2023 ACG-IRG Pilot Grant

Identifying non-genetic drivers of oncogenic plasticity and tumorigenesis

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Abstract:

All forms of cancer begin with genetic alterations in otherwise healthy cells. Yet, these alone are insufficient to predict an individual's disease onset and risks, indicating that nongenetic events within the tumor ecosystem ('niches') play a role in unleashing tumorigenesis. Stem cells are the origin of many life- threatening malignancies and are notorious for their tight dependency on the surrounding microenvironment. Despite undisputed importance, our understanding of how the ecosystems that stem cells inhabit direct oncogenic fate flexibility is limited. Equally, it remains a mystery whether early-stage tumor initiation through advanced disease progression is supported by overlapping or distinct niches. These gaps in knowledge can largely be attributed to a dearth of tools and models that capture the oncogenic stem cell identity landscape in intact tissues.

The lymphatic vascular network is an emerging, previously unrecognized niche entity for epithelial stem cells, yet much of the mystery of the lymphatic niches in directing tumorigenesis remains untapped. **The goal** of this proposal is to determine how vascular circuits shape the stem cell oncogenic landscape throughout the tumor's life history. Using deep imaging and sequencing approaches in skin squamous cell carcinoma (SCC), we discovered that lymphatic vascular insufficiency predisposes to malignant transformation. Detailed temporal volumetric imaging revealed that oncogenic plasticity propelling the transition from benign to metastatic carcinoma is preceded by dynamic lymphatic remodeling. **These results raise the intriguing possibility** that lymphatic niches evolve during disease progression, directing oncogenic tolerance in tumor-initiating cells while becoming a significant barrier to cancer treatments. The proposed research aims to determine how lymphatic circuits shape oncogenic tolerance during tumor initiation ***(Aim 1)*** and define vascular dependencies in tumor adaptation and vulnerability ***(Aim 2)***. Our innovative strategy to functionally tag and trace mutated yet untransformed cells in concert with their evolving vascular niches will reveal new insights into how aberrant cells integrate systemic changes from their surroundings that may broaden their oncogenic strategies. We will further interrogate the role of the lymphangiogenic factor ANGPTL7, highly expressed by metastatic tumor-initiating stem cells, in shaping the lymphatic niche and providing a protective vascular shield that renders therapy ineffective. Our proposed enhancer-based proximity sensor technology, combined with tissue-specific gene delivery system and volumetric imaging will allow us to capture early and transitional cell states in rare tumor- initiating stem cells with unprecedented resolution. This proposed project is a renewal request of a previously funded ACS Institutional Research Grant, which will allow my lab to form a solid foundation for our first R01 grant and upcoming publications. Since lymphatic-stem cell connection appears to be conserved across various tissues, we predict that our findings hold curative potential for numerous types of cancers, making a profound impact on patient survival. A successful outcome of these studies holds promise for the development of therapeutics that block early cancer progression and pave the way to combat advanced metastatic disease.