCTION FORMATION

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The role of energetic contribution of trans interactions between cadherins during adherens junction (AJ) formation has been debatable. To elucidate the influence of binding energies of trans interactions on different phases of AJ formation, we engineered E Cadherin constructs whose extracellular domain was replaced by Halo tag to conjugate ssDNA oligonucleotides. Cells with complementary ssDNA initiated trans interactions, followed by AJ formation. Engineered cadherins lacked ability to activate Rac and Rho signalling on trans ligation, but proceeded to form wild type like AJ organization on stimulation with drugs to sequentially downregulate and upregulate tension. The junction formation was temporally divided into two phases; Phase I characterized by overall reduction in cortical tension and initiation of cell-cell contact formation, usually accompanied with a peak in Rac1 activity. Phase II involves activation of RhoA and upregulation of cortical tension, which leads to junctional reorganization and expansion. The contact lengths between a cell pair at the end of the first phase of junction formation was proportional to the binding energies of the oligonucleotides, however, this effect was completely abolished when cortical contractility was exogenously upregulated using Nocodazole or Calyculin A after initial contact formation. Overall, adhesion energy was a determinant of junction size only in early junction formation, however, it seems to have no influence on junction size after re-establishment of cortical contractility/ RhoA activation.

TRUSS-LIKE ARRANGEMENT OF CADHERINS IS RESPONSIBLE FOR DESMOSOME STRENGTH

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Desmosomes are long-lasting cell-cell junctions that endow mature tissues with mechanical stability. The core of the desmosomal adhesion is formed by cadherins, specialised calcium-dependent transmembrane proteins. Together with other adaptor proteins, the cadherins connect cortices of neighbouring cells. Robustness to external stress comes from a particularly dense arrangement of cadherins, which form characteristic electron-dense structures visible in EM micrographs. However, the structural details of desmosomal cadherin assemblies remain controversial despite their relevance for various diseases. To address and resolve these controversies, we performed large-scale molecular dynamics simulations of a different 3D cadherin arrangements in the desmosome. We found that only an antiparallel, truss-like arrangement of cadherins can explain both the mechanical robustness and the spacing observed between plasma membranes in the desmosome. We validated our predictions by cryo-electron tomography of the desmosomes from mouse liver.

PTEN FUNCTIONS IN COLLECTIVE MIGRATION

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Collective cell migration relies on the synchronization between cytoskeleton regulation, maintenance of cell-cell adhesions and adhesions with the extracellular matrix. Aberrant collective motility has been linked with several pathologies, and participates in cancer invasion and metastasis. Here we study the role of the tumour suppressor PTEN and its contribution to collective migration. PTEN is one of the most mutated or deleted tumour suppressor in human cancer and it is characterized by a double phosphatase activity, for lipids and for proteins. The lipid phosphatase activity has gained much attention as main antagoniser of the PI3K-Akt pathway for survival and proliferation. PTEN lipid phosphatase activity has also been shown crucial for the polarisation and migration of migrating single cells. In this study we are elucidating the role of PTEN in collective migration using in vitro wound-healing assay and an in vivo model of endothelial migration. We show that both the lipid and protein phosphatase activities of PTEN participate in the control of adherens junctions by controlling p120catenin phosphorylation and tissue integrity. We also show the prominent role of PTEN protein phosphatase activity in the control of the actin cytoskeleton organization and the speed of migration via the regulation of ROCK and LKB1 signaling.

PLANAR CELL POLARITY-DISRUPTING MUTATION ALTERS CELSR1-MEDIATED CELL ADHESION AND DYNAMICS

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Planar cell polarity (PCP), the collective polarization of cells along a tissue plane, is fundamental to early embryonic development and tissue organization in complex, multicellular organisms. Compromised PCP results in severe developmental disorders including neural tube defects, ciliopathies and cardiomyopathies. A hallmark of PCP is the asymmetric localization of core PCP components at cell junctions bridged by principle PCP protein, Celsr, an atypical cadherin. We lack a detailed understanding of Celsr1 extracellular interactions at the molecular level. Overall, this work seeks to elucidate how Celsr1 mediates cell adhesion to coordinate functional PCP and how this is altered by the PCP-disrupting mutation Crash (Crsh). Crsh maps to the cadherin repeats within Celsr1s extracellular domain, suggesting it may perturb Celsr1 adhesion.

Using the mammalian epidermis as a model system and a combination of junctional recruitment and cell aggregation assays, we show that Celsr1 mediates calcium-dependent, homophilic cell adhesion through its extracellular domain. Surprisingly, Crsh mediates cell aggregation comparable to wildtype (WT), demonstrating this variant mediates trans-adhesive interactions. Yet when mixed, Crsh and WT expressing cells sort out into distinct aggregates, indicating this point mutation alters Celsr1 adhesive properties. Crsh displays more diffuse cell surface distribution and reduced junctional stability as measured by FRAP, suggesting Crsh is defective in lateral clustering. Importantly, chemically induced cis-dimerization of Crsh rescues junctional enrichment and trans-interactions with WT, indicating a role for cis-interactions to stabilize Celsr1 adhesion.

Finally, we use super-resolution imaging to investigate the subcellular organization of PCP junctions and reveal how alterations in Celsr1 adhesion affect this organization. Collectively, our results support a model in which the Crsh-pertaining region of Celsr1 is responsible for mediating cis-interactions that function to stabilize and reinforce the adhesive complex, a critical prerequisite for PCP organization and functional asymmetry.

HYDRAULIC FRACTURE OF MEMBRANE ADHESION CONTACTS

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What happens to adhering cells when they expel water through their membranes; is adhesion lost or are the cell contacts being remodelled? It turns out these questions are of wide biological relevance- from osmotically shrinking cells to active pumping of water in embryo tissues and formation of lumen. To get a quantitative understanding we use biomimetic model system, consisting of giant unilamellar vesicles coupled to a supported lipid bilayer or to other vesicles via strong biotin-neutravidin links, or via the much weaker cadherin bonds. Upon osmotic vesicle shrinking, the adjacent membranes locally disconnect and deform into water-filled pockets, also observed in cells.

At the same time, the adhesion bonds are sheared away from the disconnecting membranes, and later recover with time. Using our simplified system, we are able to elucidate the mechanisms of water pocket formation and determine its dependance on the membrane water permeability, the bond properties and the magnitude of the osmotic shock. The evolution of the water pockets provide some hints to the behaviour of the plasma membrane during cell contact remodeling.

FORCE TRANSMISSION AT CELL ADHESIONS

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In multicellular organisms, cells generate and undergo mechanical forces that may shape tissues and regulate genetic programs, but the underlying mechanisms remain largely unknown. Using genetically encoded biosensors of molecular tension, it is now possible to monitor in space and time the forces exerted on specific cell adhesion proteins in situ. Doing so, we have assessed in cell culture models how adhesion proteins respond to intra- and extracellular mechanical cues, and how their tension relates to the activation of cell signaling pathways and cell-scale forces upon induction of generic morphogenetic processes. Our results reveal varied mechanisms for force transmission across scales and their efficiencies, and how cell mechanosensation may arise from these processes.

MECHANICS AND DYNAMICS OF CELL-CELL ADHESION IN PLANTS

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How cell-cell adhesion is achieved is a fundamental question in the development of multicellular organisms. Surprisingly, this question remains largely under-explored in plants and much remains to be discovered. In plants, cell-cell adhesion is physically mediated by the cell wall. This is not only passive: in previous work we identified a complex signaling pathway for the active maintenance of cell-cell adhesion in plants (Verger et al. 2016). Furthermore, we demonstrated how tensile stress in tissues tends to pull the cells apart in the epidermis during growth and development and may also act as an instructive cue for cell adhesion maintenance in plants (Verger et al. 2018). In turn, loss of cell adhesion impairs proper development.

For instance, we showed how torsion relies on adhesion and anisotrotpic growth in stems (Verger et al. 2019). Here, we identified a set of mutants, from the model species Arabidopsis thaliana, displaying characteristic cell-cell adhesion defects. These include mutants in actin filament nucleation (ARP2/3 and SCAR/WAVE complexes), epidermal identity transcription factors (ATML1 and PDF2) and a mechanosensitive calcium channel (DEFECTIVE KERNEL1). While we are investigating the actual cause for the loss of cell adhesion in these mutants, our current hypothesis is that mechanical stress in the epidermis triggers a reorganization of the actin network in order to polarize polysaccharides depositions towards cell-cell connections which are the most under mechanical stress' threat to reinforce and maintain adhesion. Maintenance of cell adhesion would further promote the supracellular propagation of mechanical stress in a "tension-adhesion" feedback loop, suggesting a convergent principle for the maintenance of cell adhesion between plants and animals, but based on divergent adhesion mechanisms (e.g. cell wall in plants).

