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Mini review

XPA: A key scaffold for human nucleotide excision repair

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ABSTRACT

Nucleotide excision repair (NER) is essential for removing many types of DNA lesions from the genome, yet the mechanisms of NER in humans remain poorly understood. This review summarizes our current understanding of the structure, biochemistry, interaction partners, mechanisms, and disease-associated mutations of one of the critical NER proteins, XPA.

Contents

Abbreviations: NER, nucleotide excision repair; *XP*, *Xeroderma pigmentosum*; TFIIH, transcription factor II H; RPA, replication protein A; WT, wild type; FL, full-length; AAF, *N*-(deoxyguanosin-8-yl)-2-acetylaminofluorene; (6-4)PP, (6-4)photoproduct; CPD, cyclobutane pyrimidine dimer; DDB, damaged DNA-binding protein; CAK, cyclin-activated kinase; TTD, trichothiodystrophy; PCNA, proliferating cell nuclear antigen; APIM, AlkB homolog 2 PCNA interacting motif; NLS, nuclear localization signal.

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1. Introduction

Nucleotide excision repair (NER) is the primary pathway for the repair of a wide range of bulky DNA adducts, such as those formed by UV irradiation, environmental toxins and certain anti-tumor agents [1–3]. The protein XPA is believed to play a key role as a scaffold that organizes the damaged DNA and other proteins to ensure lesions are appropriately excised. Defects in NER can result in the genetic disorder *Xeroderma pigmentosum* (*XP*) [4–7]. *XP* is characterized by extreme sensitivity to sunlight and very high rates of skin cancer [4,6], with the most severe cases displaying neurological degeneration with loss of mental and sensory faculties [4,8–10]. The association of XPA mutants with the most severe clinical *XP* symptoms underscores the critical role of this protein in NER.

Substantial progress has been made in elucidating the mechanisms of NER in prokaryotes, but understanding of human NER has lagged behind due to the lack of conservation of proteins and complex regulation of the ~30 proteins involved [11]. NER occurs in coordination with transcription (transcription coupled (TC) NER) and more generally throughout the genome (global genome (GG) NER). Once the presence of damage is recognized, a series of protein factors are recruited to verify the presence of damage, cleave the damaged nucleotide 5′ and 3′ of the lesion, fill in the gap using the undamaged strand as template, and seal the resulting gap.

XPA is involved in both TC-NER and GG-NER; the other proteins involved and their roles in these two sub-pathways are described elsewhere [12–24]. In both pathways, XPA is recruited to the damage site by the transcription factor II H (TFIIH) complex that is responsible for unwinding double-stranded DNA around the damaged nucleotide creating the NER bubble. XPA is generally understood to function in damage-verification and assembly of NER incision complexes [1,25–27]. XPA is recruited at the same time, and functions in coordination with, the eukaryotic ssDNA binding protein replication protein A (RPA). Together, they help recruit and properly position the excision nucleases. RPA binds to the undamaged single strand, suggesting that XPA interacts with the damaged strand [19,20]. However, XPA prefers to bind ss-dsDNA junctions and duplexes with overhangs. Although XPA has been studied for >20 years, several key questions remain about its function, including: (1) What is the structural basis of XPA interaction with protein binding partners and how does this lead to their positioning within the complex? (2) Is XPA involved in pathways other than NER? (3) How do different XPA mutations relate to NER outcomes and disease phenotypes? In the following sections, we highlight current knowledge of the interactions of human XPA with DNA, other NER proteins and proteins outside of NER, and the relationship between XPA mutants and *XP* disorders. In the last section, we discuss future directions for XPA studies that can enrich our understanding of NER and *XP* disorders.

2. XPA structure and interactions with DNA

XPA is a modular protein whose primary function is mediated through its interaction with the NER bubble. The DNA binding apparatus of XPA has been mapped to its globular central domain [28,29], but the molecular details of how XPA is engaged on the NER bubble have yet to be established. Mutations in the DNA binding region are associated with the most severe symptoms of *XP* patients, including accelerated aging and neurodegeneration, suggesting the importance of XPA-DNA interaction [30]. However, since some protein interactions also map to this region, understanding the molecular basis of the malfunctions of disease-associated mutations in this region requires a more complete understanding of XPA-DNA interactions in the context of its protein interactions in NER complexes.

2.1. XPA structure

XPA is a relatively small 273 residue protein that does not possess enzymatic activity but interacts with many other NER proteins, consistent with its role as a scaffold. A domain map of XPA is shown in Fig. 1. XPA is organized around a central globular domain ($XPA_{98–219}$). 3D structures of this domain were determined inde-

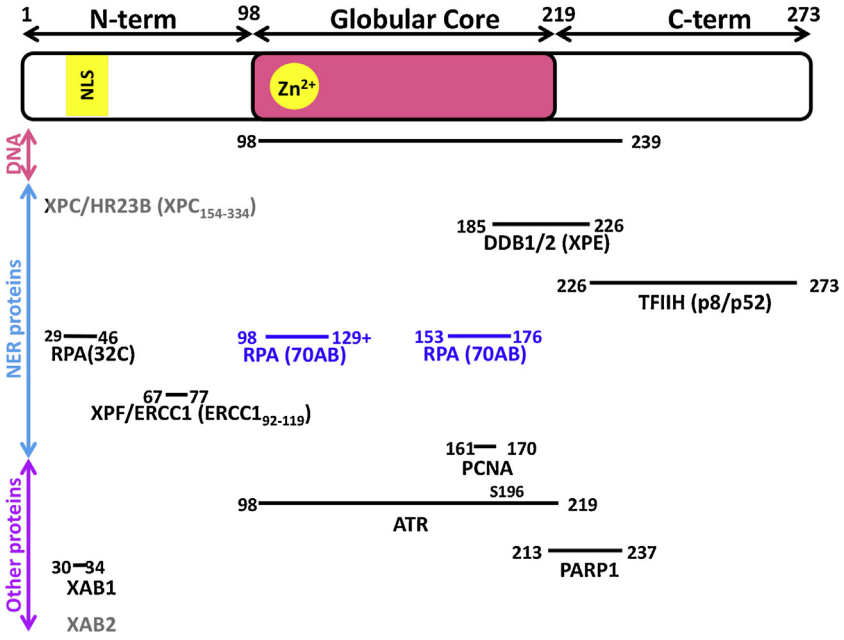

Fig. 1. Domain map of XPA and interaction partners. Schematic domain structure of human XPA protein (top). The region containing the globular core is colored pink, with the location of the Zn finger indicated as a yellow circle. The nuclear localization signal (NLS) is colored yellow. The N- and C-termini are dynamically disordered. Known interaction partners are shown below the domain map, aligned with the XPA residues involved in each interaction. Gray proteins are those known to interact with XPA but for which the sites of interaction have not been determined. Blue indicates a binding partner for which the binding sites on XPA remain controversial. If known, the domain or residues involved in XPA binding are given in parenthesis.