BP 23: Focus: Physics of Stem Cells

Time: Wednesday 9:30–12:45 Location: ZEU 250

BP 23.1 Wed 9:30 ZEU 250

Multi-scale imaging and analysis identify pan-embryo cell dynamics of germlayer formation in zebrafish — Gopi Shah[1], Konstantin Thierbach[2], Benjamin Schmid[1], Johannes Waschke[3], Anna Reade[4], Mario Hlawitschka[3], Ingo Roeder[2], •Nico Scherf[1,2], and Jan Huisken[1] — [1]Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany. — [2]Institute for Medical Informatics and Biometry, TU Dresden, Germany — [3]Faculty of Computer Science and Media, Leipzig University of Applied Sciences, Germany — [4]Department of Biochemistry and Biophysics, University of California San Francisco, USA

The coordination of cell movements across spatio-temporal scales ensures precise posi- tioning of organs during vertebrate gastrulation. Mechanisms governing such morphogenetic movements have been studied only within a local region, a single germlayer or in whole embryos without cell identity. Scale-bridging imaging and automated analysis of cell dynamics are needed for a deeper understanding of tissue formation during gastrulation. Here, we report pan-embryo analyses of formation and dynamics of all three germlayers simultaneously within a developing zebrafish embryo. We show that a distinct distribution of cells in each germlayer is established during early gastrulation via cell movement char- acteristics predominantly determined by position within the embryo. The differences in initial germlayer distributions are amplified by a global movement, organizing the organ precursors along the embryonic body axis and giving rise to the blueprint of organ formation.

BP 23.2 Wed 9:45 ZEU 250

How Tissue Microenvironment Impacts Pluripotent Cell Differentiation — •Allyson Quinn Ryan — MPI-CBG, Dresden, Germany

The importance of stem cell population maintenance throughout both development and adulthood has been evident for several decades. Classically, how these populations are regulated is investigated through genetic and cell biological studies. However, work in the past 20 years has shown forces exerted by tissue microenvironments to be of equal importance as molecular and transcriptional profiles to cell potency and identity.1-3 In the context of the mammalian blastocyst, a multicellular system eventually comprised of three epithelial cell lineages, it has recently been shown that emergence of its asymmetrically localized fluid lumen influences the specification and positioning of the two multipotent interior cell lineages.4 The positioning and size of the blastocyst lumen are controlled through mechanisms favoring physical stability of the embryo in its entirety.5,6 Combined, these results point towards a framework of noncellular tissue entities influencing the specification and maturation of developmental tissues originating from progenitor populations of varying potency.

1. A. J. Engler et al., Cell 126, 677-689 (2005).
2. M. Théry et al. Nat., Cell Biol. 7, 947-953 (2005).
3. A.R. Cameron et al., Biomaterials 32, 5979-5993 (2011).
4. A.Q. Ryan et al. Dev., Cell 51, 1-14 (2019).
5. J.C. Chan et al., Nature 571, 112-116 (2019).
6. J.G. Dumortier et al. Science 365, 465-468 (2019).

BP 23.3 Wed 10:00 ZEU 250

Competition for stem cell fate determinants as a mechanism for tissue homeostasis — •David J. Jörg[1,2], Yu Kitadate[3,4], Shosei Yoshida[3,4], and Benjamin D. Simons[1,2,5] — [1]Cavendish Laboratory, University of Cambridge, Cambridge CB3 0HE, UK — [2]Gurdon Institute, University of Cambridge, Cambridge CB2 1QN, UK — [3]Division of Germ Cell Biology, National Institute for Basic Biology, National Institutes of Natural Sciences, Okazaki, Japan — [4]Department of Basic Biology, School of Life Science, Graduate University for Advanced Studies (Sokendai), Okazaki, Japan — [5]Department of Applied Mathematics and Theoretical Physics, Centre for Mathematical Sciences, University of Cambridge, Wilberforce Road, Cambridge CB3 0WA, UK

Stem cells maintain tissues by generating differentiated cell types while simultaneously self-renewing their own population. The mechanisms that allow stem cell populations to control their density, maintain robust homeostasis and recover from injury remain elusive. Motivated by recent experimental advances, here we develop a robust mechanism of stem cell self-renewal based on competition for diffusible fate determinants. We show that the mechanism is characterized by signature dynamic and statistical properties, from stem cell density fluctuations and transient large-scale oscillation dynamics during recovery, to scaling clonal dynamics and front-like boundary propagation. We suggest that competition for fate determinants provides a generic mechanism by which stem cells can self-organize to achieve density homeostasis in an open niche environment.

Invited Talk BP 23.4 Wed 10:30 ZEU 250

Mechanical signalling in cell fate choice — •Kevin Chalut — Wellcome-MRC Stem Cell Institute, University of Cambridge, Cambridge, UK

Abstract. Mechanical signaling in cell fate choice plays a significant role in tuning stem cell function. Specifically, my lab has shown that mechanics tunes the response of stem cells to biochemical signaling to steer fate choice. The feedback loop between mechanics and biochemical signaling has significant impact on cellular plasticity both in development and stem cells. I will show that, by tuning the mechanical microenvironment, we can reverse the loss of plasticity associated with ageing of stem cells in the brain. I will also show that, in vivo, we can *fool* the stem cells in an aged brain into functioning as if they are in a soft, neonatal-like environment, thereby leading them to function like young stem cells. This result could have significant impact on treatments of disease like multiple sclerosis. I will then explore how cell surface mechanics in general contextualizes signalling to drive cell fate choice, both in embryonic stem cells and in vivo.