References: Verger, S., et al., 2016. Development Verger, S., et al., 2018. eLife Verger, S., et al., 2019. Front. Plant Sci.

KERATIN ISOTYPES REGULATE DESMOSOME PROTEIN COMPOSITION AND ADHESIVE STRENGTH

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[2]Ludwig-Maximilians-Universität München, Institute of Anatomy and Cell Biology, Munich, Germany

Desmosomes are intercellular junctions that mediate strong cohesion and communication in tissues exposed to high mechanical strain, such as stratified epithelia and the heart. Desmosome adhesive strength depends on the abundance of constituent proteins, their intracellular distribution, posttranslational modifications and associated proteins. The regulation of these parameters during epidermal differentiation, wound healing and pathogenesis remains incompletely understood. Here, we report a novel mechanism by which keratin isotypes regulate desmosome composition and adhesive strength by comparing the impact of K14 and K17 on Dsg1 and Dsg3. Upon Ca2+-induced differentiation, the presence of K17 caused a significant reduction of Dsg1 and a slight increase in Dsg3, whereas K14 promoted the expression of Dsg1. Atomic force microscopy (AFM) and immunofluorescence analysis revealed increased extradesmosomal Dsg1/3 along the plasma membrane and intracellularly. AFM measurements uncovered reduced Dsg3 unbinding forces in the presence of K17. Dsg1 knockdown further weakened adhesion. This indicated that Dsg isotype and abundance contribute to desmosome adhesion.

Finally, expression of K17 prevented formation of hyperadhesive desmosomes and delayed expression of terminal differentiation markers such as loricrin and hornerin. Our data unravel the complexity of mechanisms by which keratin isotypes regulate desmosome composition and adhesive strength during keratinocyte differentiation and activation.

TIGHT JUNCTION MECHANICS AND SIGNALING

Sandra Citi
University of Geneva, Switzerland

No Abstract

SHINING LIGHT ON TOPOLOGY IN EARLY T-CELL ACTIVATION – A NOVEL BILAYER SYSTEM

Markus Körbel[1]; Edward Jenkins[2]; Kevin Y Chen[1]; Simon J Davis[2]; David Klenerman[1];
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The very first contacts of a T cell with an antigen presenting cell (APC) are key to understanding antigen discrimination in adaptive immunity. The use of supported lipid bilayers (SLBs) to mimic the APC simplifies imaging analysis and allows controlled changes in contacting-surface composition. In studies of the immune synapse, SLBs are commonly functionalized with peptide-bound MHC (pMHC) and ICAM-1, with pMHC acting as an adhesion molecule and a molecular trigger, and ICAM-1 behaving both as an adhesion protein and a steric barrier to engage pMHC, respectively. By replacing it with CD58, a small adhesion molecule, and the extracellular part of CD45, as glycocalyx, we aimed to produce a more realistic model system allowing new insights into T-cell signalling.

On the new surface, the adhesive behaviour of T cells could be fine-tuned by varying the CD45 to CD58 ratio: low densities of CD45 allowed cell attachment and spreading, and higher densities prevented contact formation. At intermediate glycoprotein densities, cells only attached and started to signal if pMHC was present. We utilized the size-based exclusion of CD45 in the SLB together with cell membrane labelling to image contact formation via live TIRF microscopy. Initial small, diffraction-limited contacts that formed and grew were highly dynamic, dominated by centripetal movements at later stages. The small, initial contacts represented the footprint of microvilli, a dominant feature of T-cell topology. T cells treated with agents that reduce microvilli on their cell membrane were unable to detect or respond to pMHC molecules in our model SLB. Our results suggest that T-cell microvilli provide a structure to both penetrate the glycocalyx barrier and detect antigens.

CADHERIN-COATED EMULSIONS AS BIOMIMETIC TISSUES

Jasna Brujic
New York University, New York, New York, USA

No Abstract

MOLECULAR FORCE TRANSDUCTION AT INTERCELLULAR ADHESIONS

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[2]University of California at San Diego, La Jolla, CA, USA
[3]Johns Hopkins University, Baltimore, MD, USA

Deborah Leckband [1], Brendan Sullivan [1], Ismaeel Muhamed [1], Poonam Seghal [1], Taejin Kim [1], Yingxiao Wang [2], Kalina Hristova [3], Taylor Light [3].
1. University of Illinois at Urbana-Champaign, IL. 2. University of California at San Diego, La Jolla, CA 3. Johns Hopkins University, Baltimore, MD

The broad goal of these studies is to identify molecular mechanisms by which protein nanomachines at cadherin-based intercellular junctions transduce force. We use quantitative fluorescence imaging, in conjunction with mechanical measurements such as magnetic twisting cytometry and traction force microscopy to identify rapid, early molecular events in intercellular force transduction. Alpha catenin is a demonstrated force transducer at intercellular junctions that mechanically couples cadherins to F-actin. We engineered a FRET-based conformation sensor to visualize force-dependent conformation changes in alpha catenin in live cells. Dynamic fluorescence imaging demonstrated that alpha catenin undergoes a force-dependent conformational change at stressed intercellular junctions that facilitates the slower recruitment of an actin binding protein vinculin and the subsequent, local actin remodeling.

Using these approaches, we also identified a second cadherin-mediated force transduction mechanism in epithelia. In this second mechanism, perturbing cadherin receptors activates epidermal growth factor receptor signaling and downstream integrins. Studies suggest that increased tension on cadherin bonds induces the disruption of growth factor receptor complexes at the plasma membrane to potentiate EGF-dependent signaling. Both mechano-transduction mechanisms require alpha catenin, which is required for cadherin-mediated force transmission. However each mechanism triggers distinct molecular cascades with different effects on cell mechanics. In conclusion, these results demonstrate two different molecular mechanisms by which proteins transduce force at intercellular adhesions. One involves the force-actuated conformation change in alpha catenin. In the second, increased force on cadherin bonds actuates growth factor receptor signaling, by disrupting protein-protein interactions.

PHOSPHOTYROSINE-DRIVING PROTEIN CONDENSATION PHASE TRANSITIONS AND THE MECHANICS OF SIGNALING THROUGH THE T CELL RECEPTOR

Jay T. Groves;
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Activation of the T cell receptor (TCR) leads to phosphorylation of the intrinsically disordered scaffold protein, LAT, on the membrane. Grb2 is recruited to phosphorylated tyrosine (pY) sites on LAT, which subsequently recruits the Ras activator, SOS. SOS is bivalent for Grb2 and this whole system can undergo a gelation phase transition into a condensed 2D phase of associated proteins on the membrane surface. This presentation will discuss a variety of new experiments mapping the early mechanics of TCR signaling and the role of the LAT condensation phase transition as a signal regulatory mechanism. One fundamental finding is that a kinetic proof reading mechanism, based on the molecular binding dwell time of SOS at the membrane, may provide a critical level of noise suppression in TCR signaling, enabling the T cell to be a single molecule sensor, even in noisy environments. Other aspects of the phase transition in T cell signal regulation will also be discussed.

POSTER ABSTRACTS

MONDAY, OCTOBER 14
POSTER SESSION I
16:35 – 18:00
Mezzanine

All posters are available for viewing during all poster sessions; however, below are the formal presentations for Monday. Presenting authors with odd-numbered poster boards should present from 16:35 – 17:22 and those with even-numbered poster boards should present from 17:22 – 18:00. The presenters listed below are required to remain in front of their poster boards to meet with attendees.

Arora, Aditya	**1-POS**	**Board 1**
Arslan, Feyza Nur	**2-POS**	**Board 2**
Bidone, Tamara	**3-POS**	**Board 3**
Blom, Kristian	**4-POS**	**Board 4**
Bouizakarne, Sara	**5-POS**	**Board 5**
Cammarota, Christian	**6-POS**	**Board 6**
Chen, Chi-Shuo	**7-POS**	**Board 7**
Cui, Bianxiao	**8-POS**	**Board 8**
Dunsing, Valentin	**9-POS**	**Board 9**
Eckert, Julia	**10-POS**	**Board 10**
Fu, Chaoyu	**11-POS**	**Board 11**
Grigolon, Silvia	**12-POS**	**Board 12**
Guthold, Martin	**13-POS**	**Board 13**
Katsuno-Kambe, Hiroko	**14-POS**	**Board 14**
Körbel, Markus	**15-POS**	**Board 15**

Posters should be set up the morning of October 14 and removed by noon October 17.

