Universität Basel

Research Project

Dynamic organization of chromosomes during development

Third-party funded project

Project title Dynamic organization of chromosomes during development
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Dynamic Organization of Chromosomes during Development.The goal of this proposal is to map genome architecture during embryogenesis with single-cell resolution, to elucidate the role of chromosome structure in essential cellular processes. To understand the function of the genome, it is not sufficient to know its sequence and local epigenetic features - we must also consider the large-scale physical architecture of entire chromosomes and their positioning within the nucleus. The 3D organization of chromosomes is a key contributor of essential genomic functions, including replication, repair, recombination, and the regulation of gene expression. Recently developed methods to measure chromosome architecture have shown that the genome folds into structures of increasing sizes during interphase: loops, domains, compartments, and territories1,2. However, previous studies have mainly used genome-wide biochemical methods on cultured cell populations to indirectly infer structure and inform computational models of how chromosomes fold in the nucleus. As a result, many gaps remain in our knowledge regarding the role of chromosome structure in vivo. Specifically, how does chromosome organization change in the cells and tissues of an animal? Second, do chromosome structure changes reflect cellular replication, growth and division, or are they a feature of cell fate specification - or a combination of both? The first question will be addressed in Aim 1, and the second in Aim 2. To address these aims, I will exploit the stereotyped cell lineage of C. elegans, where each cell has been identified, and I will track chromosome conformation for specific cell types and their progenitors during embryonic development. I will directly map chromosome structure using a novel high-throughput imaging approach that preserves the cellular, tissue, and organismal contexts of chromosomes.In Aim 1, I will compare the interphase chromosome architecture of different cell lineages in the embryo to define cell-type specific architectures. The germline lineage is the most likely to have a unique architecture, and I will focus on comparing germline and somatic cells to address the relationship between structure and cell identity. I will determine if specific conformations precede, coincide, or follow functional transcriptional output and lineage restriction, which will help to elucidate the causal relationships between these events. In Aim 2, I will map chromosome architecture through the stages of the cell cycle to model the structural transitions that occur as embryonic cells grow and divide. This aim will identify inherited conformational signatures and identify the conformational rearrangements that occur as embryonic cells replicate, divide, and re-establish interphase architecture. I will collaborate with polymer physicists to incorporate structural measurements into computational models of chromosome transitions in the cell cycle. The results of my work will be a conformational atlas of chromosomes in embryogenesis, with a focus on cell type and cell cycle dynamics. I will determine how the specific history of a cell informs its current and future molecular state. This study will conform to the goals of SPARK by bringing new technologies to Switzerland, and through the unique integration of high-throughput imaging with unsupervised clustering and polymer modeling. My work will provide

an unconventional analysis of 3D genome architecture in animals at the single-cell level, elucidating the links between chromosome organization and cellular lineage for the first time.

Keywords cell lineage; chromosome tracing; 4D genome; embryonic development; polymer modeling; unsupervised clustering; cell cycle
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