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Review

HMGB1: Roles in base excision repair and related function

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ABSTRACT

High mobility group box 1 (HMGB1) is a nonhistone architectural protein that is involved in many biological processes including chromatin remodeling, transcription, cell signaling of inflammation, DNA damage repair and others. Recent studies have identified the cross-link of HMGB1 with a DNA base excision repair intermediate indicating that this protein is involved in base excision repair (BER) pathway. Further characterization of the roles of HMGB1 in BER demonstrates that the protein acts as a cofactor to regulate BER sub-pathways by inhibiting single-nucleotide BER and stimulating long-patch BER through modulating the activities of base excision repair enzymes. Directing of base lesion repair to the long-patch sub-pathway can result in trinucleotide repeat instability suggesting an important role of HMGB1 in modulating genome stability.

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1. Introduction and background

High mobility group box 1 protein (HMGB1) belongs to the family of the high mobility group (HMG) nuclear proteins. It is an abundant nonhistone chromosomal protein with a concentration of 10^6 per cell [1]. The HMGB1 protein contains an N-terminal Box A domain, a central Box B domain and C-terminal acidic tail (Fig. 1) [2,3]. The HMGB1 Box A and B domains contain 80 to 90 basic amino acids and share ~30% identity in their amino acid sequences. The C-terminal acidic tail contains ~30 consecutive aspartate and glutamate residues [4]. It has been found that the HMGB1 Box A domain is responsible for HMGB1 binding to DNA damage [5], whereas the Box B exhibits pro-inflammatory activities, in addition to DNA binding [6]. The acidic tail of HMGB1 is involved in regulating DNA binding and DNA damage repair [7,8].

Structural studies have revealed that both Box A and Box B domains contain three alpha-helices, named helix I, helix II and helix III and two loops, loop I and loop II [5,9]. These domains adopt a unique "L" shape structure that has two arms of 31 and 36 Å in length, respectively, in the case of the rat HMGB1 Box B domain (Fig. 1) [9]. The short arm contains helix I and helix II. The long arm consists of helix III and an N-terminal unstructured segment in parallel with the helix (Fig. 1). The "L" shape structure of the HMGB1 Box B domain is maintained by a cluster of highly conserved amino acid residues that are located in the junction between the two arms (Phe14, Phe17, Trp45, Lys53 and Tyr56) (Fig. 1). The conserved basic residues (Lys26, Lys39 and Arg22 etc.) are mainly distributed around the concave surface in between the two arms, indicating that they may be involved in DNA binding (Fig. 1). These residues may allow the concave surface to contact with the minor groove of double-strand DNA. Interestingly, it has been found that HMGB1 Box A domain also can bind to the DNA minor grove by intercalating the aromatic side chain of Phe37 at helix II into a hydrophobic cleft between two base pairs induced by DNA damage such as cisplatin cross-linking (Fig. 1) [5]. This results in the bending of the DNA duplex towards the major groove by 61° indicating that HMGB1 can induce a significant change in DNA structures.

The intrinsic capacity of HMGB1 for altering DNA structures allows it to participate in many biological processes [10–12]. These include regulation of chromatin structure [13], transcription [14], DNA damage repair and recombination [12]. HMGB1 also has been shown to participate in inflammation by acting as an inflammatory signal transducer [15]. The importance of HMGB1 in DNA damage and repair was initially identified in studies that revealed the ability of HMGB1 to bind to a variety of bulky DNA lesions induced by chemotherapeutic agents such as cisplantin [5], psoralen combined with UVC [16,17], as well as environmental carcinogens such as acetylaminofluorene [18] and UVC [19]. Cellular and genetics studies also demonstrated that mammalian HMGB1 and its yeast homologue were critical for maintaining genome stability [20]. Since DNA damage is one of the mechanisms that cause genome instability, this study further suggests that HMGB1 might participate in DNA repair toward maintaining genome stability. Recent cell biology and biochemical studies indicated that HMGB1 is actively involved in modulating the efficiency of all four major DNA repair pathways, i.e., nucleotide excision repair (NER) [21,22], base excision repair (BER) [23], mismatch repair [24] and double strand break repair and nonhomologous end-joining [25,26].