1-POS Board 1

CORTICAL CONTRACTILITY OVERRIDES THE INFLUENCE OF BINDING ENERGY OF TRANS INTERACTIONS DURING ADHERENS JUNCTION FORMATION

Aditya Arora[1]; Ivar Noordstra[2]; Srikanth Budnar[2]; Alpha Yap[2]; Virgile Viasnoff[1];
[1]National University of Singapore, Mechanobiology Institute, Singapore, Singapore
[2]The University of Queensland, Institute for Molecular Bioscience, Brisbane, Australia

The role of energetic contribution of trans interactions between cadherins during adherens junction (AJ) formation has been debatable. To elucidate the influence of binding energies of trans interactions on different phases of AJ formation, we engineered E Cadherin constructs whose extracellular domain was replaced by Halo tag to conjugate ssDNA oligonucleotides. Cells with complementary ssDNA initiated trans interactions, followed by AJ formation. Engineered cadherins lacked ability to activate Rac and Rho signalling on trans ligation, but proceeded to form wild type like AJ organization on stimulation with drugs to sequentially downregulate and upregulate tension. The junction formation was temporally divided into two phases; Phase I characterized by overall reduction in cortical tension and initiation of cell-cell contact formation, usually accompanied with a peak in Rac1 activity. Phase II involves activation of RhoA and upregulation of cortical tension, which leads to junctional reorganization and expansion. The contact lengths between a cell pair at the end of the first phase of junction formation was proportional to the binding energies of the oligonucleotides, however, this effect was completely abolished when cortical contractility was exogenously upregulated using Nocodazole or Calyculin A after initial contact formation. Overall, adhesion energy was a determinant of junction size only in early junction formation, however, it seems to have no influence on junction size after re-establishment of cortical contractility/ RhoA activation.

2-POS Board 2

FUNCTION OF BLEBS IN CELL-CELL ADHESION STUDIED ON SUPPORTED LIPID BILAYERS

Feyza Nur Arslan[1]; Martin Loose[1]; Carl-Philipp Heisenberg[1];
[1]Institute of Science and Technology (IST) Austria, Klosterneuburg, Austria

Bleb-like protrusions are thought to contribute to locomotion of various cell types in development and disease. In zebrafish embryos, morphologically distinct blebs that travel around the cell periphery are commonly observed in intact as well as dissociated embryos, and have been implicated in progenitor cell migration. Yet, whether blebs have also other functions during the course of development, in particular in cell-cell adhesion, remains to be elucidated. Here, we have devised a biomimetic system consisting of supported lipid bilayers (SLBs) functionalized with zebrafish E-cadherin ectodomain (E-cad-ECD) as a cell-surface model. This system enables us to control bilayer composition and perform high spatiotemporal resolution imaging on cell-bilayer contacts of seeded zebrafish progenitor cells. We found that blebs frequently form and retract at the edge of cell-substrate contacts and trigger a temporary local enrichment of actin and E-cadherin at the contact edge during retraction. This local enrichment is followed by enhanced clustering and immobilization of E-cadherin at the contact, which again modulates contact growth. To determine the potential role of blebs in cell-cell contact formation, we are currently studying contact dynamics under conditions where we manipulate bleb formation by changing membrane-to-cortex attachment or actomyosin contractility.

3-POS Board 3

COMPUTATIONAL MODEL OF CELL ADHESIONS MECHANOBIOLOGY

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Cell-cell junctions and cell-substrate adhesions are specialized regions of the plasma membrane that couple the contractile cytoskeleton network to the extracellular environment. They are critical in several cell and tissue activities, including tissue morphogenesis, cell migration and wound healing. Central elements of adhesions are transmembrane receptors: cadherins mediate cell-cell junctions and integrins form cell-substrate adhesions. Cadherin and integrin sense, resist and transmit cytoskeletal contractility. In particular, adhesion resistance to contractility makes cadherin and integrin cell mechanosensors, that have specific responses to mechanical signals.

Unfortunately, the biophysical mechanisms by which adhesions reinforce in response to stress are not fully understood. In this study, we developed a computational model based on Brownian Dynamics in order to study mechanisms of adhesion reinforcement via two biophysical mechanisms: catch-bond kinetics and clustering. Our model shows that a dynamic interplay between the two biophysical mechanisms can promote adhesions stabilization. Moreover, combination of catch-bond kinetics with receptor clustering allow identifying different regimes of adhesion tension, that are necessary to transmit stresses via variations in junctional tension and cell-substrate interactions. These results provide important insights into the biophysical principles and mechanisms of adhesion mechanosensing, with functional consequences on both cell and tissue physiology.

4-POS Board 4

CELLULAR ADHESION DYMAMICS UNDER AN EXTERNAL FORCE

Kristian Blom[1]; Aljaz Godec[1];
[1]Max-Planck-Institute for Biophysical Chemistry, Theoretical and Computational Biophysics, Goettingen, Germany

Most of our current understanding about cellular adhesion dynamics derives from the theory of non-interacting receptor-ligand adhesion pairs. However, recent experiments have revealed collective properties of adhesion clusters, which arise from a coupling of nearby individual adhesion bonds through deformations of the fluctuating membrane. So far it is remains unclear how this coupling affects the dynamics of cluster formation and dissolution, which yields a fundamental question to be answered. In order to arrive at a deeper understanding of adhesion cluster dynamics under an external force, we incorporated both the coupling of adhesion bonds due to membrane fluctuations as well as an external force into a theory of adhesion cluster stability on a mesoscopic scale. With this model we provide rigorous results for the depinning time statistics, i.e. the time to complete cluster dissolution, for various initial geometries. Furthermore, by calculating the splitting probabilities for different cluster dissolution mechanisms, we provide a dynamical phase diagram for the path taken to the dissolved state. Our results reveal that both the depinning time statistics and cluster dissolution mechanism depend non-trivially on the coupling, the external force, and initial geometry, thereby providing deeper insight on the manner that cells could actively control their binding strength.

5-POS Board 5

ACTIN DYNAMICS AND CELLULAR FORCES IN VIVO AND IN VITRO

Sara Bouizakarne[1,2]; Alice Nicolas[1]; Jocelyn Etienne[2]; Grégoire Michaux[3];
[1]Laboratoire des Technologies de la microélectronique, Grenoble, France
[2]Laboratoire Interdisciplinaire de Physique, Saint Martin d'Hères, France
[3]Institut de Génétique et de Développement de Rennes , Rennes , France

Morphogenesis is a developmental process by which shape is acquired. During morphogenesis, tissues change their shape, a process often mediated by myosin-driven cell contractility. The C.elegans embryo has been established as a model to investigate the relationship between cell contractility and shape changes. One important morphogenetic step in C.elegans is elongation, that converts the embryo from bean-shaped to the characteristic elongated worm shape. Elongation occurs via changes in cells' shapes that depend on the forces created by the embryonic cells and the resistance of the biological tissue. Actin organization was shown to play an essential role during this elongation (Vuong-Brender TT et al, Elife 2017). Its transition from disordered, thin filaments to parallel thick bundles is suspected to be at the origin of an anisotropic tension that correlates with a planar polarization of the cortex and the elongation of the embryo (Gillard G. et al, Current Biology 2019).

Here we address the role of actin organization on embryonic tensions. First, we use laser ablations in the actin cortex to probe actin tension during the elongation of the embryos. The ablation is performed in a rectangular-shaped torus, to mechanically separate a small patch of actin from the rest of the cortex and allow the analysis of the tissue relaxation with well-defined boundary conditions. Second, we develop an in vitro model that mimics actin organization during elongation in order to correlate it with cellular forces. Using A431 as an epithelial cellular model, we correlate actin organization with cellular forces. Actin organization will further be tuned either via chemical or mechanical patterning on soft hydrogels, so to explore the mechanical effects of the actin patterns that are observed in vivo. Exploitation of both techniques is expected to provide a better characterization of actin dynamics during the course of C.elegans embryonic elongation.

