Balgrist University Hospital

Master`s Thesis Project

Universität Zürich[UZH]

Characterization of the Effects of Notch signaling on cellular subpopulations in Rhabdomyosarcoma

Background

Rhabdomyosarcoma (RMS) is an aggressive tumor of mesenchymal origin and the most frequent soft tissue sarcoma in children. Due to the similarity of RMS cells to muscle cells, it is assumed that the tumor develops from the muscle lineage. RMS tumors contain cells resembling different stages of muscle differentiation, including muscle stem cell-like (MuSC-like) cells, highly proliferative cells derived from them, and differentiated cells (**Fig. A**). This hierarchical cellular heterogeneity may have an important impact on the effectiveness of standard therapy. MuSC-like cells are relatively quiescent and may therefore be less sensitive to chemotherapeutic agents, which primarily kill proliferating cells (**Fig. B**).

In normal adult muscle, muscle stem cells are located between the muscle fiber and the basal lamina and are maintained in a quiescent state. A key signaling pathway involved in maintaining this quiescence is the Notch pathway. Upon muscle injury, Notch activity is downregulated and the stem cells become activated. Interestingly, different components of the Notch signaling pathway are strongly upregulated in MuSC-like cells in RMS. This raises the question of whether targeted manipulation of Notch signaling could drive these cells into a proliferative state that responds better to therapy.

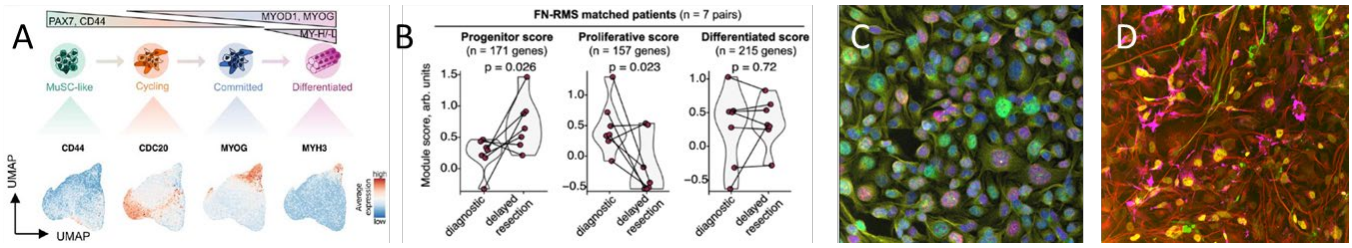

Figure: Cellular subpopulations in rhabdomyosarcoma. **A,** RNA-seq based identification of cellular subpopulations in RMS tumors identifies cells resembling different stages of muscle differentiation (Danielli et al.). **B,** Muscle stem cell-like (progenitor) cells accumulate under therapy in patient tumors (left panel). **C, D,** Representative multiplex immunofluorescence images generated using the established iterative immunofluorescence imaging (4i) approach in RMS models under basal conditions. **C,** Composite image showing a subset of three markers and DAPI to visualize cellular state and proliferation. **D,** Composite image showing a different subset of four markers highlighting stem-like and differentiated cellular states.

Project

We aim to characterize the role of the Notch signaling pathway in the biology of distinct cellular subpopulations within RMS tumors.

- You will refine our ex vivo culture conditions to better mimic the muscle stem cell niche, with a particular focus on enhancing and controlling Notch pathway activation. This system will allow us to investigate how Notch signaling influences the distribution of RMS cellular states and modulates the response of RMS cells to standard therapies.
- You will selectively disrupt Notch signaling at the molecular level using CRISPR-mediated knockout approaches and specific pathway inhibitors, with the goal of identifying critical molecular regulators of the RMS cellular hierarchy.
- You will apply multiplex imaging approaches (**Fig. C, D**) to spatially and quantitatively characterize RMS subpopulations following targeted Notch modulation, either alone or in combination with current chemotherapy regimens. Together, these experiments will provide an integrated view of how Notch signaling influences RMS cellular states and treatment-induced cellular dynamics.

Host Laboratory

Our laboratory specializes in sarcoma biology and combines highly translational research with more fundamental studies of tumor biology. Our translational projects include the development of patient-derived models and drug -profiling approaches aimed at identifying treatment vulnerabilities in individual tumors (*Breunis et al.*). In parallel, we investigate fundamental mechanisms underlying sarcoma development, including the function of the oncogenic drivers responsible for these tumors (*Khan et al.*; *Grossetete et al.*).

Our laboratory is located at the Balgrist Campus, a research building providing a state-of-the-art biomedical research environment in Zurich. It is situated in close proximity to the new research building of the University Children's Hospital Zurich, with which we maintain close collaborations through joint research projects, seminars, and weekly scientific progress meetings.

Contact

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Bibliography from the laboratory

- Breunis et al. Patient-derived tumoroids from CIC::DUX4 rearranged sarcoma identify MCL1 as a therapeutic target. (2025) **Nature communications.**
- Danielli et al. Single-cell profiling of alveolar rhabdomyosarcoma reveals RAS pathway inhibitors as cell-fate hijackers with therapeutic relevance. (2023) **Science advances.**
- Khan et al. PAX3-FOXO1 uses its activation domain to recruit CBP/P300 and shape RNA Pol2 cluster distribution. (2023) **Nature communications.**
- Grossetete et al. The hegemonic EWSR1::ETS oncoprotein overrules core regulatory circuitry principles in Ewing sarcoma. (2026) **npj Precision Oncology.**