2022 ACG-IRG Pilot Grant

Probing the Stem Cell-Lymphatic Interactome in Cancer Initiation and Metastatic Invasion

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Abstract:

Squamous cell carcinoma (SCC) represents one of the most common and life-threatening cancers worldwide and is comprised of a diverse array of human malignancies, including cutaneous, head and neck, and lung cancers. SCCs exhibit high rates of tumor recurrence following anti-cancer therapy, and resistance to treatment has been linked to the persistence of subsets of long-lived, tumor-initiating stem cells that reside at the tumor-stromal interface. It is increasingly evident that the fate and fitness of cancer stem cells can change depending on tight interactions with their supportive microenvironments (niches). Recently, my work uncovered the lymphatic vasculature network as a new niche entity for epithelial stem cells. Despite the extensive bandwidth of functions controlled by the lymphatic system, much of the mystery of how the lymphatic niches evolve to support cancer initiation and invasion remains elusive. We know little about whether the architectural design of the cancer niche can be tailored to suit the need of its resident tumor-initiating stem cells, and knowledge of how the physical placement of the niche can instruct drug resistance remains elusive. Equally important, it remains a mystery how the tumor's cell–of–origin affects metastatic proclivity to invade and seed metastasis through lymphatics and not blood vessels. The immense impact of metastatic diseases in our fast-growing world population calls for a new and innovative approach.

My laboratory innovates to develop novel tools and provide molecular understanding to probe how the lymphatic vascular niche and the surrounding interstitium control cancer initiation and metastatic patterning. The proposed research aims to (I) dissect how interstitial fluid dynamics confer tumor initiation and growth and (II) decipher whether the cancer cell-of-origin shapes the lymphatic niche to promote drug resistance and metastatic proclivity. By establishing a comprehensive map of the full spectrum of interactions between tumor-initiating stem cells and their vascular microenvironment, we hope to identify signals and biophysical properties that confer cancer stem cells with the ability to invade and resist anti-cancer therapies. By understanding the cellular origin of tumors and their communication with the lymphatic niches, we hope to uncover new avenues that will move us towards personalized medicine to better contain and eradicate lymph node metastasis. The proposed research will pioneer fluid dynamic-based methodologies and utilize a tissue-specific gene modulation system to bridge molecular and biophysical territories of the lymphatic-cancer stem cell niches while revealing fundamental principles of lymphvascular invasion and metastatic progression. A successful outcome of these studies will lay the groundwork for developing new stem-cell-based therapies that may revolutionize the way we combat metastatic diseases.