6-POS Board 6

BIOLOGICAL AND PHYSICAL BASIS FOR EPITHELIAL CELL REINTEGRATION

Christian Cammarota[1]; Colleen Mallie[2]; Tyler Wilson[2]; Nicole Dawney[2]; David Q Matus[3]; Dan Bergstralh[1,2];
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Proliferating epithelia face a challenge: dividing cells must increase in size despite spatial constraints presented by their neighbors. Mitotic epithelial cells often move apically, likely as a way to escape epithelial confinement by extending into the third dimension. The resulting daughter cells must subsequently reintegrate into the tissue so that proper tissue architecture is maintained. Reintegration is a poorly understood process, and we are using the Drosophila follicular epithelium to investigate the physical and biological driving forces behind it. A suite of lateral Ig-superfamily adhesion proteins, named Neuroglian, Fasciclin 2, and Fasciclin 3 in the fly, are integral to reintegration. We have determined that these Ig-superfamily adhesion proteins work in parallel rather than as steps in a linear pathway, suggesting that reintegration is an effect of total cell-cell adhesion. Intracellular binding of these proteins also plays a key role in reintegration, likely by allowing force transmission to the cytoskeleton. We propose that the function of these proteins is to build an anchored track that reintegrating cells can adhere to. This adhesion provides the force necessary to reinsert an apically positioned daughter cell into the tissue. Furthermore, our work in non-fly models suggests that this set of proteins and their role in reintegration may be conserved throughout proliferative epithelia.

7-POS Board 7

ALDOLASE TRIGGERS METABOLIC REPROGRAMING IN COLORECTAL CANCER IN HYPOXIA AND STIFF DESMOPLASTIC MICROENVIRONMENTS

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[2] Linkou Chang Gung Memorial Hospital, Department of Gastroenterology and Hepatology, Taoyuan, Taiwan
[3]Chang Gung University, College of Medicine, Taoyuan, Taiwan
[4]Linkou Chang Gung Memorial Hospital, Liver Research Center, Taoyuan, Taiwan

Colorectal cancer (CRC) progression is highly associated with desmoplasia. Aerobic glycolysis is another distinct feature that appears during the CRC phase of the adenoma-carcinoma sequence. However, the interconnections between the desmoplastic microenvironment and metabolic reprogramming remain largely unexplored. In our in vitro model, we investigated the compounding influences of hypoxia and substrate stiffness, 2 critical physical features of desmoplasia, on CRC metabolic shift by using engineered polyacrylamide gels. Unexpectedly, we found that, compared to cells on a soft gel (approximately 1.5 kPa, normal tissue), cells on a stiff gel (approximately 8.7 kPa, desmoplastic tissue) exhibited reduced glucose uptake and glycolysis under both normoxia and hypoxia.

In addition, the increasing substrate stiffness activated focal adhesion kinase (FAK)/phosphoinositide 3-kinase signaling, but not mitochondrial respiratory inhibitor HIF1α. However, the presence of aldolase B (ALDOB) reverted the CRC metabolic response to mechanosignaling; enhanced glucose uptake (approximately 2- to 3-fold) and obvious aerobatic glycolysis (approximately 1.7-fold) with decreased mitochondrial oxidative phosphorylation was observed. The cytoskeleton assembly and FAK/RhoA pathways were associated with this ALDOB activity. ALDOB also changed the response of CRC traction force, which is related to tumor metastasis, to hypoxia/normoxia. In summary, our data implied a counter influence between hypoxia and substrate stiffness on glucose uptake, and ALDOB upregulation can flip the balance, which drives aerobatic glycolysis synergistically. Our results not only highlight the potential of metabolic reprogramming led by physical alterations in the microenvironment, but also extend our understanding of the essential role of ALDOB in CRC progression from a biophysical perspective.

8-POS Board 8

SURFACE TOPOGRAPHY MODULATES CELL MECHANOSENSING OF EXTRACELLULAR MATRIX

Bianxiao Cui[1];
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The interaction between the cell membrane and the extracellular matrix is crucial for many cellular functions by modulating mechanosensitive signaling pathways. Physical properties of the extracellular matrix such as stiffness and topography affect such interactions. Our recent work reveals that surface topography of tens to hundreds of nanometer scale modulates cell adhesion and cell signaling by activating intracellular curvature-sensitive proteins. We use vertical nanostructures protruding from a flat surface as a platform to induce precise curvatures on the cell membrane and to probe biological processes in live cells. Vertical nanopillars deform the plasma membrane inwards and induce membrane curvature when the cell engulfs them, leading to a reduction of the membrane-substrate gap distance. We found that the high membrane curvature induced by vertical nanopillars significantly affects the distribution of curvature-sensitive proteins and modules cell adhesion. Our studies show a strong interplay between biological cells and nano-featured surfaces, which is an essential consideration for future development of interfacing devices.

9-POS Board 9

DIRECT QUANTIFICATION OF PROTEIN INTERACTIONS AND DYNAMICS AT CELL-CELL ADHESION SITES VIA FLUORESCENCE FLUCTUATION SPECTROSCOPY

Valentin Dunsing[1]; Salvatore Chiantia[1];
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Cell-cell adhesion is mediated by the interactions of specific proteins, e.g. adhesion receptors, at the contact sites of neighboring cells. Here, we present an assay that allows the direct quantification of such interactions in living cells. This assay consists of two steps: mixing of cells expressing the proteins of interest fused to different fluorescent proteins, followed by fluorescence fluctuation spectroscopy measurements at cell-cell contacts sites. Based on cross-correlation and moment analysis of the detected signals, we are able to quantify binding, diffusion dynamics and oligomerization of protein complexes formed at the contact site. As an example, we investigate the interactions and dynamics of Amyloid-precursor-like protein 1 (APLP1), a neuronal type I transmembrane protein playing an important role in synaptic adhesion and synaptogenesis. Past investigations indicated that APLP1 is involved in the formation of protein-protein complexes that bridge the junctions between neighboring cells.

Nevertheless, APLP1-APLP1 trans interactions have never been directly observed in higher eukaryotic cells. Our results show that APLP1 forms homotypic trans complexes at cell-cell contacts. In the presence of zinc ions, the protein forms macroscopic clusters, exhibiting an even higher degree of trans binding and strongly reduced dynamics. Further evidence from giant plasma membrane vesicles and live cell actin staining suggests that the presence of an intact cortical cytoskeleton may be required for zinc-induced cis multimerization. Subsequently, large adhesion platforms bridging interacting cells are formed through APLP1-APLP1 direct trans interactions. Taken together, our results provide evidence that APLP1 functions as a neuronal zinc-dependent adhesion protein and provide a more detailed understanding of the molecular mechanism driving the formation of APLP1 adhesion platforms. Further, they demonstrate that fluorescence fluctuation spectroscopy techniques are useful tools for the investigation of protein-protein interactions at cell-cell adhesion sites.

10-POS Board 10

TENSILE STRENGTH VS. SHEAR STRESS – AN APPROACH TO MEASURE INTERNAL TENSIONS BETWEEN CELL-CELL JUNCTIONS

Julia Eckert[1]; Luca Giomi[1]; Thomas Schmidt[1];
[1]Physics of Life Processes, Leiden Institute of Physics, Leiden University, Leiden, The Netherlands

Cell-cell junctions and cell-extracellular-matrix adhesions are important for communication and coordination within tissues. Thereby, cells sense and apply different mechanical types of stress, for example during migration of cell clusters, tissue expansion or tissue compression. During all these cues, internal tensions act at the interface, of cell-matrix and of cell-cell junctions. Where stress at the cellmatrix interface have been extensively studied, cellular stress and forces at the cell-cell junctions in tissue are less well characterized.

We have developed a methodology to measure both the external stress of cells towards the matrix and the internal stress between cells. Our methodology allows us to distinguish and to compare tensile vs shear stress on cell-cell junctions. Based on micropillar arrays for cell traction force measurements, we produced PDMS micropillar array-blocks, of size resembling that of individual cells, separated by micrometer-spacings. Cells adhere to individual blocks and are allowed to connect over the spacings. A controlled stretch allows us to change either the distance or the parallel position of the blocks with respect to each other. Thereby we are able to apply pure tensile or pure shear stress on the cell-cell junctions up to the point where they break.

Our new methodology opens the way to study the influence of mechanical stress on cell-cell adhesions and to measure directly the internal tension between involved junctions of different types of cells.

