Analysis of Kv1.3 Channel Gene Signature in T Lymphocytes

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Introduction: Head and Neck Squamous Cell Carcinoma (HNSCC) is the 6th most common cancer in the US with a 5-year survival rate of less than 50%. Relapse and metastasis are common and can occur because tumors evade the immune system. T lymphocytes in the tumor microenvironment suppress tumor development and are associated with better survival. The activation and proliferation of T lymphocytes depends on calcium signaling which is controlled by Kv1.3 voltage-gated potassium channels. However, the regulation of Kv1.3 in cancer immune surveillance is not well understood.

Hypothesis: We hypothesized that genes encoding proteins regulating Kv1.3 channel expression and activity will impact T lymphocyte immune surveillance and HNSCC disease progression.

Methods: Positive and negative regulators of Kv1.3 in T lymphocytes were identified through literature search. To validate whether the literature-derived Kv1.3 gene signature was predictive of Kv1.3 expression/function state we utilized a pre-existing large gene dataset obtained by NanoString technology from kidneys of Lupus Nephritis (LN) and Diabetic Nephropathy (DN) patients whose infiltrating T lymphocytes have increased Kv1.3 expression. We also assessed mRNA expression of Kv1.3 regulatory genes on HNSCC patient survival using OncoLnc.

Results: 22 positive and 23 negative regulators of Kv1.3 were identified from the literature. FAS, a positive regulator, was significantly upregulated while EGF, a negative regulator, was significantly downregulated in both LN and DN datasets. FAS increases Kv1.3 current through activation of the caspase cascade. EGF inhibits Kv1.3 current and downregulates expression through clathrin-mediated endocytosis. While FAS mRNA expression does not significantly impact HNSCC patient survival, lower EGF expression leads to improved HNSCC patient survival.

Conclusions: Our findings indicate that FAS and EGF may be key regulatory elements of Kv1.3 in T lymphocytes. FAS and EGF maintain tissue homeostasis by coordinating proliferation and apoptosis. The regulatory effects of FAS and EGF on Kv1.3 will be confirmed in T lymphocytes and applied to an HNSCC dataset to predict the status of Kv1.3 as it relates to disease progression and response to therapy. Understanding Kv1.3 regulation and subsequent T lymphocyte immune surveillance in the tumor microenvironment can impact the development of immunotherapies and improve patient survival.

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