Universität Basel

Research Project

Cellular and molecular mechanisms of asymmetric stem cell division II

Third-party funded project

Project title Cellular and molecular mechanisms of asymmetric stem cell division II
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Project start 01.08.2015
Probable end 31.07.2017
Status Completed

Asymmetric cell division (ACD) generates cellular diversity. Stem and progenitor cells in particular utilize ACD to self-renew the stem/progenitor cell while also forming differentiated siblings. In order to fully exploit the potential of stem cells for future therapeutic approaches, it is absolutely necessary to reach an in-depth understanding of basic stem cell biology. Many diseases such as breast cancer susceptibility, acute promyelocytic leukemia, the initiation of colon cancer but also the neurodevelopmental disorders like microcephaly are due to defective asymmetric cell division. Thus, understanding the basic biology of ACD will improve our knowledge of asymmetric stem cell division during development and disease.

We are using Drosophila neural stem cells called neuroblasts, the precursors of the fly central nervous system to study stem cell biology in general and asymmetric cell division in particular. We are focusing on the following three main topics relevant to asymmetric stem cell divisions: (1) centrosome asymmetry, (2) Myosin dynamics and cleavage furrow positioning and (3) biophysical mechanisms involved in asymmetric cell division. Neuroblasts are polarized cells and divide in a stem cell-like fashion, undergoing repeated self-renewing asymmetric divisions. The mitotic spindle invariably orients itself along the neuroblast intrinsic apical-basal polarity axis and asymmetric cleavage furrow positioning results in a physical and molecular asymmetric cell division, generating a large self-renewed apical neuroblast and a smaller differentiating basal ganglion mother cell (GMC). Drosophila neuroblasts provide an ideal experimental system since precise genetic manipulations are possible and superb imaging properties are available.

My lab has shown that the conserved centriolar component Bld10 (Cep135 in vertebrates) is required to establish centrosome asymmetry, a requirement for correct spindle orientation. In addition to Bld10, we isolated several new components involved in centrosome asymmetry, instrumental in obtaining a thorough molecular understanding of this process. In the future, we will take advantage of this knowledge to further investigate the function of centrosome asymmetry during development.

We are also studying Myosin dynamics during asymmetric cell division. Recently, I showed that Drosophila neuroblasts are utilizing a spindle-independent, polarity-dependent mechanism for cleavage furrow positioning. This pathway, consisting of the conserved polarity proteins Discs large 1 (Dlg) and Partner of Inscuteable (Pins; LGN/AGS3 in vertebrates) instructs the asymmetric localization of Myosin. Controlled cleavage furrow positioning is important for accurate cell fate

determinant segregation and the correct partitioning of chromosomes. Molecular insight into this polarity-dependent pathway is currently lacking but recent evidence suggests that other cell types across the animal kingdom also utilize spindle-independent furrowing mechanisms. We have developed photoconversion assays to study the dynamics of Myosin during ACD and also identified Protein Kinase N as a putative effector in the polarity-dependent pathway. Furthermore, in a forward genetic RNAi based live imaging screen, we found several additional candidates, required for correct cleavage furrow positioning. We also implemented novel assays and tools, such as atomic force microscopy (AFM) on isolated Drosophila neuroblasts, to measure biophysical forces underlying ACD. However, future studies will be required to learn more about the cellular, molecular and biophysical mechanisms underlying cleavage furrow positioning.
Based on these findings and achievements, we will continue to use Drosophila larval neuroblasts to pursue the following main aims:

Aim 1: we will investigate the mechanism and function of centrosome asymmetry during asymmetric cell division.
Aim 2: we will investigate cellular, molecular and biophysical mechanisms involved in cleavage furrow positioning and the establishing of physical asymmetry.

Financed by
Swiss National Science Foundation (SNSF)

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