SEMINAR

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TITLE

Notch and Foxi3 signaling dynamics modulates cell-type composition in the embryonic epidermis of zebrafish

MONDAY - 27.06.2022
TIME 11:00
ROOM SV 1717

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ABSTRACT

Complex body structures emerge from patterned embryonic tissues. How these embryonic patterns are themselves generated is a fundamental question of biology, with implications for the transformation of body structure throughout evolution and the development of inherited disease. The skin of zebrafish embryos scattered multitype of ionocytes, which are specialized cells scattered on epithelia and fish gills for maintaining ionic homeostasis, and five sub-types were identified in zebrafish by their physiological properties and ion channel/transporter markers. It is suggested that the ionocyte patterning process involves the lateral inhibition by Notch signaling and the downstream positive regulatory loop of foxi3a/b to determine the cell fates. However, there is still a lack of the comprehensive lineage map to the differentiation paths, and there are few researches on the temporal control and dynamics to this Notch-Foxi3 signaling axis due to technical challenges. By reanalyzing a deltaC transgenic reporter line, we first discovered the there were at least 2-wave deltaC expression within a short time to divide sub-lineage lines of ionocytes after 2~3 cell divisions. To further reveal the differentiation trajectories of skin ionocytes and the temporal-spatial dynamics, we generated a foxi3b::foxi3b-venus, foxi3a::foxi3a-mKate2 double transgenic zebrafish line, named AkBash. AkBash recapitulated temporal expression patterns of the endogenous foxi3b. Surprisingly, we discovered that AkBash lost all NaRCs (Na+-K+-ATPase-rich cells) and NCCs (Na+-Cl- cotransporter cells) but showed significantly more HRCs (H+ pump-rich cells) detoured from the NaRC lineage. Moreover, a simplified modeling on 2D cell grids was conducted. We found that distinct cell types could be generated simultaneously in ionocyte progenitors, given that both the expression and degradation rates were higher from one foxi3 to the other. Moreover, the cell types became more uniform by matching the expression rates of both foxi3, as expected in AkBash. In summary, the ionocyte progenitor patterning in zebrafish are coordinated with multi-waves for Notch signaling and cell divisions, and the following sub-type determinations are sensitive to the temporal dynamics and the balance of the regulatory loop between foxi3b and foxi3a, which further influences the composition of ionocytes.