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Review

The ubiquitin receptor Rad23: At the crossroads of nucleotide excision repair and proteasomal degradation

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ABSTRACT

A protein that exemplifies the intimate link between the ubiquitin/proteasome system (UPS) and DNA repair is the yeast nucleotide excision repair (NER) protein Rad23 and its human orthologs hHR23A and hHR23B. Rad23, which was originally identified as an important factor involved in the recognition of DNA lesions, also plays a central role in targeting ubiquitylated proteins for proteasomal degradation, an activity that it shares with other ubiquitin receptors like Dsk2 and Ddi1. Although the finding that Rad23 serves as a ubiquitin receptor explains to a large extent its importance in proteasomal degradation, the precise mode of action of Rad23 in NER and the possible link with the UPS is less clear. In this review, we discuss our present knowledge on the functions of Rad23 in protein degradation and DNA repair and speculate on the importance of the dual roles of Rad23 for the cell's ability to cope with stress conditions.

Contents

Abbreviations: CS, Cockayne syndrome; DUBs, deubiquitylation enzymes; ER, endoplasmic reticulum; ERAD, ER-associated degradation; GGR, global genomic NER; hHR23, human homologue Rad23; mHR23, murine homologue Rad23; NER, nucleotide excision repair; TFIIH, transcription factor II H; TTD, trichothiodystrophy; UBA, ubiquitin-associated domain; UBD, ubiquitin binding domain; UbL, ubiquitin-like domain; UIM, ubiquitin-interacting motif; UFD, ubiquitin fusion degradation; UPS, ubiquitin/proteasome system; UV, ultraviolet; XP, xeroderma pigmentosum.

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1. Introduction

1.1. Nucleotide excision repair (NER)

Cells are inevitably exposed to intrinsic and extrinsic agents that inflict damage to their genomic content [1]. To maintain the integrity of their genomes, cells are equipped with a number of sophisticated repair machineries that identify and restore damaged DNA. One of the extrinsic conditions that pose a threat to the stability of genomic DNA is ultraviolet (UV) light. NER is a versatile and highly conserved process that is responsible for the identification and removal of helix-distorting DNA lesions. Since the majority of lesions that are removed by NER, such as cyclobutane pyrimidine dimers (CPDs) and 6–4 photoproducts (6–4PP), are caused by shortwave UV light, NER is an important defence mechanism that protects against sunlight-inflicted DNA damage [1]. It is therefore not surprising that mutations in genes encoding proteins involved in NER are linked to the inheritable syndrome xeroderma pigmentosum (XP), which gives rise to symptoms such as extreme UV sensitivity of the skin and a strong predisposition for the development of malignant skin tumors [2]. In addition to the human homologues of Rad23 (hHR23) A and B, the proteins encoded by the *XPA, XPB, XPC, XPD, XPE(DDB2)*, *XPF* and *XPG* genes are involved in NER. Mutations in some of these genes (i.e. *XPB, XPD* and *XPG*) are not only linked to XP but also give rise to combined features of XP and Cockayne syndrome (CS), whereas other mutations in the transcription factor II H (TFIIH, i.e. *XPB*, *XPD* and *TTDA*) cause trichothiodystrophy (TTD). Patients suffering from CS or TTD display, besides UV sensitivity, also severe neurological aberrations and premature aging [2,3].

The sequence of events that results in repair of photolesions can be roughly divided in four distinct steps: recognition, unwinding, incision and repair synthesis (Fig. 1). Helix-distorting lesions in mammalian cells are, in the case of global genomic NER (GGR), directly recognized by the DNA binding protein XPC [4], which is found in complex with hHR23A or B [5], and operates in concert with a cullin 4A-based ubiquitin ligase that includes the subunit DDB2/XPE [6,7] (Fig. 1, left panel). Lesion recognition is followed by the successive recruitment of XPA, RPA and the TFIIH transcription/repair complex, which includes the DNA helicases XPB and XPD, responsible for unwinding the DNA [8,9]. Finally, the endonucleases XPG and XPF/ERCC1 are required for the excision of a 25–30 nucleotide long patch of single-stranded DNA including the helix-distorting lesion [10]. Repair synthesis of the removed strand by DNA polymerase followed by ligation executes the final steps of a processive DNA polymerase [11].