11-POS Board 11

LIGAND-INDEPENDENT EGFR ACTIVITY PROMOTES DYNAMIC JUNCTION REMODELLING

Chaoyu Fu[1]; Wilfried Engl[1]; Michael Sheetz[1]; Virgile Viasnoff[1];
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A fundamental interrelationship between cell adhesion and Receptor Tyrosine Kinases (RTKs) governs the behavior of cells within tissues. Epidermal Growth Factor Receptor (EGFR), a well-studied RTK, and its activation by its ligand EGF are well known to weaken cell adhesion by promoting E-cadherin (E-cad) endocytosis or disrupting the association of E-cad to the actin cytoskeleton. However, the function of ligand-independent EGFR activity on E-cad adhesion remains largely elusive. This population of EGFR can be transiently activated by E-cad homophilic interactions in a ligand-independent manner during cell-cell contact formation. Here, we find a cooperativity effect between ligand-independent EGFR activity and E-cad adhesion, which promotes dynamic junction remodeling. We use a suspended cell doublet system to achieve the best control over junction formation dynamics and avoid any integrin signaling. We find during de novo junction formation, ligand-independent EGFR activity is triggered by E-cad interactions.

This transiently activated EGFR regulates actomyosin cytoskeleton dynamics distal from the cell-cell contact as it slows down actin dynamics in the free cortex of doublets. By using junction formation time (τ) as a parameter to describe the speed of junction expansion in suspension, we find further junctions develop faster than the initial one and this priming effect of junction formation is regulated by ligand-independent EGFR activity. Since junction expansion is thought to be regulated by both actin polymerization and myosin contractility, we reasonably hypothesize that the slow actin dynamics in the free cortex of doublets affects the speed of further junction formation. To this end, we use several drugs targeting actomyosin cytoskeleton and measure their effect on junction formation speed. Consistently, we found slow actin dynamics and low cortical tension increase junction formation speed. Furthermore, we found ligand-independent EGFR activity promotes cell neighbor changing ability and collective cell migration, whereas it does not affect single cell motility.

12-POS Board 12

A PHYSICO-CHEMICAL MODEL OF CELL-CELL CONTACT FORMATION

Silvia Grigolon[1]; Jana Slovakova[2]; Mateusz Sikora[2]; Carl-Philipp Heisenberg[2]; Guillaume Salbreux[1];
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Cell-cell contact growth and size is crucial for tissue integrity and proper development. Recent years have seen an in-depth study of the physical forces governing cell-cell contact formation and shape and of the chemical kinetics governing the linker molecules separately. Yet, how the interplay between the physical and chemical levels can induce and shape cell contacts and which are the key mechanisms governing this process is not known yet. In this work, we propose a novel complete model of cell contact formation and growth. By a combination of active-gel theory and linkers chemical dynamics, we aim to clarify the force diagram and the chemical processes that can allow for cell contact formation, growth and maintenance as observed in vertebrate early development.

13-POS Board 13

THE INFLUENCE OF NEIGHBORING CELLS ON CELL STIFFNESS IN A BREAST CANCER MODEL AND MYELOMA

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[2]Wake Forest University, Radiology, Winston-Salem, NC, USA

Background. Over the last several years, numerous studies have shown that cancer cells and normal cells have different physical properties. Cells interact with each other and with their substrates, and questions how the micro-environment affects physical properties of cells remain unanswered.

Methods and Objective. Using an Atomic Force Microscope (AFM) with a 5.3 mm diameter spherical probe, we investigated how neighboring cells affect cell mechanical properties in a breast cancer model and in myeloma.

Results. We found that neighboring cells have a significant, complex effect on cell mechanical properties in both systems. Human Mammary Epithelial Cells and cancer derivatives. We obtained stiffness values for normal, immortal, tumorigenic, and metastatic cells of 870 Pa, 870 Pa, 490 Pa, and 580 Pa, respectively. That is, cells become softer as they advance to the tumorigenic and metastatic phase. We also found a distinct contrast in the influence of a cell's microenvironment on cell stiffness. Normal mammary epithelial cells inside a monolayer are stiffer than isolated cells. This stiffening effect was not seen in the cancer cell lines, indicating that the stiffness of cancer cells is less sensitive to the microenvironment than normal cells. Myeloma. We studied the effect of myeloma cells on bone marrow stromal cells (BMSCs). We found that the higher stiffness of BMSCs was not a unique characteristic of BMSCs from multiple myeloma (MM) patients (M-BMSCs). BMSCs from MGUS (Monoclonal gammopathy of undetermined significance) patients were also stiffer than the BMSCs from healthy volunteers (N-BMSCs). The stiffness of M-BMSCs was enhanced when co-cultured with myeloma cells.

In contrast, no changes were seen in myeloma cell-primed MGUS- and N-BMSCs. Our findings demonstrate that CD138- myeloma cell-directed cross-talk with BMSCs and reveal that CD138- myeloma cells regulate M-BMSC stiffness through SDF-1/CXCR4/AKT signaling.

14-POS Board 14

RELATIONSHIP BETWEEN EPITHELIAL TUBE FORMATION AND MECHANICAL FORCES IN THREE-DIMENSIONAL ECM

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Tubular formation is a fundamental process in tissue development. In particular, epithelia tissues such as lung, mammary gland and kidney form multiple tubular structures to transport gases and liquids. However, it is still unclear how groups of cells determine the orientation axis of the overall tubular structures. Notably, recent studies suggest that the extracellular matrix (ECM) might be involved in patterning of tubular structures. To understand whether the ECM plays a role in tubular formation, we cultured epithelial cells in three-dimensional gels in vitro. When MCF10A epithelial cells are cultured in Matrigel, they formed acini structures. Interestingly, these cells formed both acini and cord-like structures when cultured in collagen gel. To understand whether the cord-like structures observed in collagen gel originated from acini structures, we harvested acini from Matrigel and transferred them into collagen gels.

Remarkably, we found that acini began elongating in collagen gels. In addition, inhibition of actomyosin contractility perturbed acini elongation. These findings suggest that cellular contractility is pivotal for acini elongation. We therefore wondered how cellular contractility might influence symmetry breaking at the supracellular level of aggregates. We hypothesized that mechanical forces generated by cells might reorganize collagen fibers of the ECM. Using second harmonic generation microscopy, we found that collagen fibers are rearranged when acini elongate. Furthermore, application of a uniaxial stretch on collagen gels aligned fibers and acini elongated along the stretch axis even after the stretch was released. We hypothesize that acini can detect the axis of short-term stretch by recognizing the aligned fibers. In conclusion, these results highlight the potential relationship between mechanical forces and ECM reorganization in tubulogenesisis.

15-POS Board 15

SHINING LIGHT ON TOPOLOGY IN EARLY T-CELL ACTIVATION – A NOVEL BILAYER SYSTEM

Markus Körbel[1]; Edward Jenkins[2]; Kevin Y Chen[1]; Simon J Davis[2]; David Klenerman[1];
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The very first contacts of a T cell with an antigen presenting cell (APC) are key to understanding antigen discrimination in adaptive immunity. The use of supported lipid bilayers (SLBs) to mimic the APC simplifies imaging analysis and allows controlled changes in contacting-surface composition. In studies of the immune synapse, SLBs are commonly functionalized with peptide-bound MHC (pMHC) and ICAM-1, with pMHC acting as an adhesion molecule and a molecular trigger, and ICAM-1 behaving both as an adhesion protein and a steric barrier to engage pMHC, respectively. By replacing it with CD58, a small adhesion molecule, and the extracellular part of CD45, as glycocalyx, we aimed to produce a more realistic model system allowing new insights into T-cell signalling.

On the new surface, the adhesive behaviour of T cells could be fine-tuned by varying the CD45 to CD58 ratio: low densities of CD45 allowed cell attachment and spreading, and higher densities prevented contact formation. At intermediate glycoprotein densities, cells only attached and started to signal if pMHC was present. We utilized the size-based exclusion of CD45 in the SLB together with cell membrane labelling to image contact formation via live TIRF microscopy. Initial small, diffraction-limited contacts that formed and grew were highly dynamic, dominated by centripetal movements at later stages. The small, initial contacts represented the footprint of microvilli, a dominant feature of T-cell topology. T cells treated with agents that reduce microvilli on their cell membrane were unable to detect or respond to pMHC molecules in our model SLB. Our results suggest that T-cell microvilli provide a structure to both penetrate the glycocalyx barrier and detect antigens.

TUESDAY, OCTOBER 15
POSTER SESSION II
16:35 – 18:00
Mezzanine

All posters are available for viewing during all poster sessions; however, below are the formal presentations for Tuesday. Presenting authors with odd-numbered poster boards should present from 16:35 – 17:22 and those with even-numbered poster boards should present from 17:22 – 18:00. The presenters listed below are required to remain in front of their poster boards to meet with attendees.

