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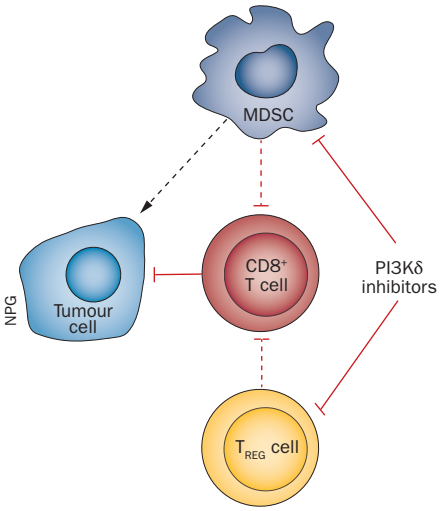
IMMUNOTHERAPY

PI3Kδ inhibition lifts the breaks on antitumour immunity

Phosphatidylinositol-3-kinase δ (PI3Kδ) inhibition has shown promise in the treatment of haematological cancers. To date, this approach was thought to be unfeasible in solid cancers owing to the immune-restricted expression of PI3Kδ; however, a new study suggests the contrary.

On the basis of prior studies that found impaired maintenance and functionality of peripheral regulatory T cell (T_{REG}) populations in PI3Kδ-mutant mice, Khaled Ali and co-workers hypothesized that disrupting immune tolerance by T_{REG} cells might lift the breaks on antitumour immunity. "Through the experiments in our current *Nature* manuscript, we confirmed that a dominant T_{REG}-cell dysfunction in PI3Kδ-mutant mice does indeed allow for competent T-cell-mediated anticancer immunity to build," explains Ali. "Despite effector ($CD8^+$) T cells having a more naive phenotype, competent antitumour immune responses occurred in these mice leading to, in many cases, complete tumour elimination and long-term memory responses."



Interestingly, the researchers also provided evidence that PI3Kδ inactivation suppressed the formation of myeloid-derived suppressor cells (MDSC), and reduced their capacity to suppress T-cell proliferation *in vitro*. "It is likely that T_{REG}-cell deficiencies only permit ignition of immune responses; what allows these incipient antitumour immune responses to perpetuate are these defects in the tumour promoting and immune suppressive activities of MDSCs," suggests Ali.

Importantly, these anticancer effects could be recapitulated by pharmacological inhibition of PI3Kδ, specifically in a model of spontaneous pancreatic ductal adenocarcinoma—a difficult-to-treat cancer. Thus, "collectively, our data provide the rationale and a tractable way to target immune suppressive T_{REG} cells, as well as potentially to restrain the tumour promoting activity of MDSCs in solid cancers using a small molecule PI3Kδ antagonist," claims Ali. "PI3Kδ inhibitors might complement immunotherapies, such as anti-PD-1 antibodies, that enhance effector T-cell function," he concludes.

David Killock

Original article Ali, K. *et al*. Inactivation of PI(3)K p110δ breaks regulatory T-cell-mediated immune tolerance to cancer. *Nature* doi:10.1038/nature13444