NER is a highly conserved, versatile DNA repair mechanism that can deal with a broad variety of lesions, including UV light-inflicted DNA damage. A large number of genes that are required for resistance to DNA damaging agents have been identified in the budding yeast *Saccharomyces cerevisiae* [12]. Among these, several Rad (for *Rad*iation sensitive) genes are involved in UV resistance and display striking similarities with human XP genes (Fig. 1, right panel). Notably, Rad4, the yeast ortholog of human XPC, is involved in

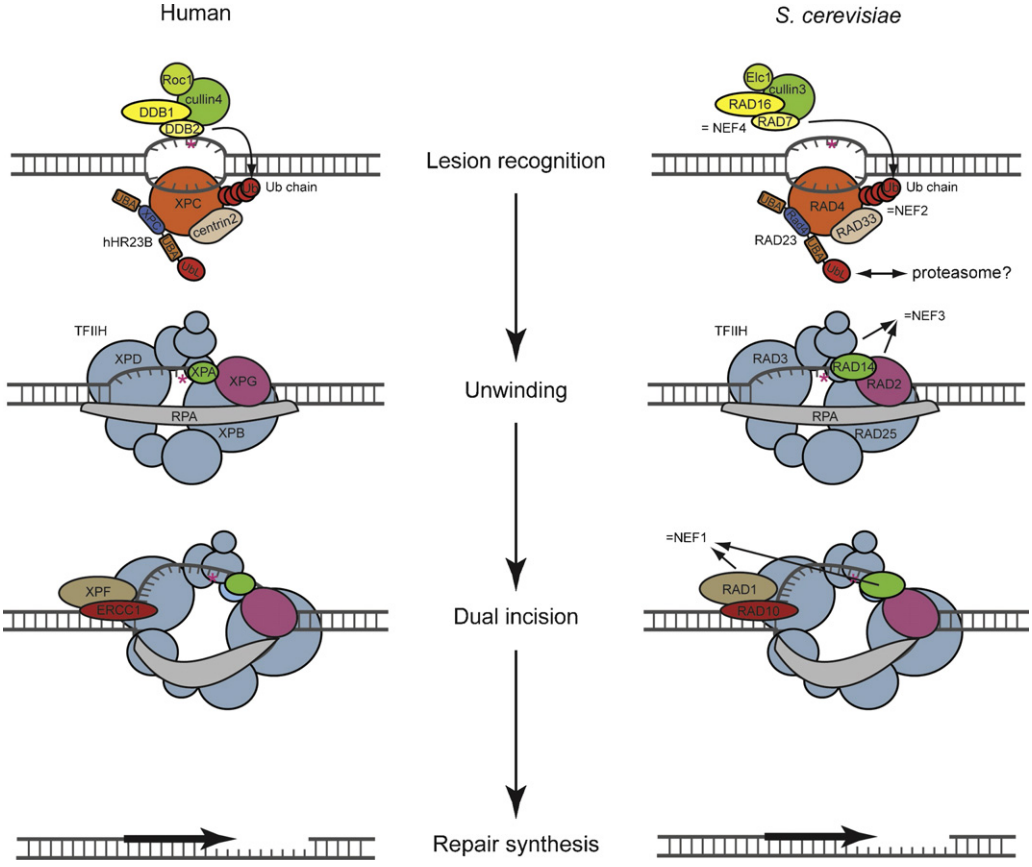

Fig. 1. Schematic representation of GGR in mammalian cells (left panel) and budding yeast (right panel). The process can be divided in the recognition, unwinding, incision and repair synthesis steps. The XP proteins (mammalian cells) and Rad proteins (yeast) involved in each of the steps are shown. For yeast, the complexes NEF1–4 are also indicated. Briefly, helix-distorting lesions are recognized by XPC (mammalian cells) and Rad4 (yeast), which are in complex with hHR23/Centrin and Rad23/Rad33 (Rad4/Rad23 = NEF2), respectively. The unrelated ubiquitin ligases DDB1/DBB2(XPE)/Cullin4/Roc1 (mammalian cells) and Rad7/Rad16/Cullin3/Elc1 (Rad7/Rad16 = NEF4) (yeast) ubiquitylate XPC and Rad4, respectively. This results in the recruitment of XPA, XPG, TFIIH (including XPB and XPD) (mammalian cells) and Rad14, Rad2, TFIIH (including Rad25 and Rad3) (Rad2/TFIIH = NEF3) (yeast). RPA binds the single-stranded DNA opposite to the lesion. Finally, XPF/ERCC1 (mammalian cells) and Rad1/Rad10 (yeast) are bound to the lesion (Rad1/Rad10/Rad14 = NEF1). For more details see Sections 1.1 and 3.2.