Kyumurkov, Alexander	**16-POS**	**Board 16**
Lee, Hyunsu	**17-POS**	**Board 17**
Mastrogiovanni, Marta	**18-POS**	**Board 18**
May, Elizabeth	**19-POS**	**Board 19**
Omar, Yannick Azhri Din	**20-POS**	**Board 20**
Pinon, Léa	**21-POS**	**Board 21**
Riedel-Kruse, Ingmar	**22-POS**	**Board 22**
Sahu, Preeti	**23-POS**	**Board 23**
Sikora, Mateusz	**24-POS**	**Board 24**
Sivasankar, Sanjeevi	**25-POS**	**Board 25**
Stahley, Sara	**26-POS**	**Board 26**
Teo, Jessica Li Chang	**27-POS**	**Board 27**
Undieh, Adaeze	**28-POS**	**Board 28**
Verger, Stéphane	**29-POS**	**Board 29**
Zhang, Ye	**30-POS**	**Board 30**

Posters should be set up the morning of October 14 and removed by noon October 17.

16-POS Board 16

RECEPTOR TYROSINE KINASE REGULATION OF EPIDERMAL JUNCTIONAL MECHANICS AND BARRIER FUNCTION

Alexander Kyumurkov[1]; Emmi Wachsmuth[1]; Carien Niessen[1];
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The insulin and IGF-1 growth factor receptor tyrosine kinases (IR, IGF-1R) are key regulators of growth. Recent work have also implicated these receptors in the regulation of oriented division, intercellular junction and epithelial barrier formation. Specifically, we showed that epidermal insulin/IGF-1 signaling (IIS) controls epidermal morphogenesis, stratification and barrier formation through as yet in part undefined mechanisms. To address whether and how epidermal IIS control junction and epithelial tight junction (TJ) barrier function directly, we performed transepithelial resistance measurements on keratinocytes from mice with an epidermal deletion of IR and/or IGF-1R. Only loss of both receptors but not IGF1-1R alone strongly impaired TJ barrier formation ability. In agreement, high-resolution whole mount imaging on IGF-1R$^{epi-/-}$ epidermis did not reveal a strong differences in TJ ZO-1 staining nor F-actin in the TJ-containing SG2 layer.

However, phospho-myosin staining was altered, indicating that IGF-1R regulates actomyosin-dependent tensile responses. Employing unilateral cyclic stretch we showed that stress fibers in IGF-1R$^{-/-}$ keratinocytes were much thicker and showed increased phospho-myosin, indicating a role for IGF-1R in regulating tensile properties. Moreover vinculin, but not paxillin-stained adhesions, were reinforced in the IGF1R$^{-/-}$ keratinocytes, coinciding with stiffening of the cortical actomyosin network of these cells. At present, we are performing laser ablation and atomic force microscopy to probe whether IGF-1R regulates junctional and cortical tension. In addition, to control spatiotemporally activation of IGF-1R we are developing optogenetic IGF1R probes. In conclusions, our data show that epidermal IIS signaling regulates junctions and the actomyosin cytoskeleton to control epidermal barrier function.

17-POS Board 17

EFFECT OF ADHERENS JUNCTIONS ON MECHANICAL PROPERTIES OF HUMAN MAMMARY EPITHELIAL CELLS.

Hyunsu Lee[1]; Martin Guthold[1]; Keith Bonin[1];
[1]Wake Forest University, Physics, Winston Salem, NC, USA

Epithelial cells form a protective layer lining the outer surface of organs and tissues. Mammary epithelial cells form as single layers to provide the main structural component of mammary ducts. The mechanical properties of these epithelial cells are critical in tissue development and in maintaining mechanical homeostasis. The cytoskeleton of cells plays an important role in determining the mechanical properties of cells. In addition, intercellular adherens junctions – connections between the cytoskeletons of different cells – may also have a strong influence on the mechanical properties of cells in an epithelium. We used atomic force microscopy indentation to investigate the mechanical properties of human mammary epithelial cells (HMECs) in different states, ranging from isolated cells to confluent, highly polarized cells.

Our results show that the stiffness of polarized cells in a monolayer increases fivefold, compared to single cells and unpolarized, confluent cells. Furthermore, we found that the stiffness of the polarized cells decreases to the level of single cells when adherens junctions are interrupted by removing free calcium ions with EDTA. Our data suggest that intercellular connections of actin fibers through adherens junctions are a primary contributor to the stiffness of cells in an epithelium.

18-POS Board 18

THE TUMOR SUPPRESSOR ADENOMATOUS POLYPOSIS COLI AS A REGULATOR OF T CELL MOTILITY AND POLARITY

Marta Mastrogiovanni[1,2]; Céline Couche[1]; Thierry Rose[3]; Jérôme Delon[4]; Andrés Alcover[1]; Vincenzo Di Bartolo[1];
[1]Institut Pasteur, Immunology , Paris, France
[2]Sorbonne Université, Collège Doctoral, Paris, France
[3]Institut Pasteur, Cell Biology and Infection, Paris, France
[4]Institut Cochin, Paris, France

Adenomatous polyposis coli (APC) is a tumor suppressor whose mutations underlie a familial form of intestinal polyposis and colorectal cancers. In addition to its role in Wnt/β-catenin signaling, APC associates with microtubules and regulates cytoskeleton organization, cell polarity and migration in multiple cell types. Our laboratory showed that impairment of APC in T cells alters microtubule network and function of the transcription factor NFAT, leading to defective differentiation and cytokine production particularly in regulatory T lymphocytes (Tregs). The hypothesis of my PhD project is that APC-dependent alterations of cytoskeleton organization could impair anti-tumor immunity by affecting T cell ability to migrate into tumors, interact with cancer cells and kill them. To address these questions, I analysed chemokine-induced migration of T cell lines in transwell assays and observed that APC silencing impairs their specific migration. Real-time imaging of T cell motility highlighted that APC does not affect migration per se, but rather alters directional cell movement.

Further analyses of cell polarization and 2D-3D morphology by imaging flow cytometry and confocal microscopy indicate that APC controls T cell 3D conformation and it is involved in actin-rich blebs formation and cortical rigidity, possibly helping in converting environmental cues into proper mechanical forces to insure directional cell locomotion. Preliminary observations also suggest the involvement of APC in T cell adhesion. Therefore, kinetics and strength of cell adhesion in living conditions are currently under measurement. Similar differences in migration and polarization, although to a lower extent, have been observed when comparing $CD8^+$ T cells from control and APC-mutant mice. These studies will be soon extended to T cells from familial polyposis patients. Together, these results suggest that APC, by regulating both actin and microtubule cytoskeleton, is involved in both T cell motility and chemokine-induced polarity, which are crucial for productive anti-tumor immune responses.

19-POS Board 19

MOLECULAR INTERACTIONS FOR ESTABLISHING NEURONAL CONNECTIVITY

Elizabeth May[1]; Rachelle Gaudet[1];
[1]Harvard University, Molecular and Cellular Biology, Cambridge, MA, USA

It is increasingly clear that many neurological disorders manifest physiologically as a miswiring of neural circuits in the brain – from an individual neuron's perspective, a case of mistaken identity when it comes to finding and making appropriate connections. I investigate how neurons discriminate between correct and incorrect cell-cell contacts to determine their synaptic partners. Neuronal cell adhesion proteins called clustered protocadherins are important markers of cell identity and regulators of neuronal connectivity; juxtaposed cells in the brain compare their unique sets of cell-surface protocadherins to distinguish one another.

In my poster, I present my exploration of one specific question to understand how clustered protocadherins signal to the neuron to either synapse with or avoid another cell. What do the protein-protein interactions look like when two cells compare their respective sets of clustered protocadherins? I use a combination of X-ray crystallography for structure determination and functional assays to test the interaction properties of clustered protocadherins. Deciphering the molecular interactions of clustered protocadherins is key to understanding how they function as cell identity markers to facilitate neural circuit wiring in the brain.

20-POS Board 20

A THEORETICAL DESCRIPTION OF FRICTION AND ADHESION OF LIPID BILAYERS

Yannick Azhri Din Omar[1];
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Cell membranes are most often found to be in contact with other objects. For instance, supported lipid bilayers serve as the basis for many experimental setups to study model bilayer systems. In such setups, the lipid bilayer may either be in contact with the solid substrate surface or may be separated from it by a thin water film or polymer cushion. In epithelial sheets, cells are densely packed and pressed against one another. During cell migration, cells employ both adhesive and frictional contact to generate propulsion in different environments. All these phenomena exhibit complex contact behavior. As these examples show, contact between cell membranes, and cell membranes and substrates is ubiquitous. However, current theoretical descriptions are not able to capture the full complexity of such contact.

