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Mammalian Mediator as a functional link between enhancers and promoters

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Summary

In this issue of *Cell*, Casellas and colleagues provide insights into structural and functional aspects of the mammalian multisubunit Mediator complex, a conserved and essential transcriptional coregulator. Combining cryoEM, genetic and genomic analyses, the work sheds light on Mediator's mode of action as a functional bridge between enhancers and promoters.

The Mediator of transcription regulation (Mediator) was discovered more than 20 years ago in yeast and mammalian cells. This huge multisubunit complex is conserved in eukaryotes and is generally required for transcription by RNA polymerase (Pol) II (Soutourina, 2018). Human Mediator has been involved in many diseases, including different types of cancers and neurodevelopmental diseases. Structural and biochemical studies have revealed a modular and dynamic nature to the Mediator complex, which is composed of head, middle and tail modules, as well as a transiently-associated CDK8 kinase module. Recently, important advances have been made in understanding the yeast Mediator architecture (Nozawa et al., 2017; Robinson et al., 2016; Tsai et al., 2017). The head and middle modules constitute the Mediator essential core, whereas tail and CDK8 kinase modules have regulatory functions. To transmit regulatory signals, Mediator is recruited to enhancers (E) by interacting with transcription factors (TF) and it contacts the

transcriptional machinery including Pol II and other components of the preinitiation complex (PIC) assembled at core promoters (P) (**Figure**). Recent works in yeast emphasized a transient nature of Mediator association with core promoters and transcription components, providing evidence for different functionalities of Mediator modules (Jeronimo et al., 2016; Petrenko et al., 2016). Despite intensive work by many laboratories using yeast and mammalian models, many questions remain regarding the exact mechanism of action for this fascinating coregulator with compositional complexity and dynamics, conformational flexibility and a large number of interacting partners on the chromatin. In this issue of *Cell*, Casellas and colleagues (El Khattabi et al., 2019) provide important structural and functional insights into the mammalian Mediator's role as a functional bridge between enhancers and promoters using cryoEM, genetic, and genomic approaches (**Figure**).

Given that most of the previous structural data came from yeast models, one of the important advances of El Khattabi et al., is that it provides the cryoEM structure of mammalian Mediator at sub-nanometer resolution. A detailed structural analysis of subunit organization confirmed the remarkable similarity of the mammalian complex to the yeast core Mediator. Further investigations revealed interesting distinct features of mammalian Mediator, including a more extensive interface between core and tail modules involving metazoan-specific subunits. However, despite these new insights into the structure and mechanism of the core mammalian Mediator complex, many questions remain relating to Mediator complex interactions. Specifically, Mediator-Pol II contacts were only briefly addressed in this work and further details will be needed to understand this important interaction. Relatedly, future structural studies are needed to visualize how interactions between Mediator and its partners (for example, TFs) modulate the Mediator conformation. This will help to reveal how structural changes induced by different interactions could contribute to

Mediator function. Finally, the complex role of CDK8 kinase module needs also further investigation.

In addition to these structural insights, El Khattabi et al. provide an extensive genetic analysis of mammalian Mediator subunits in three mouse cell lines, providing unique tools for future work. This work unambiguously determined that most Mediator core subunits are essential, which is consistent with Mediator conservation in eukaryotes. Moreover, this analysis pointed out some differences between yeast and mouse cells and even between different mouse cell types that need to be further explored. Teasing apart the roles of Mediator modules in more detail, they show through genetic deletion that tail module subunits could modulate Mediator interactions with Pol II and the CDK8 kinase module. In addition to their genetic analysis, El Khattabi et al. use sophisticated degron-based constructions to deplete Mediator core subunits, showing that the full complex is required for Pol II recruitment genome-wide.

One of the key questions of the Mediator field has been to understand how Mediator, which is recruited to enhancers, can contact the transcription machinery and contribute to PIC assembly on core promoters that could be located at a considerable distance. A model of chromatin looping was proposed to explain how promoter-enhancer (P-E) proximity could be achieved. The present work directly addresses the question of whether Mediator is required for P-E contacts: El Khattabi et al. show that Pol II inhibition by α -amanitin leads to Pol II and Mediator vacating the chromatin without any impact on P-E proximity. By contrast, cohesin depletion leads to a decrease in the tethering of P-E pairs, consistent with the architectural role of cohesin in chromatin organization. The authors propose that Mediator and Pol II create a functional bridge between promoters and enhancers, but they are not absolutely required for P-E proximity. It might be interesting to consider further the previously reported physical interaction between Mediator and cohesin and

their genomic co-localization to clarify their potential cooperation. It should also be noted that Mediator still could have an architectural role in dynamic contacts, but dynamic chromatin contacts would be difficult to capture. Recent papers in yeast emphasize the dynamicity of Mediator composition and the transient nature of Mediator interactions with core promoters, suggesting Mediator dynamically links enhancer-bound activators and Pol II machinery assembled at the core promoter (Jeronimo et al., 2016; Petrenko et al., 2016). When a transient association of Mediator to core promoters was stabilized, by preventing Pol II promoter escape, a single Mediator complex was shown to bind to both enhancers and core promoters. This suggests that a Mediator, composed of all four modules including Cdk8 kinase module, associated with an enhancer transiently interacts with the PIC on core promoters through a loss of the Mediator kinase module. The exact molecular mechanisms whereby Mediator serves as a functional bridge between TFs and basal transcription machinery remain to be determined and are likely to be more complex than initially assumed. One potential mechanism is that the formation and dynamics of phase-separated condensates or membraneless compartments, which would include Mediator, regulate transcription (Boija et al., 2018; Cho et al., 2018; Sabari et al., 2018). It has been proposed that different TFs can interact with Mediator forming condensates involved in gene regulation, in particular at super enhancers, and that Mediator and Pol II associate within transcription-dependent condensates. The involvement of these condensates would mean that the effective P-E distance could be larger than the direct-contact distance. With the rapid progress in genomic and imaging approaches, it could be possible in the future to capture dynamic contacts within the chromatin and further specify the contribution of different factors in genome organization and transcription.

Figure legend

Mammalian Mediator as a functional bridge between enhancers and core promoters.

Schematics at the center represents the modular organization of the mammalian Mediator complex with 4 modules: a head module (in red), middle module (in yellow), tail module (in blue) and transiently-associated CDK8 kinase module (in green). The Mediator MED14 subunit, which links all three main modules (head, middle and tail), is indicated in orange. Subunits identified in the paper by Casellas and colleagues as essential for viability of 1, 2 or 3 mouse cell lines (T-, B- and Embryonic Stem cells) are highlighted with a corresponding number of asterisks. Metazoan-specific subunits are depicted by “s” with their module localization proposed by Casellas and colleagues. Mediator interacts with chromatin through transcription factors (TF) on enhancer regions (E) (the bottom of the Figure) as well as preinitiation complex (PIC) components including RNA polymerase II (Pol II) on core promoters (P) (the top of the Figure). Architectural proteins like cohesin create PE contacts (schematics on the left). To promote PIC assembly and to transmit the regulatory signals to basal transcription machinery, Mediator serves as a functional bridge (symbolized by a dashed line) between TF bound to enhancers and Pol II and other PIC components associated with core promoters. The exact molecular mechanisms of the Mediator mode of action remain to be determined.

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