Links

E2F4

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=Graphics&list_uids=1874

MIF

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=Graphics&list_uids=4282

RB

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=Graphics&list_uids=5925

INFLAMMATION

Well connected

The link between inflammation and cancer is well established and a connection between chromatin remodeling and cancer is evident, but, at first glance, a link between all three pathways seems surprising. This is, however, the relationship that has been unearthed by Oleksi Petrenko and Ute Moll through their studies on the pro-inflammatory protein macrophage migration inhibitory factor (MIF).

MIF activates both macrophages and T cells during an inflammatory response and has been previously shown to affect the E2F family of transcription factors. MIF-knockout cells have a reduced capacity to proliferate and to undergo oncogenic transformation, characteristics that are E2F dependent, but the nature of the molecular interaction between MIF and the E2Fs has been unclear.

The capacity of the E2F proteins to activate or repress gene expression is regulated by members of the retinoblastoma (RB) protein family. In concert with the E2Fs, RB can repress gene transcription and suppress entry into S phase by binding to specific gene promoters. Release of the E2Fs from RB family members enables E2F-dependent gene transcription. Importantly though, RB complexes can also regulate chromatin conformation and DNA replication by interacting with components of the DNA-replication complex. Petrenko and Moll used a series of gene expression and deletion experiments to establish that mouse

embryonic fibroblasts deficient in MIF expression are not compromised in their capacity to proliferate due to defects in E2F-mediated gene transcription. Instead, these fibroblasts are hampered by the inability of E2F4 to repress the capacity of RB to recruit histone deacetylases that close up the chromatin structure, and by the reduced capacity of E2F4 to promote the recruitment of histone acetyl transferases that open up the DNA and enable DNA replication in the absence of MIF expression.

These findings indicate that chronic inflammation leading to increased MIF expression will antagonize RB-mediated repression of E2F-responsive genes. This might increase the capacity for active E2Fs to initiate DNA replication, enhancing proliferation and tumorigenesis. The *in vivo* role of MIF is now being investigated by the authors.

Nicola McCarthy

References and links

ORIGINAL RESEARCH PAPER Petrenko, O. & Moll, U. M. Macrophage migration inhibitory factor MIF interferes with the Rb-E2F pathway. *Mol. Cell* **17**, 225–236 (2005)

FURTHER READING Dranoff, G. Cytokines in cancer pathogenesis and cancer therapy. *Nature Rev. Cancer* **4**, 11–22 (2004)

WEB SITE

Ute Moll's lab:

<http://www.path.sunysb.edu/faculty/umoll/default.htm>