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A novel link of Mediator with DNA repair

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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 complex with DNA transactions beyond transcription remained to be uncovered. We have recently described a novel function of Mediator connecting transcription and DNA repair.[4]

The starting point for this study was the finding of an interaction between the Mediator Med17 subunit and the Rad2 DNA repair protein. Mutations in human XPG gene, homologous to the yeast *Saccharomyces cerevisiae RAD2* gene, give rise to a xeroderma pigmentosum (XP) sometimes associated with Cockayne syndrome (CS). Rad2/XPG is implicated in nucleotide-excision DNA repair (NER), the process that removes DNA lesions arising upon UV irradiation.[5] One of the NER pathways, the transcription-coupled repair, is specific to the transcribed strand of genes.[6] Undoubtedly, maintenance of genome integrity is a prerequisite for proper cell function and of prime clinical importance for major human diseases.

What is the functional meaning of this Mediator–Rad2 contact? The two following hypotheses could be considered: Mediator might play a role in DNA repair by loading Rad2/XPG to active genes, and/or Rad2/XPG could be implicated in transcription. A transcriptional role for the NER factor Rad2/XPG has been previously suggested in yeast and more recently proposed in human cells on some nuclear receptor (NR)-dependent genes.[7,8] In spite of our efforts, we did not obtain any evidence for a major implication of this protein in yeast transcription. At this stage, it remains to be determined if XPG is important exclusively for transcription activation of NR-dependent genes and/or eventually for whole-genome transcription in mammalian cells. Based on functional genomics, molecular biology, and yeast genetics, we provided strong evidence that Mediator is involved in DNA repair through a functional link with Rad2/XPG protein, revealing a previously unknown role of the Mediator complex (**Fig. 1**). Genome-wide analysis shows that Rad2 is located on Pol II-transcribed genes, and that Rad2 occupancy of class II gene promoters is well correlated with that of Mediator. Furthermore, Mediator *med17* mutants are UV-sensitive, and this UV sensitivity 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

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relationships between fundamental processes of life. There are further exciting discoveries and new concepts to come.

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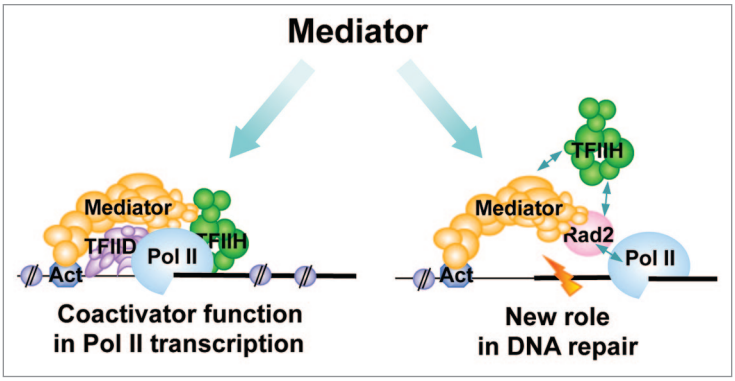

Figure 1. Coactivator function of Mediator in RNA polymerase II transcription and a new role of this complex in transcription-coupled DNA repair by Rad2/XPG recruitment. Selected components of nuclear machineries are shown. Mediator interacts with specific activators (Act) and transmits regulatory signals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