Doctoral Research Position

Phase separation driven heterochromatin formation as a regulatory mechanism for repeat silencing and cellular differentiation

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Pericentric heterochromatin in mouse and Drosophila assembles via heterochromatin protein 1 (HP1) in a self-organizing manner into distinct nuclear subcompartments that are called chromocenters. During development chromocenters change their structure and protein compositions, which affects also their function in silencing of transcription from repeat sequences. different states during cellular development. The assembly of chromocenters via a liquid-liquid phase separation processes versus other types of phase separation or cooperative binding has important functional implications for (i) the robustness of epigenetic memory in the context of repeat silencing and proper chromosome segregation, (ii) the position-effect of variegation as determined by the (dynamic) extension of a HP1 dependent heterochromatin domain and (iii) the maturation of chromatin during cellular differentiation with activity changes of different HP1 isoforms as demonstrated previously for HP1α versus HP1β in mouse embryonic stem cells (ESCs). Here, we will dissect the mechanism of chromocenter formation in dependence of the developmental state by combining experiments in vitro with purified HP1 and other chromatin proteins, a proximity based biotinylation analysis of HP1 interaction partners as well as various fluorescence microscopy-based methods for studies of chromocenter features in living cells. As cellular systems we will use mouse ESCs, neural progenitor cells differentiated from them and mouse embryonic fibroblasts as well as the fruit fly Drosophila as an organismic system. In particular we will test the hypothesis that the high plasticity of chromocenter at early developmental stage reflects the presence of liquid like HP1 droplets that serve to establish HP1 isoform dependent activity that are crucial for proper development. This overall goal will be reached via the following milestones:

- In vitro analysis of liquid droplet formation of HP1 isoforms and factors that can regulate this process.
- Map of an HP1 interactome in different cellular environments and in dependence of posttranslational modifications by proximity biotinylation
- Assignment of properties of HP1 subcompartments around centromeric chromatin in living cells and that distinguish between different phase separation mechanisms as well as “simple” cooperative binding.
- Assess the functional implications of HP1 subcompartment formation on repeat silencing and species formation in dependence of the underlying mechanism.

By combining the different methodological approaches in a cellular as well as an organismic system we will yield an integrated view of the dynamic structure-function relationship of phase-separated HP1 compartments and how they change during the transition from the plastic and highly dynamic embryo nucleus to the differentiated cell.

Your Profile

- recent degrees in Biology, Biochemistry, Biophysics, Medicine, Pharmacology/Life Sciences
- strong commitment and work ethic
- high scientific motivation
- open and interested in interdisciplinary approaches

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The contributing institutions are equal opportunity employers.