Shawn Demehri, MD, PhD

The focus of **the Demehri laboratory** is to determine the role of the immune system in regulating the early stages of cancer development in order to harness its anti-tumor potential for cancer prevention and treatment. To date, several cancer immunotherapies have been developed with proven efficacy against late-stage cancers; however, the role of the immune system in preventing the early development of cancer remains uncertain. The research in the Demehri laboratory is focused on identifying the immune mechanisms that drive an immune activation sufficient to prevent cancer formation from pre-cancerous lesions. This approach raises a great opportunity to discover novel immune pathways that can be leveraged in cancer therapy and prevention.

Demehri Laboratory

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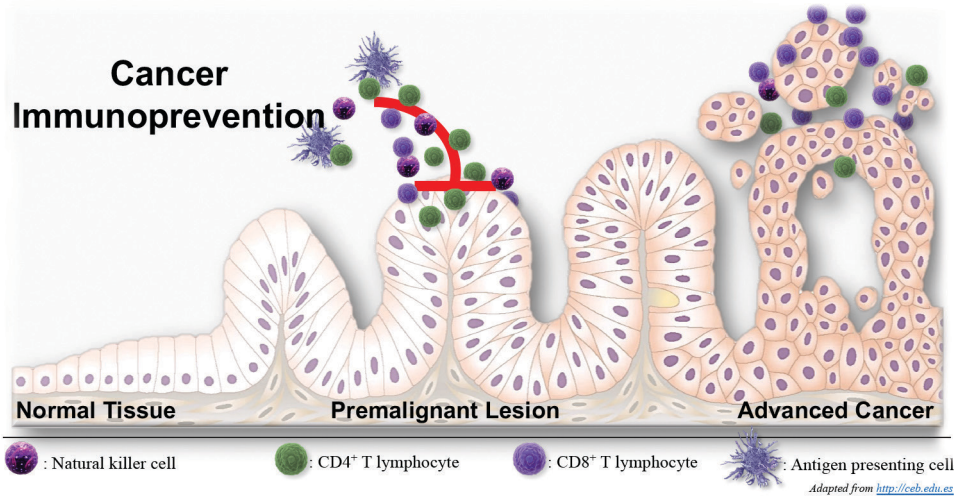
The field of cancer immunology has made substantial advances in recent years by deciphering the role of the tumor infiltrating CD8+ cytotoxic T lymphocytes (CTLs) in attacking cancer cells, which have led to promising new cancer immunotherapeutics. The current immunotherapeutic approaches, however, are largely designed to boost the anti-tumor immune response that has already formed against late-stage metastatic cancers. Therefore, the current cancer immunotherapies like immune checkpoint blockade, which rely on a pre-existing CTL infiltrate in the tumor for their effects, are proven ineffective to treat cancers that frequently lack a significant anti-tumor immune infiltrate, especially during the early in-situ phases of their development. In order to expand the potential of cancer immunotherapy, our laboratory studies the pathways that lead to immune system activation against early phases of cancer development. Devising a mechanism to activate the immune system against early-stage cancers has clear immunopreventive implications by directly blocking the cancer promotion and immunotherapeutic benefits by potentiating the immunity against late disease.

To pursue this goal, the Demehri laboratory is currently focused on three areas of research:

1) Mechanisms of CD4+ T cell activation against cancer. Our laboratory has studied the mechanism of thymic stromal lymphopoietin (TSLP) in evoking tumor suppression. TSLP is an epithelial-derived cytokine that plays a central role in stimulating CD4+ T helper 2 (Th2)-mediated allergic diseases like atopic dermatitis and asthma. We have shown that high TSLP levels establish a dominant anti-tumorigenic immune environment preventing cancer promotion. Currently, our team investigates the detailed mechanism of TSLP anti-tumor function against solid cancers and examines its application for the treatment of pre-cancerous skin and breast lesions in patients.

2) Mechanisms of natural killer (NK) cell recruitment and activation against cancer. NK cells are known for their potent anti-tumor properties. However, their role in controlling the cancer development in vivo remains unclear. Our laboratory is utilizing a virally encoded ligand for NK cells to determine the combination of signals necessary to activate NK cells against early



Immune Regulation of Early Cancer Development.

stages of carcinogenesis and to identify the mechanism of anti-tumor immunity mounted by the activated NK cells in order to block cancer promotion and progression.

3) Mechanisms of tumor promotion by the immune system. Although immune cells can mount anti-tumor immunity against cancer, they are also implicated in promoting cancer development under certain conditions. Chronic inflammation is one of the conditions that can predispose patients to cancer; however, the mechanism of such immune-mediated tumor promotion is unclear. To determine this mechanism, our laboratory studies skin and colorectal cancer development as ideal cancer models in which the spatial and temporal relationship between inflammation and cancer development can be determined with exceptional precision. We are currently investigating the immune mechanisms that promote skin cancer development in the context of chronic allergic contact dermatitis and cutaneous lupus and colorectal cancer development in the context inflammatory bowel disease.

Selected Publications:

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