TUMOUR IMMUNOLOGY

Inflammatory transformation

Clinical and epidemiological data indicate a link between inflammation and cancer, and although the transcription factor nuclear factor-κB (NF-κB) is thought to have an important role in this link, the molecular pathways involved are not known. A study published in *Cell* now describes a positive feedback loop involving NF-κB, microRNAs and interleukin-6 (IL-6) — all of which have been linked with human cancers — in the initiation and maintenance of the cellular transformation of immortalized mammary epithelial cells.

To assess the molecular pathways involved in the switch from a non-transformed to a transformed phenotype, the authors used a model of oncogenesis in which expression of the proto-oncogene SRC by immortalized mammary epithelial cells (MCF10A cells) can be induced by tamoxifen, resulting in phenotypic transformation and formation of mammospheres (multicellular structures enriched in tumour-initiating cells).

A detailed analysis of these cells identified the following pathway as being central to their transformation: SRC activation by tamoxifen induced the early activation of NF-κB, which then induced the expression of the microRNA suppressor LIN28B. LIN28B targets the let-7 microRNA family, and five members of this family, including let-7a, were shown to be markedly downregulated after tamoxifen treatment in an NF-κB- and LIN28B-dependent manner. let-7a was shown to inhibit the expression of *IL6*, so the downregulation of let-7a results in the upregulation of IL-6 expression early during transformation. Finally, IL-6 signalling through its receptor induces the expression of signal transducer and activator of transcription 3 (STAT3) and further NF-κB activation (which activates *IL6*), and this pathway was necessary for the later stages of cellular transformation.

Inhibition (or overexpression in the case of let-7a) of any molecule in this pathway inhibited cellular transformation. In addition, when tamoxifen is removed, the transformed cells remain stable for many generations in the absence of SRC activation as a result of this positive feedback loop.

Finally, the authors provided evidence to suggest that this pathway is relevant to human disease, especially breast and prostate epithelial cancers. So, this study shows that activation of an inflammatory feedback loop by transient SRC activation can induce an epigenetic switch in transformed cells that lasts for many generations, providing a molecular link between inflammation and cancer.

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ORIGINAL RESEARCH PAPER Iliopoulos, D., Hirsch, H. A. & Struhl, K. An epigenetic switch involving NF-κB, Lin28, Let-7 microRNA, and IL6 links inflammation to cell transformation. *Cell* **139**, 693–706 (2009)