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Single cell-derived clonal analysis of desmoid tumors

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My first project aims to understand the composition and cellular communication within desmoid tumors. In neoplasia, tumor cells interact with the normal stromal cells, such as the surrounding fibroblasts. This makes studying desmoid tumors, a type of soft-tissue sarcoma, difficult as both tumor and stromal cells display a mesenchymal phenotype. To elucidate the composition of desmoid tumors, we isolated and expanded single cells derived from patient desmoid tumor samples. Individual clones derived from the same tumor sample displayed differential growth morphology and beta-catenin activity. Sequencing of individual clones revealed that desmoid tumors consist of mutant sub-populations carrying the beta-catenin activating mutation, and normal sub-populations lacking the mutation. Ongoing work aims to understand how the isolated sub-populations interact with each other. Studying desmoid tumors at the clonal level will enhance our understanding of the intratumoral heterogeneity of these tumors. This will improve our efforts in drug-screening, elucidate potential mechanisms of drug resistance, and identify novel targets for future therapy.

My second project aims to investigate the underlying molecular mechanisms of the desmoid tumor phenotype. Despite the evidence that beta-catenin activation causes desmoid tumors, there is limited knowledge about cooperating pathways or downstream components that maintain the neoplastic phenotype. MicroRNAs, short non-coding RNA molecules, fine-tune gene expression levels. They interfere with translation and mRNA transcript stability by binding to their target genes in a sequence-specific manner. We investigated microRNA dysregulation in desmoid tumors by utilizing bioinformatics tools to analyze existing tumor gene expression profiles. Target genes of the microRNA-29 family were enriched in the set of up-regulated genes in desmoid tumors. Quantitative PCR confirmed the prediction that all members of the microRNA-29 family were repressed in the tumor tissues compared to unaffected tissues. Overexpressing microRNA-29 in desmoid tumor primary cell cultures decreased their proliferation rate, showing that microRNA-29 regulates desmoid tumor cell behavior. We further found that beta-catenin activation represses microRNA-29 levels. Ongoing work aims to further investigate the mechanism of microRNA-29 repression, and to study its physiological role in a transgenic mouse model. So far, there is not a single systemically effective treatment for desmoid tumors due to our limited understanding of the underlying biology. Here we identify microRNA-29 as an important regulator of desmoid tumor growth, and offer evidence for the therapeutic potential of treatments that target the expression of microRNA-29 or its targets.