For the first time, researchers at Yale Cancer Center have captured dynamic images of stem cell regeneration as it is occurring in animal tissue. Valentina Greco, PhD, Assistant Professor of Genetics and of Dermatology, and her colleagues in the Greco Lab used intravital microscopy to observe cell regeneration in real time in the hair follicles of uninjured mice. Their findings appeared last July in *Nature*. This breakthrough opens new opportunities to study the signals and pathways used by stem cells to turn cell growth on and off. Dr. Greco is researching how these signals malfunction and cause cells to proliferate wildly, producing tumors. “Using live imaging,” she said, “we have a unique opportunity to study signaling in real time, and at the resolution of the single cell.”

The genetic and molecular mechanisms used by stem cells to regulate regeneration aren’t well understood. With microscopy, Dr. Greco and her colleagues have been able to put markers into stem cells, watch those cells in action, and identify components within them that respond to different signals and play different regulatory roles.

The Greco lab has begun to address whether stem cells and their signaling regulate tumor regression. They did so by treating mice with a carcinogenic treatment (DMBA) that induces a benign epithelial tumor called keratoacanthoma, which resembles squamous cell carcinoma. They chose keratoacanthoma because it grows and regresses, similar to hair follicles (keratoacanthomas typically disappear spontaneously). The researchers wanted to know if the tumor shrank because of signals from its stem cells and, if so, what signals and pathways were involved. They were able to identify the pathways and the signals being misregulated during the tumor’s growth and regression. Next Dr. Greco and her colleagues hope to use live imaging to understand the mechanism that turns those signals on and off. Most tumors grow indefinitely, Dr. Greco said, because cancer “hijacks” cellular mechanisms. “The hope,” she added, “is to switch off the mechanism that the tumor uses for growth – to uncouple that signal – and cause the tumor to regress.”

Because metastatic cancer cells behave in some ways like stem cells, researchers have long suspected a link between the two. The relatively recent discovery of cancer stem cells only partly resolves the issue, because it remains unclear whether cancer stem cells develop from normal stem cells that have gone bad, or from other mechanisms. Dr. Greco thinks the answer will differ depending on the type of tumor and its location. “We now know that stem cells, which are apparently homogeneous, contain a huge heterogeneity, with several subset populations,” she said. This complexity, and the fact that stem cells live longer than other cell types, may account for the resurgence of cancer in patients who have received therapeutic treatment. A subset of stem cells that are aggressive might make the tumor grow, while another subset protects the mechanism used to feed the tumor for the long term. If this latter subset survives therapy, those stem cells could become the engine that re-stimulates tumor growth.

The precise biological features of these stem cell subsets and their links to cancer must be understood before effective targeted therapies can be designed to block the ones that cause tumors or its resurgence. That’s why Dr. Greco is certain that basic biology remains crucial to cancer research. For her, the goal is to break the code of stem cell signaling. “That’s the way to understand dynamic behavior,” she said. “My hope is to use live imaging to map the signaling pathways and to learn how they are integrated at the single cell level and how they influence behaviors in the process of tissue regeneration. You can imagine how that has a direct application in cancer, which utilizes all the major signaling pathways.”

Signal Transduction RESEARCH PROGRAM