

## IN BRIEF

 TUMOUR METABOLISM

## Location matters

Glutamine is heavily consumed by tumours. Yet, the regional effects of glutamine deprivation within tumours are unknown. Pan *et al.* show that low glutamine in the tumour core results in increased histone hypermethylation through a decrease in  $\alpha$ -ketoglutarate levels. Depleted glutamine-mediated histone hypermethylation causes cellular dedifferentiation of patient-derived *BRAF*<sup>V600E</sup> melanoma cells and resistance to BRAF inhibition via histone methylation on H3K27. This study highlights how regional differences in nutrient availability can influence tumour cell differentiation and drug sensitivity.

**ORIGINAL ARTICLE** Pan, M. *et al.* Regional glutamine deficiency in tumours promotes dedifferentiation through inhibition of histone demethylation. *Nat. Cell Biol.* **18**, 1090–1101 (2016)

 TUMOUR METABOLISM

## Targeting proline metabolism?

Proline is a non-essential amino acid and Sahu *et al.* show that some cancer cells are dependent on proline for clonogenicity and tumorigenic potential. These authors profiled a panel of cancer cell lines and found that proline consumption and the expression of enzymes involved in proline biosynthesis correlated with clonogenicity and tumorigenic potential. Those cancer cell lines with a dependency on proline had hyperactivation of the mTOR complex 1 (mTORC1)–4EBP1 pathway and endoplasmic reticulum stress. These data indicate that targeting proline biosynthesis and uptake may be effective in some types of cancer.

**ORIGINAL ARTICLE** Sahu, N. *et al.* Proline starvation induces unresolved ER stress and hinders mTORC1-dependent tumorigenesis. *Cell Metab.* <http://dx.doi.org/10.1016/j.cmet.2016.08.008> (2016)

 IMMUNOTHERAPY

## Checkpoint barriers

Two studies have uncovered genetic determinants that shape the response of patients with melanoma to anti-cytotoxic T lymphocyte associated antigen 4 (CTLA4) therapy. Using whole-genome sequencing, these studies identified recurrent mutations that could predict response. Riaz *et al.* found that mutations in *SERPINB3* and *SERPINB4* were associated with survival following anti-CTLA4 therapy. By contrast, Gao *et al.* reported that mutations in interferon- $\gamma$  (IFN $\gamma$ ) pathway genes correlated with primary resistance to CTLA4 blockade. These findings underline the importance of accurate patient selection for responses to immune checkpoint blockade.

**ORIGINAL ARTICLE** Gao, J. *et al.* Loss of IFN- $\gamma$  pathway genes in tumor cells as a mechanism of resistance to anti-CTLA-4 therapy. *Cell* **167**, 397–404 (2016) | Riaz, N. *et al.* Recurrent *SERPINB3* and *SERPINB4* mutations in patients who respond to anti-CTLA4 immunotherapy. *Nat. Genet.* <http://dx.doi.org/10.1038/ng.3677> (2016)

 IMMUNOLOGY

## Skin inflammation predisposes to cancer

Inflammasome complexes are important effectors of innate immune responses, and chronic inflammation in the gut has been linked to tumorigenesis. Zhong *et al.* have found germline gain-of-function mutations in the gene encoding the inflammasome receptor, NLRP1. These mutations cause two skin disorders that are associated with epidermal hyperplasia and they relieve auto-inhibition of NLRP1 activity such that carriers exhibit spontaneous inflammation.

**ORIGINAL ARTICLE** Zhong, F. L. *et al.* Germline NLRP1 mutations cause skin inflammatory and cancer susceptibility syndromes via inflammasome activation. *Cell* **167**, 187–202 (2016)