Stony Brook University
The Graduate School

Doctoral Defense Announcement

Abstract

Defining the POU2F3 transcriptional complex in normal and malignant tuft cells

By

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Tuft cells are a rare type of epithelial cell that is found in various hollow organs and in the thymus. Tuft cells expresses a variety of receptors that sense chemical cues in the environment, which triggers the release of a variety of biological molecules to initiate proper defensive responses. For example, tuft cells sense succinate secreted by the parasite tritrichomonas and then releases IL-25 to initiate type II immune responses that trigger pathogen clearance. These chemosensory and secretory capabilities of tuft cells are associated with a unique transcriptome that is controlled by a POU domain transcription factor called POU2F3. More recently, tuft cells have also been implicated in small cell lung cancer (SCLC) as a potential cell-of-origin for a subset of tumors that are addicted to POU2F3 for cell proliferation and viability. Despite the importance of tuft cells in mucosal immunity and in cancer, the transcriptional mechanisms that generate tuft cells are poorly understood. During my thesis research, I discovered that binding of POU2F3 to two uncharacterized proteins, which we have named OCA-T1 and OCA-T2, is critical for the generation and maintenance of tuft cells. OCA-T proteins are paralogs of the B cell-specific coactivator OCA-B, which are encoded in a gene cluster and share a conserved peptide that binds to POU2F family transcription factors on DNA. We also demonstrate that binding between POU2F3 and the OCA-T proteins is essential in the maintenance of SCLC in vitro and in vivo. We generated OCA-T1 knockout mice, which are viable and fertile with normal anatomy, but these animals lack tuft cells in several organs, including the trachea, intestine, and gall bladder. Taken together, this research has revealed a protein-protein interaction that is required for tuft cell development with therapeutic potential in SCLC.

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