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ADDENDUM

A unified model for the molecular basis of *Xeroderma pigmentosum*-Cockayne Syndrome

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Nucleotide Excision Repair (NER) is a pathway that removes lesions distorting the DNA helix. The molecular basis of the rare diseases *Xeroderma pigmentosum* (XP) and Cockayne Syndrome (CS) are explained based on the defects happening in 2 NER branches: Global-Genome Repair and Transcription-Coupled Repair, respectively. Nevertheless, both afflictions sporadically occur together, giving rise to XP/CS; however, the molecular basis of XP/CS is not understood very well. Many efforts have been made to clarify why mutations in only 4 NER genes, namely *XPB, XPD, XPF* and *XPG*, are the basis of this disease. Effort has also been made to unravel why mutations within these genes lead to XP, XP/CS, or other pathologies. We have recently contributed to the disclosure of this puzzle by characterizing Rad3/XPD mutations in *Saccharomyces cerevisiae* and human cells. Based on our, and others', observations, we propose a model compatible with all XP/CS cases and the current bibliography.

Keywords: Cockayne Syndrome, CAK, nucleotide excision repair (NER), Rad3/XPD, XPG, XPB, *Xeroderma pigmentosum*

Abbreviations: CS, Cockayne Syndrome; NER, Nucleotide Excision Repair; ssDNA, single stranded DNA; dsDNA, double stranded DNA; GGR, Global Genome Repair; TCR, Transcription-Coupled Repair; XP, *Xeroderma pigmentosum*; HR, Homologous Recombination; *rem*, *re*combination and *m*utation; CAK, Cyclin-Activated Kinase; UV, Ultraviolet Light; DSB, Double Strand Break.

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Introduction

Xeroderma pigmentosum (XP) and Cockayne syndrome (CS) are rare autosomal inherited recessive disorders. XP is characterized by cutaneous symptoms because of exposure to sunlight, pigmentation abnormalities, skin atrophy and a high incidence of skin cancer (up to 10000-fold increase)[1] and mucous membrane cancer due to the defect in repair of UV- or carcinogen-induced lesions. About 20% of XP patients also display neurological defects that could be explained by neuronal degeneration caused by defects in repair of oxidative damage in the brain region. CS patients display severe growth failure and neurological dysfunction due to demyelization, as well as cachectic dwarfism, ocular abnormalities, sensorineural deafness, dental cavities, microcephaly, skeletal abnormalities, intracranial calcification and mental retardation (For a review see refs.2, 3). In addition, there is a small group of patients that exhibits XP/CS, a combination of clinical symptoms of the 2 diseases.

At the cellular level, the XP and CS conditions are both associated with defects in Nucleotide Excision Repair (NER). This highly orchestrated repair mechanism detects helical distortions as well as DNA thermodynamic destabilizations, signaling them as DNA lesions by specialized proteins. This drives the binding of a protein complex named TFIIH, which allows DNA unwinding, damaged DNA strand recognition and recruitment of specific nucleases that excise the damaged DNA segment. Finally, DNA synthesis fills the remaining single-stranded DNA (ssDNA) gap. The XP molecular basis is explained by defects in Global-Genome Repair (GGR), in which lesions are recognized all over the genome, whereas the molecular basis of CS has been classically explained by defects in Transcription-Coupled Repair (TCR), a NER subpathway in which the lesions are encountered and signaled by the elongating RNA polymerase II, and thus more efficiently repaired in the transcribed DNA strand.[4]

The XP/CS paradox

A dysfunction exclusively associated with NER during transcription, as that linked to CS without XP manifestation, is due to defects in the proteins CSA and CSB that recognize the lesion at the transcribed site and promote the recruitment of the rest of the NER proteins. However, there are mutations in the *XPB, XPD, XPF* or *XPG* genes associated with either XP-only or XP/CS syndromes. On top of that, all mutations described for *XPA* only confer XP syndrome. Since all the mentioned factors are important for the same repair pathway, it becomes difficult to dissect the molecular basis of XP/CS.

