

# Enhancing CD8<sup>+</sup> T cell Recruitment in Tumor Microenvironment

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## Description

Autotaxin (ATX) is responsible for the production of Lyso-phosphatidic Acid (LPA), a molecule that governs various biological processes through its interaction with specific G protein-coupled receptors known as LPAR1-6. While ATX/LPA has been implicated in promoting tumor cell migration and metastasis *via* LPAR1 and facilitating T cell motility through LPAR2, its influence within the tumor immune microenvironment has remained elusive. Our study reveals that melanoma cells secrete ATX, which exerts a chemorepulsive effect on Tumor-Infiltrating Lymphocytes (TILs) and circulating CD8<sup>+</sup> T cells in *ex vivo* experiments, with ATX acting as a facilitator in LPA production. The mechanism underlying T cell repulsion primarily involves the G $\alpha$ 12/13-coupled LPAR6 pathway. In the context of anti-cancer vaccination in tumor-bearing mice, ATX does not hinder the initiation of systemic T cell responses.

## T cell infiltration

Melanoma cells exhibit autonomous proliferation, devoid of reliance on external growth factors. Healthy melanocytes' growth and maturation appear to hinge upon signals from two distinct Receptor Tyrosine Kinases (RTKs). Conversely, activation of a lone RTK triggers a transient surge in Mitogen-Activated Protein (MAP) kinase activity, inadequate for sustaining proliferation. Key receptors in this process include the basic Fibroblast Growth-Factor (bFGF) receptor and the KIT receptor. Within the epidermis, keratinocytes synthesize bFGF, with production escalating sixfold following UV irradiation. Notably, a pivotal early event in melanocyte transformation involves the acquisition of the capacity to generate growth factors, such as bFGF, to establish autocrine stimulatory circuits. This mechanism engenders a basal level of MAP kinase pathway activation, fostering proliferation while impeding differentiation. However, it significantly suppresses the infiltration of cytotoxic CD8<sup>+</sup> T cells into tumors, consequently impeding tumor regression.

Furthermore, analysis of single-cell data from melanoma tumors supports the notion that intratumoral ATX serves as a deterrent for T cell infiltration. These findings uncover an unforeseen role for the ATX-LPAR axis in promoting metastasis while simultaneously inhibiting CD8<sup>+</sup> T cell infiltration, thereby

compromising anti-tumor immunity. This discovery suggests novel therapeutic avenues for intervention in cancer treatment. The journey of melanocytes from the neural crest to the skin hinges significantly on the activity of the RTK c-KIT and its counterpart, the KIT ligand/stem cell factor. Mutations in KIT activation have been associated with gastrointestinal stromal tumors and other rare tumor variants. Within the skin, the KIT receptor is expressed by epidermal melanocytes in nevi and melanoma cells in the basal layer, playing a crucial role in their survival and differentiation.

## Lymphoplasmocytic tumor

However, intriguingly, while constitutive activation of KIT can lead to melanocyte transformation, its expression is lost in the dermal component of nevi and in melanoma cells penetrating the dermis. This loss of KIT signaling can induce apoptosis in melanoma cells lacking it. Thus, while essential for melanocyte survival and differentiation, the attenuation of KIT signaling appears to be an early event in some melanomas' development. Notably, the migration and survival of neural crest cells as they transition to melanocytes rely on a functional KIT receptor. Plasma cell infiltration of the liver can be observed in up to 30% of individuals diagnosed with multiple myeloma. Typically, patients present symptoms such as hepatomegaly or ascites. It's crucial to differentiate between myeloma involvement and autoimmune hepatitis in cases where clinical liver injury is evident.

In myeloma, the plasma cell infiltrate mainly affects the sinusoids, with minimal involvement of the portal tracts, in contrast to autoimmune hepatitis, where the infiltrate primarily targets the portal area. Additionally, nodular regenerative hyperplasia can manifest as another pattern of liver injury in myeloma patients. Waldenström macroglobulinemia, a neoplastic disorder involving B-lymphocytes and plasma cells, may coexist with multiple myeloma. These neoplastic cells secrete immunoglobulin heavy chain, which has sporadically been linked to amyloidosis development. The lymphoplasmocytic tumor can directly impact the liver. Liver disease symptoms in these patients are typically mild, with only slight elevations in transaminase and alkaline phosphatase levels. Often, their symptoms are attributed to extrahepatic complications associated with the disease.