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EPIGENETICS

Dissecting driving DNA methylations

Cancers typically have extensive alterations to DNA and histone-modification patterns. Although tumour suppressor genes are often subjected to silencing through cancer-specific promoter DNA methylation, it is generally unknown which DNA methylation events throughout the genome are 'driver' versus 'passenger' events in tumorigenesis. A new study pinpoints various putative driver gene methylations on which cancer cells may particularly rely.

Peter Jones and colleagues compared the promoter DNA methylation profiles of parental HCT116 colorectal cancer cells with daughter clones that have engineered lesions in DNA methyltransferase genes. They reasoned that the daughter clones (that have impaired DNA methylation) will selectively retain DNA methylation at genes for which continued silencing is most required for cell survival. For the 490 identified genes, the authors analysed additional DNA methylation data sets from primary colorectal cancer samples and various normal tissues, and subdivided this list into methylations that are cancer-specific, somatic cell-specific, or culture-induced methylations.

The authors focused on the 77 genes with cancer-specific methylation, confirming their cancer-specific nature in independent DNA methylation data sets from colorectal and lung cancer, including a correlation with the downregulation of gene expression.

To confirm that repression of some of these genes was functionally linked to cell survival, the authors returned to the methylation-impaired HCT116 cells. They showed that the subset of cells in the population that were undergoing apoptosis, compared with viable cells, had less methylation of *EYA4* and interleukin-1 receptor-associated kinase 3 (*IRAK3*), but unchanged global DNA methylation. By contrast, forced apoptosis through staurosporine treatment did not demethylate these genes, implying that the demethylation caused apoptosis and not vice versa. Furthermore, lentiviral-mediated re-expression of nine of the genes individually resulted in reduced viability of both parental and methylation-impaired HCT116 cells, although it is unclear whether these ectopic expression levels are comparable to those that would be achieved through the demethylation of the endogenous genes.

It is noteworthy that none of the genes identified in this study is a well-characterized tumour suppressor gene, hence it will be important to dissect the mechanisms of why the expression of these genes would be toxic to cancer cells but tolerated prior to tumorigenesis. As one mechanism of toxicity, the expression of IRAK3 led to downregulation of the anti-apoptotic protein survivin (also known as BIRC5).

This study is useful for pinpointing genes that are promising candidates for therapeutic re-activation. The challenges for future epigenetic-based anticancer therapies include achieving specificity for the activation of intended genes, and whether the systemic delivery of such agents would have a detrimental effect on the transcriptomes and viabilities of normal cells.

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ORIGINAL RESEARCH PAPER De Carvalho, D. *et al.* DNA methylation screening identifies driver epigenetic events of cancer cell survival. *Cancer Cell* **21**, 655–667 (2012)

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