Final thesis submission: Examination - Miss Klaudia Piotrowska

Final thesis submission

Thesis

Final thesis

Abstract

Immune checkpoint blockade therapy (ICBT) has revolutionised cancer treatment, yet its efficacy remains limited to subset of patients. A significant barrier to successful treatment is the restricted infiltration of CD8+ T cells into the tumour microenvironment (TME). Cancer-associated fibroblasts (CAFs), a key component of the TME, are highly heterogeneous and perform diverse functions, including influencing immune exclusion. Myofibroblastic CAFs (myCAFs) have been implicated in immune-excluded tumours and poor ICBT responses, highlighting the need for CAF-targeting strategies to enhance immunotherapy efficacy.

This thesis investigates the role of ataxia-telangiectasia mutated (ATM) in regulating the myCAF phenotype. We demonstrate that pharmacological inhibition of ATM in TGF-β1-differentiated fibroblasts leads to the downregulation of extracellular matrix (ECM)-associated genes and myCAF markers, while upregulating iCAF markers and altering cytokine composition. These changes correlate with enhanced CD8+ T cell migration in vitro. Next, we explore the role of specific CAF-derived ECM proteins, CTHRC1, POSTN, and COL11A1 on myCAF phenotype and function. Using CRISPR-Cas9 knockout models, we assess whether targeting these genes influences CD8+ T cell migration into tumours and enhances tumour suppressive properties in mouse models. We then investigate the activation of the cGAS-STING pathway in fibroblasts following ATM inhibition. We demonstrate that TGF-β1 suppresses the cGAS-STING pathway, whereas ATM deficiency induces a type I interferon response. Using mouse models, we show that targeting fibroblast ATM promotes intratumoural CD8+ T cell infiltration and that STING expression in myCAFs is essential for suppressing tumour growth in myCAF-rich environments. Finally, we evaluate the effects of different doses of the ATM inhibitor AZD0156 on key cellular processes, including target activity inhibition, cell proliferation, cell cycle progression, DNA synthesis, and regulation of myofibroblastic markers. Our findings demonstrate that AZD0156 is effective at low doses, which may have clinical applications in minimising potential toxicities.

Our work identifies a novel pathway regulating myCAF differentiation and provides a rationale for using ATM inhibitors to overcome CAF-mediated immunotherapy resistance. By investigating ECM-targeting and ATM inhibition, we uncover new therapeutic avenues to enhance immune infiltration and improve ICBT efficacy in solid tumours.

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