T cell development and baseline functions were normal. In vitro exploration of $CD4^+$ T cells derived from these mice revealed that withdrawal of glucose but not of glutamine triggered XBP1s induction. Whereas in wild-type cells glucose withdrawal reduced mitochondrial respiration, glucose withdrawal in XBP1-deficient cells increased mitochondrial respiration, without affecting mitochondrial homeostasis or biogenesis. Importantly, XBP1-deficient $CD4^+$ T cells imported more glutamine than did wild-type cells when glucose was limited and were able to maintain mitochondrial metabolite levels derived from glutamine. In line with the role of glutamine in superior mitochondrial respiration in XBP1-deficient cells, treatment with cell-permeable α-ketoglutarate or overexpression of glutamine transporters rescued mitochondrial respiration in glucose-deprived wild-type cells or in $CD4^+$ T cells exposed to supernatants of OvCa ascites.

In an orthotopic model of OvCa in mice deficient of XBP1 in T cells, expression of genes related to T cell activation was increased, the proportions of interferon-γ-producing tumour-antigen-specific $CD4^+$ T cells was increased and the effector profile of $CD8^+$ T cells was also enhanced compared with OvCa in wild-type mice. Accordingly, the growth and growth progression of OvCa in the flanks of mice deficient of XBP1 selectively in the T cell compartment or specifically in $CD4^+$ T cells was reduced, and survival increased compared with wild-type mice.

These data show that OvCa T cells in the tumour have XBP1s induction and mitochondrial dysfunction, which reduces their antitumour capacity. This axis could present an 'immuno-metabolic checkpoint' with therapeutic potential.

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ORIGINAL ARTICLE Song, M. et al. IRE1α–XBP1 controls T cell function in ovarian cancer by regulating mitochondrial activity. *Nature* **562**, 423–428 (2018)

the gene-repressive dimethylation of histone H3 Lys9 (H3K9me2) — as MYC-interacting proteins in human cancer cell lines. The MYC–G9a interaction required the conserved MYC box II region, which is known to be essential for transcription repression and oncogenic transformation by MYC.

G9a is highly expressed in many cancers and this is associated with poor prognosis. MYC was found to induce the gene encoding G9a, and both G9a and H3K9me2 levels decreased following MYC depletion. Conversely, inducing MYC in human non-cancerous epithelial cells increased the binding of G9a to MYC-repressed genes. G9a depletion before MYC induction resulted in a decrease in H3K9me2 levels at MYC-repressed gene promoters and an increase in the levels of histone modifications associated with active transcription. Furthermore, G9a depletion decreased MYC binding and MYC-dependent gene repression, and antagonized MYC-mediated cell cycle activation. Gene derepression was recapitulated using G9a inhibitors, indicating that MYC target-gene repression is associated with the catalytic activity of G9a.

Two MYC-dependent, basal breast cancer xenograft mouse models were used to assess the effect of G9a inhibition in vivo. Cells expressing inducible G9a-targeting short hairpin RNAs (shRNAs) were subcutaneously injected into mice, and shRNA expression was induced following tumour formation. In both models, expression of MYC–G9a-repressed genes was significantly upregulated, and tumour volumes were significantly decreased following G9a depletion.

In summary, the oncogenic function of MYC is mediated by gene activation through the SEC and gene repression by G9a. It will be interesting to test whether dual inhibition of both pathways might have a synergistic negative effect on tumours.

Eytan Zlotorynski, Senior Editor,
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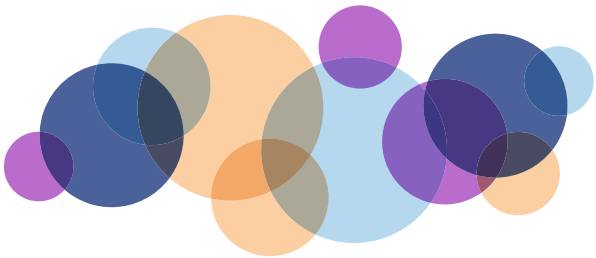

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TUMORIGENESIS

Colony takeover

Somatic mutations passively accumulate in healthy cells throughout life. Technical challenges associated with identifying mutations occurring only in a small number of cells have limited our understanding of somatic evolution in normal tissues. Yet, these studies have implications for early cancer development. Now, researchers at the Wellcome Sanger Institute have used genome sequencing to characterize the mutational landscape of normal oesophageal tissue during ageing.To detect somatic coding mutations, Martincorena, Fowler et al. utilized ultra-deep targeted sequencing of 844 small samples from a cumulative area of ~17 cm^2 of normal oesophageal epithelium taken from nine organ transplant donors aged between 20 to 75 years. This revealed that the numbers of detectable mutations as well as the size of the mutant clones increase with age, wherein the several hundred mutations present in a healthy oesophageal cell from a person in their twenties can rise to more than 2,000 mutations per cell in an older individual. Furthermore, analysis of mutational signatures revealed that most of the mutations were generated by intrinsic mutational processes related to ageing and transcription.

Interestingly, the authors identified widespread positive selection in the normal oesophagus of clones with mutations in cancer-associated genes. Of the 14 positively selected genes found, 11 were known canonical drivers of oesophageal squamous cell carcinoma (OSCC).

One such driver, *NOTCH1*, was mutated at a high frequency (12–80%) in aged normal oesophageal tissue compared with OSCCs (10%), hinting that the presence of *NOTCH1* mutations might protect against cancer. In contrast, *TP53* mutations present in over 90% of OSCCs were found in only a small fraction of normal oesophageal cells. Overall, however, the mutational burden in normal oesophageal epithelium was approximately ten times lower than in OSCCs. Other differences between mutant clones in ageing normal tissue and OSCCs were an absence of APOBEC mutagenesis and a low level of copy number changes, implying that these events may have been acquired later in the evolution of oesophageal cancers.

This work highlights the importance of studying healthy tissues to provide insight into the transition from normal to cancer but also suggests we might need to reconsider the role of some cancer-driver genes, given their high mutation frequency in normal cells.

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ORIGINAL ARTICLE Martincorena, I. & Fowler, J. C. et al. Somatic mutant clones colonize the human esophagus with age. *Science*. https://doi.org/10.1126/science.aau3879 (2018)