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EPIGENETICS

The long view

PHOTODISC

Changes in epigenetic marks, such as histone methylation and acetylation, are known to have an effect on gene expression. Susan Clark and colleagues have previously shown that large regions of chromatin in cancer cells are silenced owing to epigenetic changes. They have now found evidence that long-range epigenetic changes can also lead to increased gene expression.

The authors used prostate cancer cell lines and normal prostate cell lines to identify regions of concordant cancer-associated gene expression. They initially identified 42 domains with increased gene expression: seven of these with gene copy number amplifications were excluded. Interestingly, two domains showed a loss of DNA copy number despite having regions of increased gene transcription. Of the remaining 35 domains, 26 also showed increased expression in gene expression profiles from human prostate tumours in publicly available databases. The authors named these regions long-range epigenetic-activated (LREA) regions, which varied in size from 85.5 kb to 5.2 Mb. These regions harboured gene clusters, such as the kallikrein gene family, which includes prostate-specific antigen, and several other genes that had previously been associated with prostate cancer. An examination of both repressive and active chromatin marks in these regions revealed two particular modes of histone modification. Some regions showed a loss of repressive histone 3 lysine 27 trimethylation (H3K27me3) marks and a gain of H3K9 acetylation (H3K9ac), whereas others showed a gain in active marks such as H3K9ac and H3K4me3.

Interestingly, the authors found that some LREA regions were next to regions that showed long-range epigenetic silencing (LRES) that corresponds to a loss of H3K9ac marks and a gain of H3K27me3 marks. They also found that CpG island promoter hypermethylation, rather than CpG island hypomethylation, was more often associated with a gain of gene expression. CpG island promoter methylation that was associated with gene expression in prostate cancer involved either methylation of sequences flanking CpG islands (but not the H3K4me3 transcription start site (TSS)), which the authors termed group I, or extensive methylation across the CpG island, including the TSS (group II). The authors suggest that group I methylation changes block the binding of repressive factors, resulting in gene expression, and that group II methylation changes identify genes that are being expressed from alternative promoters.

It is currently unclear how these epigenetic alterations arise, but the position of the chromatin in the nucleus could be important.

Nicola McCarthy

> “It is currently unclear how these epigenetic alterations arise”

ORIGINAL RESEARCH PAPER Bert, S. A. *et al.* Regional activation of the cancer genome by long-range epigenetic remodeling. *Cancer Cell* 13 Dec 2012 (doi:10.1016/j.ccr.2012.11.006)
FURTHER READING Baylin, S. B. & Jones, P. A. A decade of exploring the cancer epigenome — biological and translational implications. *Nature Rev. Cancer* **11**, 726–734 (2011)