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Introduction: the regulation of eukaryotic transcription factor function

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It is now over a decade since the first eukaryotic transcription factors were cloned. Since this time, our understanding of how they function has increased substantially, and their mechanisms of action have been shown to be increasingly complex. Initial studies demonstrated that in general, transcription factors contain two domains: a DNA binding domain for recruitment to DNA and an activation or repression domain for regulating transcription [1]. It is becoming clear that whilst this paradigm is generally true, there are important exceptions. For example, transcription factors can be recruited to promoters by protein-protein interactions in the absence of a DNA-binding domain. Furthermore, transcription factors can possess both activation and repression domains. Indeed, the DNA-binding domains themselves can act as transcriptional regulatory domains. Another important concept to emerge is that transcription factors generally do not function alone, but instead they function in concert to regulate transcription. An extreme example of this is the enhanceosome model (reviewed in [2]), where multiple transcription factors are thought to interact with each other and an enhancer to form a defined structure which allows them to function in a coordinated manner to regulate transcription. Transcription factors are thought to mediate their effects by interacting with additional proteins known as coactivators or corepressors. The recent identification of numerous interacting coactivator and corepressor proteins indicates a further increase in the intricacies of transcription factor function (reviewed in [3]). This series of reviews highlights recent advances in our understanding of the complexity of function and regulation of eukaryotic transcription factors.

The review by Roberts details recent advances that have led to the elucidation of several mechanisms by which the regulatory domains found in eukaryotic transcription factors function at the molecular level. The importance of transcription factors acting to promote or overcome the repressive effects of chromatin before they can act on the basal transcription machinery is now becoming clear. This is reflected by the fact that activators can recruit chromatin remodelling complexes and that activators and repressors often recruit coregulatory complexes containing histone acetylase or deacetylase activity, respectively. These histone modification systems act to promote or destabilise the chromatin structure and hence modify the accessibility of the promoter DNA to the transcriptional machinery. Once the chromatin barrier has been removed, activator proteins can bind to components of the basal machinery and promote transcriptional initiation. The types and identities of the proteins contacted by the activation and repression domains are many and varied, reflecting the multiple ways in which transcription factors can act to regulate transcription.

The activities of transcription factors are tightly regulated. This regulation is often mediated by small molecules or by posttranslational modifications. In higher eukaryotes, the nuclear hormone receptors represent paradigms for how small effector molecules can drastically affect transcription factor function (reviewed in [3]). In the review by Reece, further elegant mechanisms are described that have been adopted by yeast transcription factors to enable them to respond to nutrient availability and the metabolic demands of the cell. Small molecules that form either substrates or intermediates of metabolic pathways can promote the assembly of higher-order activator complexes (as in the Gal4p-

Gal80p-Gal3p complex) or directly activate a transcription factor (as with Leu3p). The mechanism of action of these small molecules is thought to be via inducing conformational changes in the target proteins, which leads to a change in their activity and/or inter- and intramolecular interactions.

A further key regulatory switch which acts upon transcription factors is phosphorylation. The different aspects of transcription factor function regulated by phosphorylation are detailed in the review by Whitmarsh and Davis. Virtually all the key activities of transcription factors can be modified either positively or negatively by phosphorylation. These activities include the regulation of DNA binding, oligomerisation, coregulatory protein binding and, in addition, the structure of chromatin itself. Furthermore, phosphorylation can also regulate the stability and subcellular localisation of transcription factors [see reviews by Cartwright and Helin, and Desterro et al. for further details].

It is becoming apparent that protein acetylation also plays an important role in regulating the activity of transcription factors. This important and expanding area of research is reviewed by Bannister and Miska in this issue. Transcription factors can recruit histone acetylases and deacetylases to lead to changes in the status of local chromatin acetylation. However, it is becoming clear that the transcription factors themselves can act as targets for these modifying enzymes. Indeed, protein acetylation appears to act in an analogous manner to phosphorylation in modifying the activities of transcription factors. For example, DNA binding (of p53), transcriptional activation (of GATA-1) and coactivator binding (in the TCF-β-catenin complex) can all be regulated by a change in transcription factor acetylation. It is likely that the role of acetylation in regulating transcription factor activity will occupy a more central role in the future.

As transcription takes place in the nucleus, a change in the subcellular localisation of transcription factors is an efficient and stringent way to control transcription factor activity. Numerous examples of this type of regulation now exist and are reviewed by Cartwright and Helin. The paradigm for this type of regulation is the NFκB-IκB complex, where the inhibitory IκB protein holds the NFκB transcription factor in the cytoplasm until the appropriate activating signal is received. However, other transcription factors such as NF-AT are directly modified by phosphatases, which results in their nuclear accumulation. The importance of nuclear localisation signals in this process is demonstrated by studies on the E2F family, where family members that lack nuclear localisation signals (NLSs) require binding to another protein that contains an NLS to permit nuclear accumulation.

Finally, a further key control mechanism for eukaryotic transcription factors involves regulatory proteolysis and is reviewed by Desterro et al. This regulatory event is intimately associated with other regulatory cues such as phosphorylation and subcellular localisation. One of the best-studied examples again involves the NFκB-IκB complex, where the IκB inhibitory protein is degraded following dissociation from NFκB to permit NFκB translocation to the nucleus. The ubiquitin-proteasome pathway mediates this degradation, and it is becoming apparent that this pathway also directly regulates the abundance of transcription factors such as p53. In this pathway, the conjugation of the small protein ubiquitin to the substrates is the key initiating event. However, other ubiquitin-like molecules and associated pathways have recently been identified, one of which, SUMO-1, acts to stabilise proteins such as IκB and p53. Thus antagonistic modes of regulation can be achieved by covalently attaching small molecules to transcription factors such as ubiquitin or SUMO-1.

Whilst each review covers particular aspects of transcription factor function, it is important to realise that all the regulatory processes that impinge on transcription factor function are fully integrated. For example, the viral transcription factor VP16 can affect transcription in multiple ways by interacting with different components of the regulatory machinery. Other transcription factors such as p53 respond to changes in both its phosphorylation and acetylation status. NFκB is regulated via IκB by intracellular localisation, and IκB in turn is regulated by proteolysis that is triggered by phosphorylation of IκB. The nuclear import/export machinery itself appears also to be a critical regulator of transcription factor function and can respond to different signals. For example, components of this machinery are modified by SUMO-1 and, at least in vitro, by acetylation. Thus the regulation of transcription factor activity can take place at multiple levels, and the net output from a transcription factor depends on the types of regulatory signals operating at a particular time and place in the cell.

Whilst our understanding of transcription factor function and regulation has expanded significantly over the past decade, the increase in complexity that has been uncovered means that we are far from fully comprehending how these proteins work at the molecular level. The continued application of a combination of biochemical, genetic, molecular and structural approaches should, however, ensure that we have a more complete understanding of transcription factor function by the end of the next decade.

1 Latchman D. (1995) Gene regulation. a eukaryotic perspective. Chapman and Hall, London
2 Carey M. (1998) The enhanceosome and transcriptional synergy. Cell **92:** 5–8
3 Xu L., Glass C. K. and Rosenfeld M. G. (1999) Coactivator and corepressor complexes in nuclear receptor function. Curr. Opin. Genet. Dev. **9:** 140–147