Universität Basel

Research Project

Elucidating the gene regulatory logic of convergent cell fate specification in the developing vertebrate skeleton

Third-party funded project

Project title Elucidating the gene regulatory logic of convergent cell fate specification in the developing vertebrate skeleton
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Project start 01.12.2019
Probable end 30.11.2023
Status Completed

Cell fate specification - that is, how distinct cell types arise from a pool of precursor cells - is one of the hallmarks of embryonic development. During this process, a genome common to all cells of an organism is differentially interpreted at the gene regulatory level, to result in individualized cellular phenotypes. So far, most studies have focused on the specification of different cell types from a single progenitor pool. However, notable exceptions exist to this trajectory, such as in the vertebrate skeleton that, depending on anatomical location, develops from three distinct progenitor populations (neural crest, somitic and lateral plate mesoderm). Despite this diversity in embryonic origins and thesurrounding tissue environments, these three progenitor populations converge phenotypically to give rise to functionally equivalent skeletal cell types.

With the current project, we aim to define the gene regulatory logic underlying such cell fate convergence. Specifically, we will decode how transcriptional networks assimilate differences in progenitor transcriptomes and tissue niches to produce analogous cell types from distinct embryonic sources. Based on preliminary data from our lab, I hypothesize that progenitor-specific transcription factor profiles, resulting from cell-intrinsic and -extrinsic differences in their embryonic origins, are integrated at the cis-regulatory level, via lineage-specific enhancer elements, to result in the transcriptional and phenotypic convergence of the three skeletal precursor pools.

To functionally test these hypotheses, I propose to combine state-of-the-art functional genomics at single cell- and lineage-resolution with experimental embryology and targeted CRISPR/Cas9-genome modifications. Capitalizing on the superior temporal control in avian embryos, their ability to sustain transplantation experiments, and our expertise in developmental biology, molecular genetics and transcriptome analyses, we will:

1. Define, at single cell- and lineage-resolution, the transcriptome and chromatin dynamics of the three progenitor pools, as they converge towards a common skeletal cell fate
2. Elucidate the interplay of cell-intrinsic and cell-extrinsic parameters in this gene regulatory convergence using quail-chick grafts followed by single-cell RNA-sequencing and chromatin accessibility profiling
3. Functionally validate candidate regulatory factors underlying this convergence in vivo, using the CRISPR/Cas9system in a lineage-specific manner in chicken embryos

Collectively, our work will delineate the gene regulatory logic instructing the transcriptional and phenotypic convergence towards a common skeletal cell fate, across three distinct embryonic progenitor pools.

As such, the project promises to define novel paradigms of cell fate specification control, for the skeletal system and beyond, and open new avenues applicable to regenerative medicine.

Financed by
Swiss National Science Foundation (SNSF)

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