Here, we present the extension of a recently published framework for the irreversible thermodynamics of lipid bilayers to account for contact interactions. The presented theory employs the classical Helfrich model together with viscous surface flow. The extension to contact will first be presented in a general fashion and will then be specialized by the use of particular constitutive contact models for frictional and adhesive contact. We will further show how the effects of ligands on the cell membrane can be modeled. The presented theory is fully general and does not pose any restrictions on the permissible membrane shapes. It can thus serve to understand the effects of cell membrane friction and adhesion, both in-vivo and in-vitro.

21-POS Board 21

OIL-IN-WATER EMULSION DROPLETS AND MICROFLUIDIC TOOLS TO STUDY B CELLS POLARIZATION AND MECHANICS OF IMMUNOLOGICAL SYNAPSE

Léa Pinon[1,2,3]; Judith Pineau[2]; Olivier Mesdjian[1,3]; Lorraine Montel[1,3]; Paolo Pierobon[2]; Jacques Fattaccioli[1,3];
[1]Ecole Normale Supérieure, Chemistry, Paris, France
[2]Institut Curie, U932, Paris, France
[3]Institut Pierre Gilles de Gennes, Paris, France

Right after a pathogen invasion, organism deploys two lines of defense: the innate and adaptive immunities. The first one is a short-term response providing pathogen destruction then antigen presentation promoted by Antigen Presenting Cells (APC). The latest ensures an important long-term response mostly thanks to B lymphocytes which promote high-affinity antibodies secretion and memory B cells differentiation. B cells either catch soluble antigens in the plasma or extract them onto the APC membrane. In the latest case, APC and B cells ensure the antigen transfer via a highly organized contact: the immunological synapse. To precisely understand the physicochemical mechanics involved in this synapse, we first model cell-cell contact by creating new APC-like substrates respecting crucial properties. Emulsion droplets properly mimic antigen mobility at the oil/water interface as observed on the cellular membrane; and due to low and controllable surface tension, droplets are as deformable as real APC. We determine the visco-elastic modulus of droplets and B cells thanks to glass microplates experiment. We so optimize emulsion properties to observe the cellular response of B lymphocytes. We also use microfluidic-trap devices to ease the observation of several isolated synapses simultaneously and follow their formation over time. Consequently, we temporally and spatially control the APC-like droplet/B cell synapse.

By combining emulsion and microfluidic tools, the kinetic of lysosomes moving to the synapse area and the stress applied by the cell on the droplet are quantified. As preliminary results, we find the lysosomal recruitment only occurs during the synapse with stiff droplets: mechanical force is not enough to extract antigen. Moreover, we quantify the force applied by B cells on soft droplets. We here point out the role of APC rigidity during the immune synapse and show how droplets and microfluidic traps are promising tools to study the physicochemical parameters of cell-cell contact.

22-POS Board 22

MORPHOGENESIS AND PATTERNING OF BACTERIAL ASSEMBLIES VIA OPTOGENETIC AND SYNTHETIC CELL-CELL ADHESINS

Ingmar H. Riedel-Kruse[1,2]; David Glass[1]; Xiaofan Jin[1]; Honesty J Kim[1];
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[2]University of Arizona, Molecular and Cell Biology, Tucson, AZ, USA

Optogenetics and synthetic biology have been highly successful in engineering and studying various biological systems, but applications to investigating cell-cell adhesion have been lacking. My lab recently developed the first 100% genetically encoded synthetic platform for modular cell-cell adhesion in bacteria utilizing nano-bodies (Glass, Cell 2018), furthermore the first optogenetic control for high-resolution biofilm cell-cell and cell-surface adhesion (biofilm lithography) (Jin, PNAS 2018). Here I will discuss soon-to-be published results utilizing these new methods:

(1) We quantitatively pattern multi-strain biofilms, and we observe how cell-cell adhesion fosters multi-species cooperation and shared anti-biotic protection under various bacterial antibiotic loads.

(2) We show how cell-cell adhesion mediates sharp, macroscopic boundaries between different bacterial populations that encounter each other; a supporting biophysical model provides deeper quantitative insights regarding a patterning transition.

(3) I will give a perspective on future opportunities regarding synthetic adhesins for eukaryotes, the construction of living self-assembly biomaterials, and the engineering of synthetic multi-cellular life. In conclusion, synthetic cell-cell adhesins provide a new approach to study cell adhesion and multi-cellular patterning and morphogenesis.

23-POS Board 23

GEOMETRIC SIGNATURE OF SURFACE TENSION IN 3D TISSUES

Preeti Sahu[1]; Jennifer M Schwarz[1]; Lisa Manning[1];
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Dense biological tissues maintain sharp surfaces between cell types performing different functions. For example, in multi-layered epithelia, the bottom-most basal layer is responsible for cell proliferation. This layer is distinctly compartmentalized from the suprabasal layer above that helps maintain structural integrity, although the mechanisms for this compartmentalization remain unclear. One possible candidate is tissue surface tension, which contributes to cell sorting and compartmentalization in embryonic development.

Here, we use computational models to identify experimentally accessible signatures of tissue surface tension between two distinct layers in a fully 3D simulation. We find that cells adjacent to a boundary with tissue surface tension exhibit several distinct features, including a bimodal distribution of facet areas along the boundary and a clear change in overall cell shape consistent with nematic-like ordering along the boundary. The magnitude of these geometric cell shape changes scales directly with the magnitude of the tissue surface tension, suggesting that experiments might estimate the magnitude of surface tension simply by segmenting a 3D tissue. As a next step, we will investigate how proliferating cells in the basal layer are able to push into the layer above in spite of the mechanical barrier in between.

24-POS Board 24

TRUSS-LIKE ARRANGEMENT OF CADHERINS IS RESPONSIBLE FOR DESMOSOME STRENGTH

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Desmosomes are long-lasting cell-cell junctions that endow mature tissues with mechanical stability. The core of the desmosomal adhesion is formed by cadherins, specialised calcium-dependent transmembrane proteins. Together with other adaptor proteins, the cadherins connect cortices of neighbouring cells. Robustness to external stress comes from a particularly dense arrangement of cadherins, which form characteristic electron-dense structures visible in EM micrographs. However, the structural details of desmosomal cadherin assemblies remain controversial despite their relevance for various diseases.

To address and resolve these controversies, we performed large-scale molecular dynamics simulations of a different 3D cadherin arrangements in the desmosome. We found that only an antiparallel, truss-like arrangement of cadherins can explain both the mechanical robustness and the spacing observed between plasma membranes in the desmosome. We validated our predictions by cryo-electron tomography of the desmosomes from mouse liver.

25-POS Board 25

INSIDE-OUT REGULATION OF CADHERIN ADHESION

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During morphogenesis and wound healing, cellular migration and rearrangements rely on tightly regulated changes in cadherin adhesion. However, the molecular mechanisms by which cadherin adhesion is regulated remains poorly understood. To addresses this critical gap, we integrated biophysical measurements of cadherin structure-function with cell biological manipulations of cadherin-cytoskeleton interactions. Our data demonstrates, for the first time, that changes in E-cadherin (Ecad) ectodomain structure and adhesion are regulated from the inside-out by Ecad linkage to the actin cytoskeleton.Ecad ectodomains bind in two load bearing adhesive conformations: strand-swap dimers and X-dimers. We have previously used ultrasensitive, single molecule Atomic Force Microscopy (AFM) to show that X-dimers and strand-swap dimers have different adhesive properties [1-3]. Here we use high resolution, live cell AFM to correlate the structure and adhesion of Ecad ectodomains to their cytoskeletal linked states in parental, α-catenin knockout, and vinculin knockout MDCK cells. We demonstrate that in MDCK cells, only a third of non-junctional Ecad robustly bind to the actin cytoskeleton; the remaining Ecad only transiently associate with cortical actin. Robust linkage of Ecad to the cytoskeleton requires both α-catenin and vinculin.

