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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 α-ketoglutarate levels. Depleted glutamine-mediated histone hypermethylation causes cellular dedifferentiation of patient-derived *BRAF*^{V600E} 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-γ (IFNγ) 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-γ 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)