The characterization of a particular subset of mutants of the yeast *Saccharomyces cerevisiae* has proven useful to start understanding this puzzle.[5] We have further worked with mutations of the Rad3/XPD helicase, central to the above-mentioned TFIIH complex. This helicase hydrolyses ATP to open the DNA around the NER lesion so that it can be removed. However, TFIIH also has a fundamental role in the initiation of transcription, since it allows promoter opening *via* another helicase, Rad25/XPB, and promotes RNA polymerase escape to start elongation.[6] The latter function is achieved by the kinase activity of the CDK Activating Kinase (CAK), a subcomplex of TFIIH. In transcription, the Rad3/XPD role is strictly structural, serving to bridge the CAK with the rest of the complex.[6,7] Fundamentally, *rad3* mutants can be ascribed either to those being highly UV-sensitive, because of a NER defect, and those bearing transcription initiation problems, due to a defect in the TFIIH assembly. We have used a battery of *rad3* mutants whose main feature was none of the above: irrespective of their UV sensitivity and without any apparent transcription defect, they require for survival an *a priori* unrelated DNA repair system, homologous recombination (HR), to be intact. These *rad3* mutants are named *rem* (for increased *re*combination and *m*utation levels)[8] and they all share the feature of harbouring their mutation in the ATP-binding groove of the protein.[9] This fact was highly intriguing since all reported XP/CS patients linked to an XPD deficiency bear their mutations within this same domain.

To understand the molecular defect occurring in these mutants we envision the ATPase activity of Rad3 during NER as 2 sides of a coin: it becomes critical for its helicase ability, but it conditions affinity of the protein for ssDNA[9] (**Fig. 1**). On this premise, when the mutations in the ATP-binding groove affect it so dramatically that no helicase activity at all can be exerted, the DNA will remain unwound and the TFIIH complex harbouring the mutant Rad3 will float away leaving the lesion unrepaired.[10] This should lead to high UV sensitivity, that is, mimicking an XP phenotype. On the contrary, if the mutation has a weak effect that allows DNA melting, once bound, it will promote a stronger binding of the TFIIH complex to the opened DNA.[5] This scenario will not only allow damage excision (at least to a certain extent) but it will affect the on-time recruitment of the DNA synthesis machinery,[11] leaving a long-lasting ssDNA repair intermediate. In non-cycling cells this may lead to extensive resection of the processed DNA strand, subsequent accumulation of ssDNA and therefore genetic instability.[12] In dividing cells, the ssDNA gap would be converted into a double strand break (DSB) when an incoming replication fork hits the unfinished NER intermediate.[5] This replication-born DSB requires repair via HR. In addition, the longer persistence of the TFIIH complex at the damaged sites would prevent it from performing new rounds of transcription initiation at promoters, explaining why transcription defects may arise after DNA damage. Altogether, this cascade of events would explain an XP/CS-like phenotype. In this view, the transcription-related defects would be TCR-independent, and therefore serve to explain the paradox presented above. Our model is in agreement with recent findings in various different models: recreation of mutations in the ATP-binding groove of *Sulfolobus acidocaldarius* XPD leads both to a loss of helicase activity and a gain of affinity for ssDNA;[13] in mice, an XP-D/CS-mimicking mutation has been shown to provoke an unfinished NER intermediate that leads to extensive

