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METABOLISM

Epigenetic links to the web of Krebs

Connections between metabolic disruption and altered epigenetic modifications are increasingly being realized in cancer. Much attention has focused on DNA hypermethylation that results from the mutation of isoforms of the metabolic enzyme isocitrate dehydrogenase. Two new studies show that similar epigenomic alterations result from cancer-associated mutations of the Krebs cycle enzyme succinate dehydrogenase (SDH).

To examine the effects of SDH mutations on gastrointestinal stromal tumour (GIST) epigenomes, Killian *et al.* characterized the 5-methyl cytosine (5mC) DNA methylation profiles of 24 SDH-mutant GIST samples compared with 39 GISTs that harboured mutations in the KIT kinase pathway and also with various normal tissues. Whereas DNA methylation in KIT-mutant GISTs was generally similar to that of normal tissues, SDH-mutant GISTs showed characteristic hypermethylation patterns. Furthermore, similar DNA hypermethylation occurred in 20 SDH-mutant versus nine SDH-wild-type paragangliomas and pheochromocytomas.

Interestingly, KIT-mutant GISTs had relatively unstable genomes, with frequent copy number alterations, compared with SDH-mutant GISTs, which had remarkably stable genomes. Such findings suggest that an altered epigenome in SDH-mutant GISTs might be sufficient to be an oncogenic driver in the absence of widespread genetic alterations.

Succinate is known both to accumulate in SDH-mutant tumours and to inhibit the TET family of dioxygenases, which oxidize 5mC to 5-hydroxymethylcytosine (5hmC) during DNA demethylation. As evidence that this mechanism underlies the observed DNA hypermethylation, the authors found loss of genomic 5hmC in SDH-mutant GIST relative to KIT-mutant GIST. This mechanism mirrors the proposed TET-inhibitory role of accumulated 2-hydroxyglutarate in IDH-mutant cancers; indeed, clustering analyses confirmed the similarities in DNA methylation profiles between IDH-mutant gliomas and SDH-mutant cancers of various tissue types.

In a separate study, Letouzé *et al.* also carried out DNA methylation profiling: they analysed 145 paragangliomas and pheochromocytomas, and also showed that SDH mutations are associated with genomic hypermethylation. From this large collection of tumours they found that, of the four SDH subunits, mutations in SDHB were associated with the greatest hypermethylation and the most aggressive clinical behaviour. Additionally, in the only hypermethylated SDH-wild-type tumour sample, the authors used exome sequencing to identify mutations in a different Krebs cycle enzyme, fumarate hydratase. Thus, different Krebs cycle lesions can result in similar epigenetic outcomes.

To further characterize the functional consequences of SDH mutation, Letouzé *et al.* generated conditional *Sdhb*-deficient mice. As for the human tumours, neuroendocrine chromaffin cells from these mice showed increased 5mC and decreased 5hmC levels relative to *Sdhb*-wild-type cells. Additionally, they also had increased histone methylation, which may be a consequence of the inhibitory effects of succinate on the Jumonji family of histone demethylases. The epigenetic effects of *Sdhb* deficiency were associated with the altered expression of various genes, including neuroendocrine differentiation genes, although whether such expression changes contribute to tumorigenesis is currently unclear. Importantly, *Sdhb* loss caused an enhanced migratory capacity of chromaffin cells *in vitro*; this was reversed by treating with the demethylating agent 5-aza-2′-deoxycytidine, thus the migratory capacity seems to be a consequence of the DNA hypermethylation.

It will be interesting to see whether DNA methylation will be a promising therapeutic target for human cancers harbouring Krebs cycle mutations.

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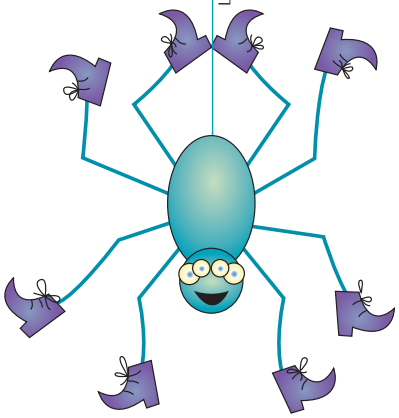

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> “different Krebs cycle lesions can result in similar epigenetic outcomes”

ORIGINAL RESEARCH PAPERS Killian, J. K. *et al.* Succinate dehydrogenase mutation underlies global epigenomic divergence in gastrointestinal stromal tumor. *Cancer Discov.* **3**, 648–657 (2013) | Letouzé, E. *et al.* SDH mutations establish a hypermethylator phenotype in paraganglioma. *Cancer Cell* 21 May 2013 (doi:10.1016/j.ccr.2013.04.018)