30 min. coffee break

BP 23.5 Wed 11:30 ZEU 250

Robustness and timing of cellular differentiation through population based symmetry-breaking — Angel Stanoev, Dhruv Raina, Christian Schröter, and •Aneta Koseska — Department of Systemic Cell Biology, Max Planck Institute of Molecular Physiology, Dortmund

During mammalian development, cell types expressing mutually exclusive genetic markers are iteratively differentiated from a multilineage primed state. The current dynamical framework of differentiation, single-cell multistability, however requires that initial conditions in the multilineage primed state are appropriately controlled to result in robust proportions of differentiated fates.

We propose a fundamentally different dynamical treatment in which cellular identities emerge and are maintained on population level, as a novel unique solution of the coupled system. We show that the subcritical organization of such a coupled system close to the bifurcation point enables symmetry-breaking to be triggered by cell number increase in a timed, self-organized manner. Robust cell type proportions are thereby an inherent feature of the resulting inhomogeneous solution. In accordance with this theory, we demonstrate experimentally that a population-based mechanism governs cell differentiation in an embryonic stem cell model for an early lineage decision of mammalian embryogenesis. Our results therefore suggest that robustness and accuracy can emerge from the cooperative behavior of growing cell populations during development.

BP 23.6 Wed 11:45 ZEU 250

Embryo segmentation by stem cells with genetic clocks and timers. — •Jose Negrete Jr[1,2], Laurel A Rohde[1], Arianne Bercowsky-Rama[1], Alfonso Martinez-Arias[3], Frank Jülicher[2], and Andrew C Oates[1] — [1]École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland — [2]Max Planck Institute for the Physics of Complex Systems, Dresden, Germany — [3]University of Cambridge, Cambridge, United Kingdom

Spatial gene expression patterns define regions where specialized cells emerge within an embryo. Patterning may arise from cell signaling, as in lateral induction/inhibition, or from single cells containing genetic timers, as observed in the daughters of neuroblasts. Here, we study the dynamics of the segmentation clock in zebrafish embryos. We show that isolated stem cells extracted from embryos are able to recapitulate the same behavior as in vivo. Their behavior is consistent with a theoretical model of a noisy genetic timer driving a downstream noisy

genetic oscillator. Finally, we show that a spatiotemporal model of sequentially activated genetic timers and oscillators is able to reproduce the dynamics of embryo segmentation under different perturbations. This shows that patterning by the segmentation clock proceeds from a mixture of cell signaling and genetic timers.

BP 23.7 Wed 12:00 ZEU 250

Setting up the epigenome: a collective phenomenon — Fabrizio Olmeda[1], Stephen Clark[2], Tim Lohoff[2], Heather Lee[3], Wolf Reik[2,4], and •Steffen Rulands[1,5] — [1]Max Planck Institute for the Physics of Complex Systems, Dresden, Germany — [2]The Babraham Institute, Babraham, UK — [3]The University of Newcastle, Callaghan NSW, Australia — [4]University of Cambridge, Cambridge, UK — [5]Center for Systems Biology Dresden, Dresden, Germany

During early development, when cells for the first time differentiate into somatic cell types, the genome undergoes large-scale changes in epigenetic DNA modifications (DNA methylation) and chromatin structure. As a result of these processes cells carry distinct epigenetic marks that assign their fate during later stages of development and adulthood. Aberrations in these marks can lead to the death of the embryo and, in adulthood, are one of the hallmarks of cancer. But how are these epigenetic marks so robustly established? Combining novel methods from single-cell multi-genomics with non-equilibrium physics we find universal scaling behaviour in the processes leading to the establishment of epigenetic marks. We show that these phenomena result from long-range interactions mediated by the interplay between chemical and topological modifications of the DNA. Our work sheds new light on epigenetic mechanisms involved in cellular decision making. It also highlights how mechanistic insights into the molecular processes governing cell-fate decisions can be gained by the combination of methods from genomics and non-equilibrium physics.

BP 23.8 Wed 12:30 ZEU 250

Reversibility and heterogeneity as building principles of hematopoietic stem cell organization — •Ingmar Glauche[1] and Ingo Roeder[1,2] — [1]Institute for Medical Informatics and Biometry, Carl Gustav Carus Faculty of Medicine, Technische Universität Dresden, Germany — [2]National Center for Tumor Diseases (NCT), Partner Site Dresden, Germany

Hematopoietic stem cells (HSCs) retain the ability to maintain their own population while at the same time generate all types of the peripheral blood. In contrast to other somatic stem cells, HSCs undergo periods of extended quiescence, in which they do not proliferate but retain their stemness.

We have been developing conceptual and mathematical models of HSC organization for almost two decades. Central to all these models is the conceptual idea that stem cells can reversibly change between different states of activity, thereby introducing an intrinsic level of heterogeneity. Even the simplest assumption, that HSCs can either be in a proliferative state or a state of extended quiescence, proved sufficient to explain the wide range of phenomena observed in hematopoietic stem cell biology. We successfully apply to this concept to competitive transplantation assays in mouse, to the analysis of label dilution data and to stem cell aging. Most importantly, this concept was also instrumental to describe and predict pathogenesis and treatment in acute and chronic leukemias. We conclude that stemness is not a static feature, but should be understood as an emergent and reversible property resulting from the interaction of cells with their current environment.