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Elevated potassium levels suppress T cell activation within tumors

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Tumors progress in immunocompetent hosts despite the ability of the adaptive immune system to recognize cancer cells. Ion gradients regulate T cell function but their role in intratumoral immune responses is unexplored. We found that the concentration of K^+ was strikingly elevated within tumors while the concentration of the divalent cations Ca^{2+} and Mg^{2+} was similar to serum levels. High K^+ levels significantly blunted cytokine production and suppression TCR stimulation induced gene transcription in $CD8^+$ and $CD4^+$ effector T cells. Moreover, polarization of $CD8^+$ and $CD4^+$ T cells in high K^+ suppressed effector differentiation and promoted the formation of $CD4^+$ $Foxp3^+$ T_{reg} cells. Surprisingly, this was not due to an attenuation of TCR induced Ca^{2+} flux, but rather to reduced activation of the serine/threonine Akt-mTOR pathway and could be partially reversed by overexpression of constitutively active Akt1. This coincided with the finding that okadaic acid, an inhibitor of the serine/threonine phosphatase PP2A, rendered effector cells resistant to the inhibitory effects of high K^+ and restored cytokine function within tumors. Additionally, expression of a peptide inhibitor targeting the PP2A complex provided resistance to the inhibitory effect of elevated K^+. These findings identify a novel mechanism of ionic regulation of TCR induced signals and immunosuppression within tumors whereby locally high extracellular concentrations of normally intracellular ions suppress immune function to promote tumor growth.

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