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Mediator special issue

Mediator comes of age

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The series of reviews on the Mediator of transcriptional regulation in this issue of *TiBS* heralds the arrival of Mediator as a central player in the transcription scene. Long viewed with skepticism, the Mediator idea is now firmly established. Mediator is recognized as a major conduit of regulatory information from enhancers to promoters, connecting regulatory proteins (activators and repressors) with the RNA polymerase II (pol II) transcription machinery in the entire range of eukaryotes from yeast to humans.

The central importance of Mediator is sometimes obscured by the sheer volume of reports on coactivators, co-repressors and other regulatory factors. There is a crucial distinction to be made in this regard: Mediator is general in that it is required for transcription of all pol II promoters, whereas the other factors are specific because they are involved in the transcriptional regulation of a particular promoter or a subset of promoters. Mediator is properly viewed as a component of the core transcription machinery, comparable in importance to pol II and the general transcription factors. Mediator is not only a coactivator, but also a co-repressor and a general transcription factor.

This series of reviews is introduced by a description of the discovery of Mediator and a discussion of the mechanism of transcriptional activation. There were three major obstacles to the discovery and establishment of the Mediator idea: (i) the early belief that activators function directly rather than through an intermediary factor, (ii) the biochemical problem of isolating Mediator from yeast, (iii) and a reluctance to accept the universality of Mediator, especially its relevance to human transcription. The mechanism of transcriptional activation remains an unsolved problem, with little indication as yet of the step(s) of the transcription initiation process affected or the role of Mediator in the process.

Björklund and Gustafsson review the current status of work on yeast Mediator. They detail combined genetic and biochemical analyses most readily performed in the yeast system. Notable insights include the disproof of the 'holoenzyme hypothesis' (the supposed recruitment of Mediator as part of a preformed pol II transcription initiation complex), the role of two distinct forms of Mediator in activation and repression, and the interplay of post-translational modifications between Mediator targets and Mediator itself.

Kim and Lis review studies of *Drosophila* Mediator, highlighting, in particular, the biological roles of individual Mediator subunits. The biological role of a subunit correlates with its degree of evolutionary conservation. Thus, the most conserved subunits are required for the transcription of all developmentally regulated genes, whereas the least conserved subunits are relatively gene-specific.

Conaway *et al.* bring clarity to the previously confused subject of mammalian Mediator. This confusion was engendered by the isolation of human Mediators with different subunit compositions in different laboratories. Sophisticated proteomics and genomic analyses have now shown that, essentially, all human Mediators contain the same set of 30 subunits, and that these include homologues of 22 of the 25 yeast Mediator proteins (yeast Mediator defined as a 21-subunit complex and a reversibly associating four-subunit Med12–Med13–CDK8–CycC (or Srb8–Srb9–Srb10–Srb11) complex.

Malik and Roeder review the evidence for Mediator–activator and Mediator–pol II interactions, and discuss the implications for transcriptional activation and repression. The isolation of a mammalian Mediator–nuclear-receptor complex provided the earliest evidence of direct Mediator–activator interaction, and continued investigation in this system has given insights complementary with those from studies in *Drosophila*. Although mechanistic information is presently limited, there is reason to suggest that Mediator has multiple roles in the initiation of transcription.

Finally, Chadick and Asturias present the structures of Mediator and of a Mediator–pol II complex, as revealed by electron microscopy and image processing. Despite the low resolution of the analysis, important features are plainly apparent. Mediator is compact in the 'free' state and undergoes a remarkable conformational change to a crescent shape that largely envelops pol II in a transcription initiation complex.

These reviews not only complement but also overlap with one another, serving to emphasize points of general significance and wide interest. Taken together, the reviews provide the essential basis for thinking about the Mediator problem. It is from this basis that a complete picture of eukaryotic transcriptional regulation will eventually emerge.

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