Strikingly, we show that while the ectodomains of cytoskeleton bound Ecads adopt an strand-swap dimer conformation, Ecad in the α-catenin and vinculin knockout cells only form X-dimers. Finally, we show that collective migration of epithelial cells is disrupted when α-catenin or vinculin are knocked-out. Our data directly demonstrates ‘inside-out’ regulation of cadherin ectodomain conformation by cytoplasmic proteins and connects these structural changes to collective cell migration.1. Rakshit et al., Proc. Natl. Acad. Sci. U.S.A., 2012,109 (46) : p. 18815-188202. Manibog et al., Nat. Commun., 2014, 5 (3941)3. Manibog et al., Proc. Natl. Acad. Sci. U.S.A., 2016, 113 (39): p. E5711-E5720

26-POS Board 26

PLANAR CELL POLARITY-DISRUPTING MUTATION ALTERS CELSR1-MEDIATED CELL ADHESION AND DYNAMICS

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Planar cell polarity (PCP), the collective polarization of cells along a tissue plane, is fundamental to early embryonic development and tissue organization in complex, multicellular organisms. Compromised PCP results in severe developmental disorders including neural tube defects, ciliopathies and cardiomyopathies. A hallmark of PCP is the asymmetric localization of core PCP components at cell junctions bridged by principle PCP protein, Celsr, an atypical cadherin. We lack a detailed understanding of Celsr1 extracellular interactions at the molecular level. Overall, this work seeks to elucidate how Celsr1 mediates cell adhesion to coordinate functional PCP and how this is altered by the PCP-disrupting mutation Crash (Crsh). Crsh maps to the cadherin repeats within Celsr1s extracellular domain, suggesting it may perturb Celsr1 adhesion.

Using the mammalian epidermis as a model system and a combination of junctional recruitment and cell aggregation assays, we show that Celsr1 mediates calcium-dependent, homophilic cell adhesion through its extracellular domain. Surprisingly, Crsh mediates cell aggregation comparable to wildtype (WT), demonstrating this variant mediates trans-adhesive interactions. Yet when mixed, Crsh and WT expressing cells sort out into distinct aggregates, indicating this point mutation alters Celsr1 adhesive properties. Crsh displays more diffuse cell surface distribution and reduced junctional stability as measured by FRAP, suggesting Crsh is defective in lateral clustering. Importantly, chemically induced cis-dimerization of Crsh rescues junctional enrichment and trans-interactions with WT, indicating a role for cis-interactions to stabilize Celsr1 adhesion.

Finally, we use super-resolution imaging to investigate the subcellular organization of PCP junctions and reveal how alterations in Celsr1 adhesion affect this organization. Collectively, our results support a model in which the Crsh-pertaining region of Celsr1 is responsible for mediating cis-interactions that function to stabilize and reinforce the adhesive complex, a critical prerequisite for PCP organization and functional asymmetry.

27-POS Board 27

EPITHELIAL CAVEOLIN-1 MAINTAINS MONOLAYER TENSION TO DRIVE ONCOGENIC CELL EXTRUSION

Jessica Li Chang Teo[1]; Guillermo A. Gomez[2]; Ivar Noordstra[1]; Suzie Verma[1]; Vanesa Tomatis[1]; Bipul R. Acharya[1]; Lakshmi Balasubramaniam[3]; Hiroko Kambe[1]; Rachel Templin[1]; Kerrie-Ann McMahon[1]; Robert J. Ju[4]; Samantha J. Stebhens[4]; Benoit Ladoux[3]; Robert G. Parton[1,5]; Alpha S. Yap[1];
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Epithelial homeostasis and integrity are governed by cell-cell and cell-matrix adhesions. Of note, the E-cadherin-containing adherens junctions have been shown to be an important centre for mechanotransduction, by coupling the actomyosin cortices of neighbouring cells. Interestingly mechanosensitive membrane organelles, Caveolae, are found to localize near the apico-lateral region of AML12 epithelial cells where the adherens junctions reside. Caveolae have been reported to be involved in multiple biological processes such as lipid homeostasis, cellular signalling and endocytosis. However, open questions remain as to whether caveolae's mechanosensitive nature regulates overall monolayer mechanics and what are the mechanisms involved.

In this study, we report that caveolae regulate epithelial mechanics and consequently affect apical oncogenic cell extrusion. Downregulation of caveolin-1/caveolae increase tension which is detectable at the molecular, junctional and monolayer level. This increase in tension appears to be driven by an increase in PI(4,5)P2 localization at cell junctions which recruits and stabilizes the formin, FMNL2. Enrichment of FMNL2 at cell junctions led to elevated levels of junctional F-actin that are more stable and better organized. Interestingly, we found that caveolin-1/caveolae are required to promote apical oncogenic cell extrusion in a non-cell autonomous fashion. Downregulation of caveolin-1/caveolae in the epithelium surrounding the oncogene-expressing cell reduced apical oncogenic cell extrusion. Remarkably, perturbation of the interaction between PI(4,5)P2 and FMNL2 restored monolayer tension and oncogenic cell extrusion in caveolin-1 knockdown cells. Therefore, caveolin-1/caveolae appear to regulate a PI(4,5)P2-FMNL2-actin axis to control monolayer tension and apical oncogenic cell extrusion.

28-POS Board 28

NOVEL MAGNETO-ACTUATED LIVE CELL RHEOMETER: INTEGRATED IMAGING AND MECHANICAL MEASUREMENT OF LIVE CELL MONOLAYERS AND TISSUES

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The mechanical properties of cells are known to influence their function in both health and disease. Cell and tissue rheology has been found to play a crucial role in embryonic development, and abnormal cellular mechanics has been linked to the pathology of many major diseases, including atherosclerosis and breast cancer. To facilitate the integrated study of multicellular mechanics multiple length scales, we have developed an advanced technique – the magneto-actuated live cell rheometer – for measuring the rheology of 2D and 3D cellular collectives. This novel approach offers several improvements over current methods, including whole monolayer/tissue measurement, a simple and well-defined mechanical stimulus, creep and oscillatory rheology capability, integrated imaging, and environmental control. We apply this system to two use cases: measuring characteristic changes in endothelium mechanics in response to inflammation, and studying the multiscale rheology of cellular aggregates.

29-POS Board 29

MECHANICS AND DYNAMICS OF CELL-CELL ADHESION IN PLANTS

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How cell-cell adhesion is achieved is a fundamental question in the development of multicellular organisms. Surprisingly, this question remains largely under-explored in plants and much remains to be discovered. In plants, cell-cell adhesion is physically mediated by the cell wall. This is not only passive: in previous work we identified a complex signaling pathway for the active maintenance of cell-cell adhesion in plants (Verger et al. 2016). Furthermore, we demonstrated how tensile stress in tissues tends to pull the cells apart in the epidermis during growth and development and may also act as an instructive cue for cell adhesion maintenance in plants (Verger et al. 2018). In turn, loss of cell adhesion impairs proper development.

For instance, we showed how torsion relies on adhesion and anisotrotpic growth in stems (Verger et al. 2019). Here, we identified a set of mutants, from the model species Arabidopsis thaliana, displaying characteristic cell-cell adhesion defects. These include mutants in actin filament nucleation (ARP2/3 and SCAR/WAVE complexes), epidermal identity transcription factors (ATML1 and PDF2) and a mechanosensitive calcium channel (DEFECTIVE KERNEL1). While we are investigating the actual cause for the loss of cell adhesion in these mutants, our current hypothesis is that mechanical stress in the epidermis triggers a reorganization of the actin network in order to polarize polysaccharides depositions towards cell-cell connections which are the most under mechanical stress' threat to reinforce and maintain adhesion. Maintenance of cell adhesion would further promote the supracellular propagation of mechanical stress in a "tension-adhesion" feedback loop, suggesting a convergent principle for the maintenance of cell adhesion between plants and animals, but based on divergent adhesion mechanisms (e.g. cell wall in plants).

References: Verger, S., et al., 2016. Development Verger, S., et al., 2018. eLife Verger, S., et al., 2019. Front. Plant Sci.

30-POS Board 30

REGULATE CELL-CELL INTERACTION VIA LIPID-RAFT-TARGETED MOLECULAR ASSEMBLY

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Hippo signalling pathway controls multiple cellular functions that are central to tumorigenesis. Its importance in cancer cell proliferation and metastasis has been well recognized. Here we created polypyridyl ruthenium comjugated peptide complex for lipid-raft-targeted molecular assembly. Via hydrolyzation by ovarian cancer biomarker, glycosylphatidylinositol-anchored placental alkaline phosphatase (ALPP), molecules assemble into nanostructures adhere to lipid rafts restricting their dynamics and spatial distributions. Through actin cytoskeleton, the regulation of lipid rafts stimulates Hippo signalling pathway, regulating cell-cell interaction, deactivating the core oncogene YAP in cancer cells suppressing cancer cell migration and inducing cancer cell apoptosis.