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ANTICANCER DRUGS

Horizons broaden for PI3K δ inhibitors

Inhibitors of the p110 δ isoform of the enzyme phosphoinositide 3-kinase (PI3K) have shown considerable efficacy in some leukaemias, but have not previously been considered for the treatment of solid tumours as p110 δ is primarily expressed in white blood cells. Now, findings published in *Nature* suggest that such drugs could have therapeutic potential in a broad range of cancers.

Ali *et al.* used mice harbouring genetically silenced p110 δ (p110 δ^{D910A} mice). Compared with wild-type counterparts, mutant mice showed significant resistance to the growth and dissemination of a broad range of cancer cell lines, including lung cancer, melanoma and breast cancer. In the case of 4T1 breast cancer, disease resistance could be further augmented in p110 δ^{D910A} mice by surgical intervention. Moreover, mutant mice developed immune memory that conferred long-term protection to repeated challenge with cancer cells.

Following surgical removal of 4T1 primary tumours, all wild-type mice showed tumour regrowth and metastasis, and died within 50 days. By contrast, over half of the p110 δ^{D910A} mice survived beyond 100 days after tumour resection, suggesting that p110 δ inhibition

“a small-molecule inhibitor of p110 δ ... suppressed tumour growth and spread”

could help to prevent relapse after surgery. Overall, the findings in transgenic mice indicate that suppression of p110 δ inhibits the growth and spread of various cancer types.

How might such effects be mediated? p110 δ^{D910A} mice are known to show impaired function of regulatory T (T_{Reg}) cells — a T cell subtype that can put the brakes on the immune response against tumours. Consistent with this scenario, Ali *et al.* found that T_{Reg} cells in the draining lymph nodes of p110 δ^{D910A} mice bearing 4T1 tumours did not expand as robustly as they did in wild-type mice with such tumours. Moreover, adoptive transfer of T_{Reg} cells from wild-type mice into the mutant mice restored EL4 thymoma growth and reduced the relative abundance of tumour-infiltrating CD8⁺ T cells.

Myeloid-derived suppressor cells (MDSCs) — a population of bone marrow-derived myeloid cells known to have a role in immune suppression in cancer — were also substantially reduced in mutant mice. Furthermore, only MDSCs from wild-type, but not p110 δ^{D910A} , mice had a suppressive effect on T cell proliferation *in vitro*.

So, dysfunctional activity of p110 δ^{D910A} T_{Reg} cells and MDSCs

seemed to facilitate the induction of antitumour immune responses and underscore the observed cancer resistance of the mutant mice.

To determine which effector cells were responsible for tumour resistance in the absence of T_{Reg} cell-mediated suppression, the researchers performed antibody-mediated depletion of CD8⁺ or CD4⁺ T cells in p110 δ^{D910A} mice 10 days after injection with 4T1 breast cancer cells. Tumour growth was restored only in mice depleted of CD8⁺ T cells, highlighting a key role for these cells in tumour cell killing, although an accessory role for CD4⁺ T cells cannot be ruled out.

Finally, administration of a small-molecule inhibitor of p110 δ , PI-3065, to mice with 4T1 tumours or pancreatic ductal adenocarcinoma suppressed tumour growth and spread, and long-term treatment was well tolerated.

The study suggests that, by dampening down immunoregulatory suppression, PI3K p110 δ inhibitors could enhance immune responses to a range of cancers.

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ORIGINAL RESEARCH PAPER Ali, K. *et al.* Inactivation of PI(3)K p110 δ breaks regulatory T-cell-mediated immune tolerance to cancer. *Nature* **510**, 407–411 (2014)