Overriding "Ionic-Checkpoint": A New Strategy to Boost Antitumour Responses of T Lymphocytes

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There have been substantial advances in harnessing the immune system to fight cancers using immunotherapies and engineered T cells. However, tumor-mediated immunosuppression represents a major obstacle to these approaches. Dying necrotic cells in the tumour microenvironment release substantial amount of intracellular potassium (K^+) causing increased concentration (25-60 mM) of extracellular K^+ ($[K^+]_e$). Tumor-infiltrating lymphocytes (TIL) bathed in this $[K^+]_e$-rich fluid are suppressed by an "ionic-checkpoint" and fail to mount an efficient antitumor response. Here, we demonstrate that T cells exposed to $[K^+]_e$-rich media dose-dependently accumulated intracellular K^+. Presence of high amount of $[K^+]_e$ (50 mM) resulted in significant suppression of T cell functions, including proliferation, cytokine secretion, downstream signal transduction (Akt and mTOR pathway) and antitumor responses. To test if increased K^+ efflux through K^+ channels would protect TILs from the suppressive effects of high $[K^+]_e$, we patch-clamped TILs isolated from patients with metastatic colorectal cancer and found them to express significant numbers of calcium-activated $K_{Ca}3.1$ K^+ channels. SKA-111, a drug that selectively activates $K_{Ca}3.1$, significantly enhanced channel activity in TILs and rescued the cells from high $[K^+]_e$-induced suppression. This study suggests that pharmacological activators of $K_{Ca}3.1$ enable TILs to overcome ionic-checkpoint-mediated immune suppression and mount effective antitumor activity.