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levels of circulating ARG1 were upregulated and levels of arginine downregulated compared with $Atg7^{+/+}$ mice. However, arginine levels in the tumour tissue were not as markedly downregulated as they were in mice with whole-body deletion of $Atg7$, suggesting microenvironmental sources of arginine in these tumours.

Similar results were obtained with whole-body deletion of $Atg5$, showing that these effects were specific to the functionality of autophagy rather than a specific gene. Finally, dietary arginine supplementation increased circulating arginine levels and rescued the growth of YUMM1.1 and YUMM1.3-derived tumours in $Atg7^{\Delta/\Delta}$ hosts, suggesting that autophagy in the host can maintain the availability of circulating nutrients and support tumour growth.

While arginine auxotrophy is a known metabolic vulnerability for ASS1-deficient tumours and forms the basis for potential therapeutic strategies, active autophagy in non-tumour tissues can promote growth of these tumours through maintaining the supply of arginine. Thus, a better understanding of how systemic metabolism contributes to supporting tumour growth in patients with cancer is essential in order to develop and adapt future treatment options.

Ulrike Harjes

ORIGINAL ARTICLE Poillet-Perez, L. et al. Autophagy maintains tumour growth through circulating arginine. *Nature* **563**, 569–573 (2018)

$Ehmt2$ knockout in established tumours induced tumour regression, supporting G9a as a therapeutic target. However, tumours that remained in these mice or that relapsed became more aggressive, indicating that long-term inhibition of G9a, at least in the skin, can have tumour-promoting effects.

Rowbotham et al. looked for small molecules that affect lung adenocarcinoma (LAC) tumour-propagating cells (TPCs) from mice expressing oncogenic $Kras$ and lacking $Trp53$ ($Kras;Trp53$ mice). They found that UNC0638, an inhibitor of G9a and the related GLP, promoted TPC generation from LAC cells in vitro and tumour formation in mice. Gene expression and epigenetic profiling indicated that G9a, but not GLP, was downregulated in TPCs compared with non-TPCs, suggesting that G9a is responsible for the observed phenotype of UNC0638. Consistent with this, short-hairpin RNA (shRNA)-mediated depletion of G9a in $Kras;Trp53$ LACs increased tumour burden and resulted in more aggressive tumours lacking differentiation.

G9a is not commonly mutated in LAC, but the authors found that higher G9a expression correlated with better long-term (10-year) survival of patients and that expression of one H3K9 demethylase, KDM3A, correlated with worse survival. This is consistent with the mouse data; furthermore, knockdown of $Kdm3a$ in mouse LAC cells reduced their tumour-forming potential. A broad-spectrum lysine demethylase inhibitor also reduced LAC growth in mice.

These two studies support a role of G9a in promoting tumour aggressiveness in at least two different tissues and suggest that broader investigations that consider different tissue and cell types and long-term treatment should be conducted before moving therapies targeting epigenetic modifiers into clinical studies.

Sarah Seton-Rogers

ORIGINAL ARTICLES Avgustinova, A. et al. Loss of G9a preserves mutation patterns but increases chromatin accessibility, genomic instability and aggressiveness in skin tumours. *Nat. Cell Biol.* **20**, 1400–1409 (2018) | Rowbotham, S. P. et al. H3K9 methyltransferases and demethylases control lung tumor-propagating cells and lung cancer progression. *Nat. Commun.* **9**, 4559 (2018)

Credit: Andriy Popov/Alamy Stock Photo

TUMOUR IMMUNOLOGY

Your genomic inheritance matters

Cancer immunotherapy is only highly effective in a small fraction of patients. Lim et al. now show that across all cancers there is an association between germline genetic variants and the immune features of the tumour, and that genetic background might affect responses to immunotherapy.

Expression quantitative trait loci (eQTL) are genomic loci that harbour polymorphisms that are associated with gene transcript levels (eGenes). Lim et al. started their analysis by identifying eQTL–eGene pairs in each of the 24 cancer types present in The Cancer Genome Atlas (TCGA) database. After correcting for copy number alterations, which are acquired by the tumours rather than inherited, this resulted in a list of genes under germline genetic control for each tumour. The majority of these eGenes were tumour-specific; however, for each cancer type, gene ontology showed an enrichment of multiple immune-related gene sets. This suggests a germline influence on antitumour immune responses.

The authors investigated further the potential impact of germline variants on immunotherapy response. They selected eGenes under strong germline genetic control by filtering those eQTL–eGene pairs for which the genetic variants could account for most of the eGene expression variance. Of these eGenes, they focused on $ERAP2$, a gene involved in antigen processing. Analysis of the RNA sequencing data from a phase II clinical trial of anti-programmed cell death 1 ligand 1 (PDL1) in urothelial bladder cancer showed that $ERAP2$ expression was significantly associated with patients' overall survival. Unfortunately, no genetic data were available for this trial and, therefore, the association of the relative eQTL with survival could not be confirmed. Nonetheless, these data support a role for inherited genetic variants in determining immunotherapy efficacy.

Finally, the authors tested whether germline genetics influences immune cell infiltration by checking the association of genetic polymorphisms with gene signatures of several lymphoid and myeloid immune cell types. They found several gene signature QTLs (gsQTLs), many of which were significantly associated with multiple immune cell gene signatures, suggesting a widespread effect of germline genetics on immune infiltration within the tumour microenvironment.

These findings show that the immunological properties of a tumour are not only determined by the acquired genetic features of the tumour itself but also by the genomic background of the host, and that these genetic variants may play a major part in shaping individual antitumour immune responses.

Maria Giuseppina Baratta, Senior Editor,
Nature Communications

ORIGINAL ARTICLE Lim, Y. W. et al. Germline genetic polymorphisms influence tumor gene expression and immune infiltration. *Proc. Natl Acad. Sci. USA* **115**, E11701–E11710 (2018)