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IN BRIEF

IMMUNOTHERAPY

Understanding side effects

Ipilimumab, a cytotoxic T lymphocyte-associated antigen 4 (CTLA4)-blocking antibody, can induce clinical responses in cancer patients, but it can also induce some considerable and even fatal side effects. Hypophysitis (inflammation of the pituitary gland) is a side effect that occurs in a small proportion of patients treated with ipilimumab. Using a mouse model of ipilimumab-induced hypophysitis, Iwama and colleagues found that CTLA4 was expressed in certain cells within pituitary glands and these were the site of inflammation.

ORIGINAL RESEARCH PAPER Iwama, S. *et al.* Pituitary expression of CTLA-4 mediates hypophysitis secondary to administration of CTLA-4 blocking antibody. *Sci. Transl Med.* **6**, 230ra45 (2014)

THERAPEUTIC RESISTANCE

Like colon, like melanoma

The inhibition of mutant BRAF or MEK in BRAF-V600E-positive melanoma is often associated with acquired resistance, whereas BRAF-V600E-positive colon cancers are intrinsically resistant because they have activated epidermal growth factor receptor (EGFR). Sun *et al.* showed that 6 of 16 BRAF-V600E-positive melanomas that were resistant to BRAF-V600E or MEK inhibition acquired EGFR expression. The authors found that reduced levels of SOX10 (which is variably expressed in melanoma cells) activates TGFβ expression, which in turn upregulates EGFR and platelet-derived growth factor receptor-β (PDGFRβ) and leads to resistance to inhibition of mutant BRAF or MEK. Taking a 'drug holiday' may prevent selection of this pathway and allow re-sensitization to mutant BRAF and MEK inhibitors.

ORIGINAL RESEARCH PAPER Sun, C. *et al.* Reversible and adaptive resistance to BRAF(V600E) inhibition in melanoma. *Nature* **508**, 118–122 (2014)

SIGNALLING

A mevalonate pathway–Hippo pathway connection

Sorrentino and colleagues found that the transcriptional activity and nuclear localization of YAP and TAZ (mediators of the Hippo pathway) are regulated by the mevalonate pathway. Geranylgeranyl pyrophosphate is produced by the mevalonate pathway and this is required for activation of RHO GTPase, which in turn activates YAP and TAZ. Moreover, inhibition of the mevalonate pathway in *Drosophila melanogaster* suppresses the eye overgrowth phenotype that is characteristic of Hippo pathway activation.

ORIGINAL RESEARCH PAPER Sorrentino, G. *et al.* Metabolic control of YAP and TAZ by the mevalonate pathway. *Nature Cell Biol.* **16**, 357–366 (2014)

TUMOUR IMMUNOLOGY

Characterizing the tumour microenvironment

Mlecnik and colleagues found the local expression of 13 cytokines was changed in a cohort of colorectal cancer samples. Chromosome 4 deletions frequently occurred in patients with metastatic disease, and deletion of interleukin-15 (*IL15*; which is encoded on chromosome 4) and its reduced expression correlated with recurrence and reduced survival. Moreover, they found that proliferating B cells and T cells were reduced when IL-15 expression was reduced and, conversely, B cell and T cell proliferation at the invasive margin correlated with prolonged disease-free survival.

ORIGINAL RESEARCH PAPER Mlecnik, B. *et al.* Functional network pipeline reveals genetic determinants associated with in situ lymphocyte proliferation and survival of cancer patients. *Sci. Transl Med.* **6**, 228ra37 (2014)