A novel link of Mediator with DNA repair

Julie Soutourina* and Michel Werner

CEA; IBiTeC-S; FRE3377; Gif-sur-Yvette, France; CNRS; FRE3377; Gif-sur-Yvette, France; Univ Paris-Sud; FRE3377; Gif-sur-Yvette, France

Transcription is one of the key biological functions of the cell. A tight regulation of this process is extremely important for cell physiology. It is now generally accepted that a large protein complex, the Mediator of transcription regulation, is essential for eukaryotic transcription by RNA polymerase II (Pol II) in response to transcription activators.1 Unsurprisingly, Mediator has been implicated in numerous developmental processes and a number of human pathologies, including cancer. Since the discovery of Mediator more than 20 y ago, many studies have been realized on its fundamental role in transcription regulation. Our recent studies also contributed to understanding of the molecular mechanisms of Mediator coactivator function.2,3 A link of Mediator to the NER pathways, the transcription-coupled nucleotide-excision DNA repair (NER), our preliminary results suggested that Mediator-XPG contact is correlated with reduced Rad2 occupancy of class II genes and concomitant decrease of interaction with Rad2 protein. Considering the conservation of Mediator and Rad2/XPG in evolution, the molecular mechanisms governing the Mediator link with DNA repair is likely to be relevant for all eukaryotes. In support of this idea, our preliminary results suggest that Mediator-XPG contact is conserved in human cells. Our future study of the human Mediator connection to DNA repair might give insights into our understanding of human diseases like XP/CS syndromes.

We propose that Mediator facilitates Rad2/XPG recruitment to transcribed genes, setting the stage for rapid DNA lesion removal, and, thus, could function in transcription-coupled DNA repair. One of the interesting future directions consists in determining if Mediator is engaged in functional interplay with other NER factors and/or if Rad2/XPG assembles near transcription start sites with its NER partners to remove lesions on transcribed genes. Interestingly, both Mediator and Rad2/XPG are engaged in a complex interaction network with Pol II and TFIIH, one of the best-known factors implicated in both transcription and DNA repair. The mechanisms of functional orchestration of these contacts and their physiological significance remain to be investigated.

This work opens interesting perspectives on possible novel Rad2 functions, since our genome-wide analysis revealed that Rad2 is also enriched on Pol III-transcribed genes and telomeric regions. The presence of Rad2 on telomeric regions could be related or not to a recently proposed role of Mediator in telomere maintenance.

In conclusion, we propose an intriguing model that Mediator might play more roles in nuclear processes than previously assumed. This complex might serve as an assembly platform or a regulatory element linking transcription with DNA repair and, possibly, with other chromatin-related processes. Our findings open exciting perspectives for our understanding of the molecular mechanisms that connect transcription with DNA repair and that govern repair machinery recruitment. This work also illustrates that we are still far from a detailed understanding of Mediator functions and of functional

*Correspondence to: Email: julie.soutourina@cea.fr
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relationships between fundamental processes of life. There are further exciting discoveries and new concepts to come.

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Figure 1. Coactivator function of Mediator in RNA polymerase II transcription and a new role of this complex in transcription-coupled DNA repair by Rad2/XPG recruitment. Selected components of nuclear machineries are shown. Mediator interacts with specific activators (Act) and transmits regulatory signals to the Pol II transcription machinery. It also serves as a link between transcription and DNA repair via Mediator–Rad2/XPG interaction.