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Foreword

Following the elucidation of basic mechanisms of transcriptional regulation in prokaryotes, in the past three decades attention mostly turned to research of the corresponding mechanisms in eukaryotes. Although basic features of the regulatory mechanisms found in prokaryotes have been preserved, the demands of more complex transcriptional control in eucaryotes have led to the addition of new mechanisms operating at multiple regulatory levels. There is considerable evidence that the mechanism involved in transcriptional regulation are well preserved among eukaryotes. Therefore, due to the ease of its genetic manipulation yeast is an ideal eukaryotic organism for biochemical and genetic studies of these mechanisms, particularly since its complete genome sequence has become available.

Early work on eucaryotic transcriptional control focused on regulatory DNA elements and transcription factors that bind to them and regulate transcription. Actually,transcription factors involved in the process of transcription initiation and regulation can be classified into two groups. General transcription factors, including RNA polymerase II itself, which assemble on the core promoter in an ordered fashion to form a pre-initiation complex. Transcriptional activity of the given promoter is, however, greatly stimulated by a second class of factors, promoter-specific activator proteins. Activators are sequence-specific DNA-binding proteins, which bind to positive regulatory DNA elements, so called UAS elements in yeast. Being specific for genes or gene families they, typically, couple transcription to the physiological requirements of the cell. Usually, activators are latent and become functionally active during a physiological response.

Transcriptional activators contain at least two distinct domains; a DNA-binding and an activation domain. Most of the DNA-binding domains belongs to a few major families, whose structure have been determined by crystallographic or NMR analysis. The specificity and affinity of protein-DNA binding is in some cases regulated through cooperative interactions with coactivators bound to adjacent DNA sequences. Activation domains of transactivators are still rather porly understood. It is thought that they operate by contacting components of the general transcription machinery and that way control transcription initiation. Although many such interactions have been determined, the importance of these contacts in transcription remains to be established. The complexity of the role that transacting factors play in control of transcription is further demonstrated by findings that

some factors can alternatively act as activator or as a repressor, depending on their interacting partners or context.

A seprate line of work on chromatin structure and its role in the regulation of eukaryotic gene transcription in the last decade has made it clear that one of the major hurdles in transcriptional activation in vivo is the presence of nucleosomal barriers. Nucleosomes located on promoter regions repress transcription by restricting access of activators and the transcriptional machinery to the DNA template. In addition, a form of chromatin-mediated transcriptional silencing, first described at the yeast mating loci, was found to be associated with transcriptionally inactive regions in the eukaryotic genome. It is believed that heterochromatin-like conformations in these regions are responsible for transcriptional silencing. An example for this phenomenon in yeast is telomeric silencing, also known as "telomere position effect". Therefore, counteracting nucleosomal repression is a critical step in transcriptional activation in vivo.

Recent years have brought about an explosion of new findings concerning mechanisms used by eukaryotic cells to relieve nucleosomal repression. Proeins previously implicated in transcriptional control on the basis of their interactions with activator proteins were found to have catalytic activities toward the histones. The yeast transcriptional adapter, Gcn5, was thus identified as a histone acetyltransferase. Several other transcriptional adapters in higher eukaryotes were also found to possess histone acyltransferase activity, suggesting a role of histone acetylation in gene activation. Recent findings demonstrated that these enzymes are components of large multiprotein complexes, which are recruited to promoters by DNA-binding specific transcriptional activators. In analogy to histone acetyltransferase activities of coactivators, some corepressors were identified as histone deacetylases. Very intriguing are recent findings, suggesting that acetylation is probably not unique to histone proteins and that other nuclear proteins such as transcription factors can be modified by acetylation.

Despite clear evidence about the importance of histone acetylation in transcriptional activation, this is not sufficient to relieve chromatin repression. Other multiprotein complexes that "remodel" chromatin structure in an ATP-dependent manner, allowing access of specific activators and the transcriptional machinery to DNA, have also recently been identified. These complexes (an example is the yeast SWI/SNF complex) might contribute to formation of apparently nucleosome-free regions, so-called "nuclease hy persensitive sites", which are present in promoters of transcriptionally active genes.

These findings demonstrate that the mechanism of eukaryotic transcription regulation are of immense complexity and that all of the factors that are involved in the transcription process, including the chromatin template, play an active role in transcriptional control. With the emergence of new approaches and tools for the analysis of the chromatin structure and transcriptional regulation in vitro and in vivo, we can expect a rapid advance

which will revolutionise our understanding of the multilayered regulatory mechanisms of eukaryotic transcriptional control.

When we decided to have a Special Millenium Issue Transcriptional Regulation in Yeast, an idea behind it was to bring the readers recent achievemnets and excitements in one of the most attractive and rapidly developing field of molecular biology, which is at the same time of great importance for future developments in modern "molecular biotechnology". Many discoveries and important findings concerning eukaryotic transcriptional regulation have come from research in yeast and current studies in yeast post-genomic era, will no doubt be of great importance in the future understanding of the complex network controlling eukaryotic transcription.

Guest Editor:

Slobodan Barbaric