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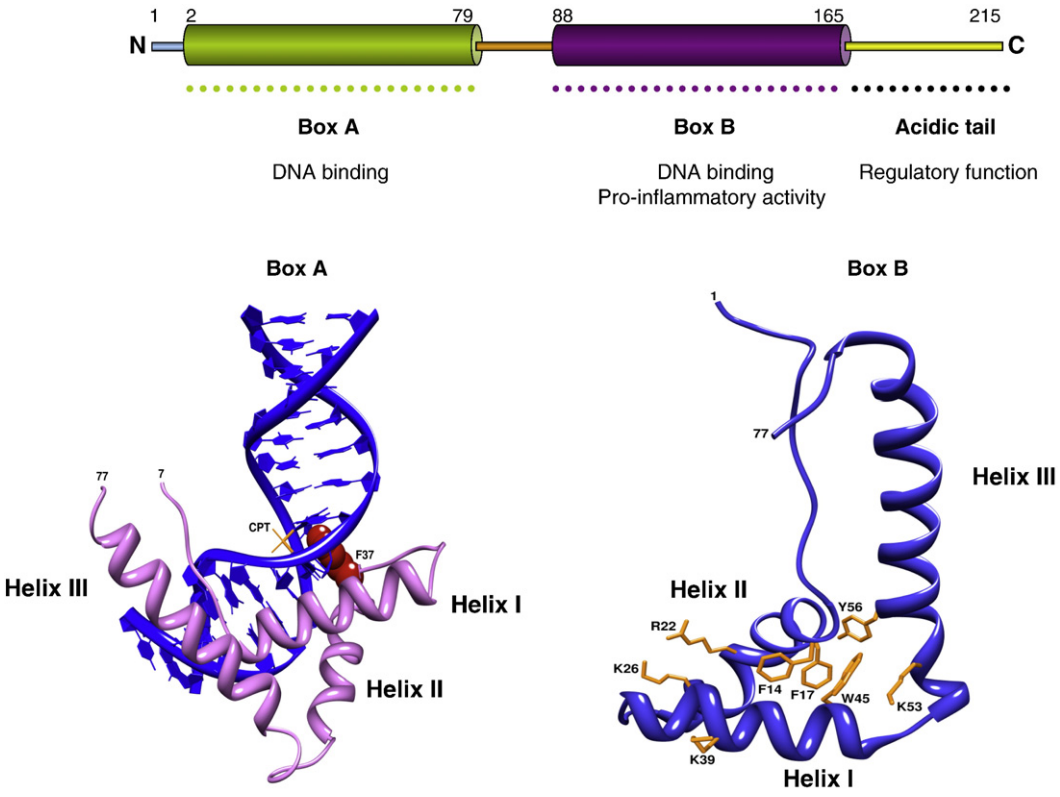

Fig. 1. Structures f HMGB1 protein domains. Tertiary structures of HMGB1 Box A-DNA and Box B were produced according to published data [5,9] using Chimera [58].

The mechanisms by which HMGB1 modulates DNA repair are still not well understood and are under intensive study. It has been found that HMGB1 binds to DNA lesions based on specific structure recognition and bends DNA [5]. This allows HMGB1 to modulate interactions between repair proteins and lesion-containing DNA [22] thereby affecting damage repair efficiency [8,22,27,28]. Since many DNA damage recognition proteins bind to lesions within distorted DNA much tighter than in normal B-form DNA [29], it is expected that HMGB1-induced DNA bending would facilitate damage recognition. However, the effects of HMGB1 on DNA repair are more complex than the DNA-bending model suggests and also may depend on the type of lesion being processed. For example, in the nucleotide excision repair pathway, it was shown that binding of HMGB1 to DNA cross-link damage induced by (2*R*, 3*R*)-diaminobutanedichloroplatinum (II) blocked the accessibility of the damage to NER proteins, resulting in inhibition of repair [28]. In contrast, HMGB1 binding to triplex-directed psoralen DNA interstrand cross-links (ICLs) facilitated the NER of these lesions [16,22].

HMGB1 also may modulate DNA repair efficiency by directly interacting with repair enzymes and cofactors [12,17]. Interaction between HMGB1 and replication protein A (RPA) resulted in formation of a HMGB1-RPA-psoralen DNA ternary complex that was proposed to help in the recruitment of NER proteins to damaged sites [16]. Moreover, HMGB1 can form a protein-DNA ternary complex with XPC-RAD23B and RPA simultaneously [17], suggesting that HMGB1 may coordinate damage recognition by these repair proteins thereby accelerating NER. In mismatch repair pathway, HMGB1 was shown to play a role in the initial mismatch recognition and incision steps by interacting with mismatch proteins such as MSH2 and MLH1 [24]. In addition, HMGB1 can substitute for the function of RPA to mediate the excision step of exonuclease 1 [30]. *In vitro* studies also identified HMGB1 stimulatory effects on DNA-PK and Ku proteins by interacting with and targeting these proteins to the ends of double-strand DNA breaks; these HMGB1 interactions facilitated damage repair [31]. In addition, HMGB1 was found to be involved in modulating nonhomologous end joining and V(D)J recombination by interacting with the key repair proteins in these pathways such as RAG proteins [32,33] and DNA ligase IV [34]. Recently, we discovered a new role of HMGB1 in that it stimulates DNA base excision repair through its interaction with BER enzymes [23].

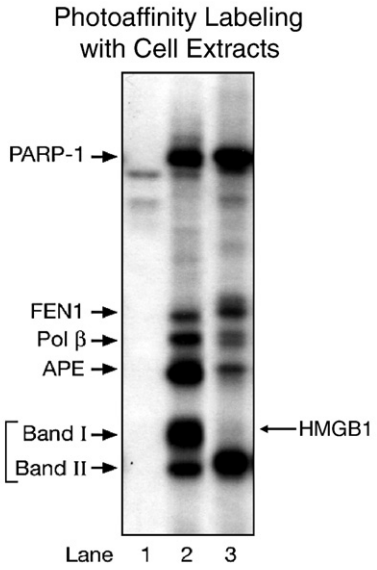

Fig. 2. Photoaffinity labeling of HMGB1 in cell extracts (from [23], Fig. S2). (A) Diagram of BER intermediate with radiolabeled uracil and the scheme of enzymatic reactions. (B) $NaBH_4$ cross-linking of proteins in various cell extracts with the substrate treated by UDG.