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Stem Cells in Silence, Action and Cancer

Adult tissue stem cells have the ability to self-renew long term and differentiate into one or more tissues. Many stem cells are used sparingly to replenish cells during normal homeostasis. However, even stem cells that are quiescent must be able to respond quickly to injury in order to fuel rapid tissue regeneration. How stem cells balance self-renewal and differentiation is of fundamental importance to our understanding of normal tissue maintenance and wound repair. Increasing evidence suggests that the regulatory circuitry governing this balancing act is at the root of some types of cancers.

The hair follicle is an excellent model system to understand how stem cells remain quiescent during times of minimal wear and tear, how these cells become mobilized during the cyclical bouts of hair growth and wound-repair, and how the normal process of stem cell activation goes awry in cancer. We’ve identified and characterized at a molecular level an important stem cell niche within the hair follicle. We’ve mapped the chromatin landscape of these stem cells while they reside quiescently in this niche, and elucidated how this changes when the stem cells become activated to proliferate and progress along their lineage to generate short-lived progeny. We’ve also shown that when these stem cells are removed from their niche and placed in culture, they undergo marked chromatin remodeling with strong parallels to the mobilization of stem cells for tissue regeneration that is induced during a wound-response.

Hair follicle stem cells are known to be a source of squamous cell carcinomas (SCCs), which as a class, are one of the most common and life-threatening cancers world-wide. We’ve applied our knowledge of normal hair follicle stem cells to explore the tumor-initiating ‘stem cells’ of SCCs. Remarkably, within the SSC, these tumor-initiating cells exist in two distinct states, one more quiescent than the other. We’ve devised a method to mark, track and transcriptionally profile these two distinct states of SCC stem cells in vivo, within the tumor.

Our findings reveal that both populations reside at the tumor-stroma interface, and are rich in integrins. The slower-cycling population is close to the perivasculature, which contains high levels of TGF-β. These stem cells undergo SMAD2-signaling, express EMT markers, break down the basement membrane and invade. They are also resistant to cisplatin chemotherapy. By contrast, the stem cells that don’t receive the TGFβ signal grow the tumor faster but undergo apoptosis upon cisplatin treatment. Thus, within the developing SCC, heterogeneity due to an ever-changing tumor microenvironment elicits distinct behaviors in its stem cells, both of which contribute to tumor growth and malignancy. We’ve now used our knowledge to begin to develop a picture of how the transcriptional and chromatin landscapes change during malignancy, and how this impacts the downstream biology of the cancer cells. As we dig deeper into applying our lessons learned from normal stem cell biology, we hope to continue to build upon our understanding of the roots of malignancy and metastasis in this deadly cancer.

STUDENTS: If you would like to attend a lunch with Dr. Fuchs following the lecture, please send an email to leah.donnelly@mcgill.ca

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