Interaction between DNA polymerase ι and Rad23 provides a link between DNA damage tolerance and DNA repair pathways

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DNA damage is caused by variable environmental agents such as UV radiations resulting in bulky DNA adduct which is eliminated through Nucleotide excision repair (NER) pathway. Recognition of the altered gene is the first step in this repair process, which involves a recognition complex formed by xeroderma pigmentosum complementation group C (XPC) protein and one of the Rad23 proteins (either Rad23A or Rad23B). The later steps of NER reaction includes preferential binding of XPC-Rad23 complex to the UV-damaged DNA followed by successive recruitment of other NER components to the lesion.

Here, we report that Rad23A and Rad23B can directly interact with DNA polymerase iota (Pol ι), a member of the DNA damage tolerance pathway. Pol ι is a low-fidelity translesion synthesis DNA polymerase, an emergency mutagenic polymerase, which is capable of DNA replication across DNA lesions. Using solution NMR spectroscopy, we show that Ubiquitin Associated Domains (UBA) of Rad 23A and Rad23B effectively interact with the DNA-binding domain of Pol ι with micromolar affinity. Chemical shift perturbation assays reveal the precise Pol ι binding interface on the surface of UBA1 and UBA2 domains of Rad23A. Interestingly, the resulting NMR mapping suggests that the Pol ι interface overlaps with the known ubiquitin-binding interface of UBAs. Indeed, further binding competition experiments show that ubiquitin can effectively disrupt Pol ι/Rad23A complex by competing with Pol ι for Rad23A UBA1 and UBA2 binding.

Other translesion synthesis DNA polymerases including Pol η, and Pol κ and Rev1 share a DNA-binding domain homologous to Pol ι, suggesting that they all may interact with Rad23 proteins in a similar manner. These results suggest that ubiquitin signaling plays an important role in switching between NER and DNA damage tolerance pathways.

Thursday, September 21, 2023
10:00 AM (UTC-05:00) Eastern Time (US & Canada) | Virtual seminar
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