Quick Guide

E2F proteins

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What is it? Physiological E2F is a heterodimer composed of an E2F subunit together with a DP subunit. There are six published members of the E2F family that are divided into three sub-groups based upon sequence homology and domain organization. Each E2F subunit has a DNA binding and dimerization domain. E2F-1, -2, -3 each have an extended amino-terminal region that binds CyclinA/Cdk2 kinase and, like E2F-4 and -5, a carboxy-terminal transcription activation domain (TAD) that also provides an interface for the pocket proteins pRb, p107 or p130. E2F-6 lacks a TAD and may be a transcriptional repressor. There are two DP subunits and most E2F heterodimers contain DP-1.

How does it work? The E2F DNA binding domain is a winged helix–turn–helix; it binds the consensus DNA sequence TTT(C/G)(C/G)CGC. E2F activates transcription, requiring an interaction between the TAD and p300/CBP coactivators.

What does it do? E2F activity coordinates gene expression as cells progress from G0 into G1 and S phase. E2F targets are required for cell cycle progression, (regulatory proteins such as Cyclins E and A and Cdc2), for DNA replication (Cdc6, ORC1 and MCM6) and for DNA synthesis (enzymes such as dihydrofolate synthetase, DNA polymerase α and thymidine kinase). E2F also regulates apoptotic genes such as Arf, p73 and Apaf1.

How is E2F regulated? E2F is regulated by members of the pocket protein family, such as pRb, which bind to the TAD. This interaction is under phosphorylation control of pRb, and is mediated by the G1 cyclin-dependent kinases (Cdk) CyclinD/Cdk4 and CyclinE/Cdk2.

So E2F is a transcriptional activator and repressor? E2F can exist in at least three different states: active, inactive and repressive. Free E2F is the active form, and inactive E2F results from the association of a pocket protein. Repressive E2F requires chromatin-regulating and remodelling proteins, including histone deacetylase (HDAC), SWI/SNF, polycomb group proteins (PCG) and histone methlytransferase (MTase).

Are all E2Fs the same? E2F-1 to -5 activate transcription. E2F-1 to -3 bind pRb, and E2F-4 and -5 bind p107 or p130, and these interactions are under cell cycle control. The combined loss of E2F-1, -2 and -3 abolishes S phase entry in fibroblasts, whereas *E2F-4*$^{-/-}$ and *E2F-5*$^{-/-}$ cells have defects in cell cycle exit. The phenotype of knockout mice with inactivated *E2F* genes are strikingly different. *E2F-1*$^{-/-}$ mice appear developmentally normal, but have defects in apoptosis in the immune system, and tumours develop in old animals. Most *E2F-3*$^{-/-}$ embryos die *in utero*; *E2F-4*$^{-/-}$ mice have aberrant erythrocyte maturation and *E2F-5*$^{-/-}$ mice develop neurological defects such as hydroencephaly. *DP-1* is an essential gene.

Is E2F affected in tumour cells? E2F activity is under aberrant control in most, if not all, human tumour cells through alteration or mutation of genes required to control the pRb–E2F interaction, such as *Rb*, *CyclinD* and the *p16* locus.

Oncogene or tumour suppressor? E2F-1 has oncogenic properties *in vivo* and *in vitro*. E2F-1 can induce apoptosis through p53-dependent and -independent mechanisms. E2F-1 is stress-responsive, and is regulated by the phosphatidyl inositol-3-kinase-like kinase family such as ATM/ATR kinases.

Where can I find out more?

Dyson, N. (1998). The regulation of E2F by pRb family proteins. Genes Dev. *12*, 2245–2262.

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Trimarchi, J.M. and Lees, J.A. (2002). Sibling rivalry in the E2F family. Nat. Rev. Mol. Cell Biol. *3*, 11–20.

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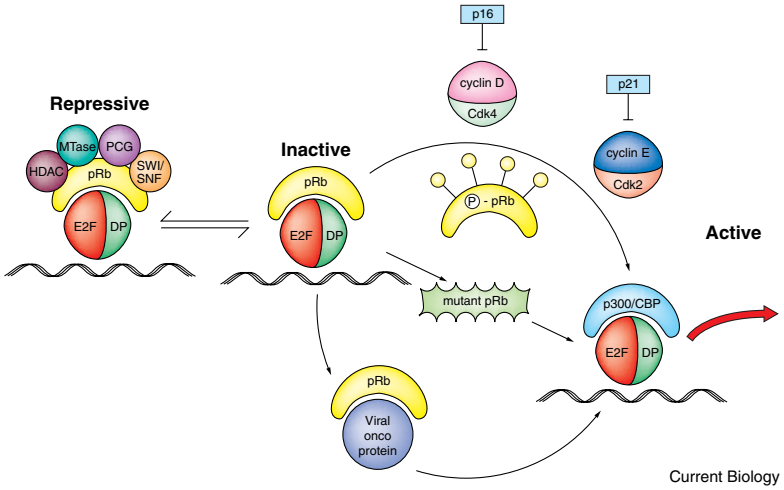

Figure 1.
In non-proliferating cells, the E2F/DP heterodimer binds pocket proteins such as pRb. During early cell cycle progression G1 cyclin-dependent kinase complexes (Cyclin D/Cdk4 and Cyclin E/Cdk2) phosphorylate pRb, releasing E2F. E2F becomes transcriptionally active through interaction with transcription cofactors such as p300/CBP. In tumour cells, mutant pRb fails to bind E2F. Similarly, viral oncoproteins bind pRb to hinder its interaction with E2F. In addition, p16 can be inactivated, or cyclin D1 over-expressed, in cancer cells. The pRb/E2F complex becomes an active transcriptional repressor by recruiting proteins, such as HDAC, MTase, PCG and SWI/SNF, that alter the chromatin environment to favour transcriptional inactivity.