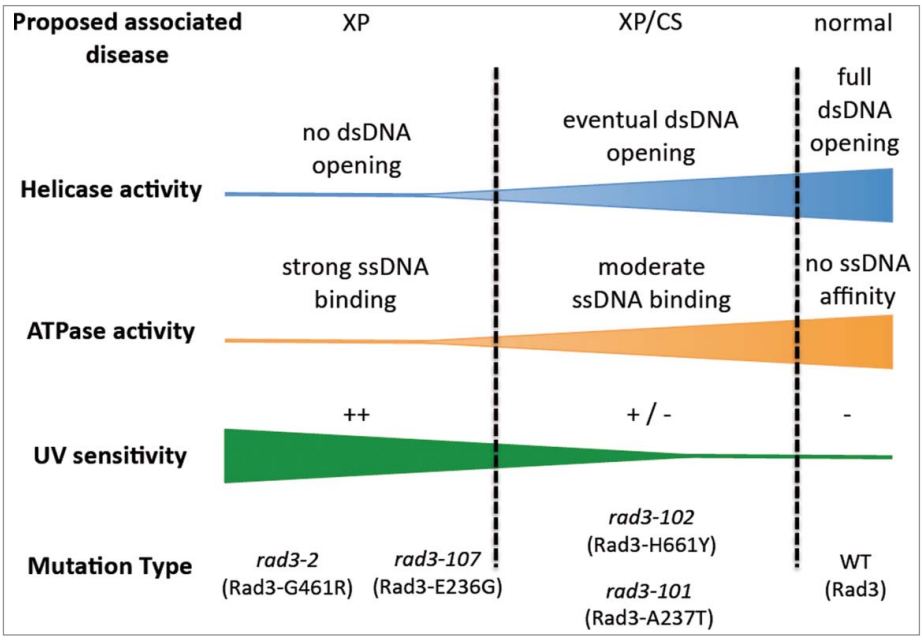

Figure 1. Proposed molecular defects in *Rad3* ATP-binding groove mutants that may help understand XP/CS. The severity of the ATPase defect of *rad3/XPD* mutants would correlate with both its incapacity of DNA bubble opening and its ssDNA affinity. Mutants more affected were presumed to be the most UV-sensitive, *rad3–2* and *rad3–107*, whereas *rad3–101* and *rad3–102* would display an intermediate defect, thus allowing eventual opening of the damaged DNA and a major permanence of the TFIIH complex at the DNA.

accumulation of ssDNA and subsequent transcription inhibition;[14] in XP-D/CS patients cells, the inhibition of transcription after UV is not general but only affects those genes whose promoters were specifically abandoned by TFIIH in response to the damage. Moreover, this correlates with heterochromatinization of the same promoters, tentatively because the retour of the complex is delayed.[15] A gradient of phenotypes is expected considering that different mutations in the ATP-binding groove of Rad3/XPD will confer different degrees of helicase inactivation and different levels of gain of affinity for ssDNA, which would explain the various outcomes in the distinct patients.

CAK dissociation from TFIIH as a marker of XP/CS

One of the approaches we have undertaken in order to obtain some idea of the molecular basis of XP/CS has been Fluorescence Recovery After Photo-bleaching (FRAP) in *S. cerevisiae Rad3* ATP-binding groove mutants.[9] After UV irradiation, the percentage of the fluorescence in the bleached area that cannot be recovered indicates the fraction of TFIIH that is engaged somewhere else performing repair. The time in which the given recovery is achieved is proportional to the molecular weight of the complex being analyzed.[16] When the latter quantification was done (by plotting the data relative to a normalized maximum value), we perceived differences in the slopes among the various strains, indicative of faster TFIIH mobility in the mutants down to reaching the WT situation, in which mobility was the slowest[9] (**Fig. 2**). The TFIIH mobility curve, expressed as the mean of the different states of association of a protein with its different partners, had indeed been characterized for a given TFIIH protein.[17] In these assays, the steepest slope would mean a higher fraction of assembled TFIIH complexes with lower molecular weight (*rad3–2* mutant (Rad3-G461R)). Still lower TFIIH molecular weight within the total TFIIH population would show up in the other mutants (with intermediately steep slopes), while the amount of TFIIH low molecular weight would be minimal in the WT strain (**Fig. 2**). Interestingly, the module whose dissociation would diminish low molecular weight TFIIH could be the CAK subcomplex. The CAK subcomplex is released from the core TFIIH during NER, which is known to stimulate incision and repair of damaged DNA, while its re-association does not occur until resumption of transcription.[18]

A relevant consequence of having an excess of free CAK is an alteration in cell cycle progression, since many key proteins controlling cell cycle stages are targets of the CAK kinase Cdk7.[19] Thus, in *Drosophila* embryos, excess of XPD titrates CAK activity resulting in defects at mitosis, while down regulation of XPD leads to an excess of free CAK and a burst in proliferation.[20] In agreement, the yeast mutants *rad3–102* (Rad3-H661Y) and *rad3–2* show faster entry into the S-phase.[5, 21] Altogether, these observations would suggest that an excess of free CAK is a feature of XP-D/CS cells. Indeed, the idea of an excess of free CAK has already been proposed as a molecular hallmark of all XP/CS pathologies.[22,23] The proposals were raised because an excess of free CAK had been reported in different XP/CS cells, as is the case of XP-G/CS cells,[24] and in XP-D/CS cells, which furthermore show aberrant chromosome segregation due to premature commitment to mitosis.[25]

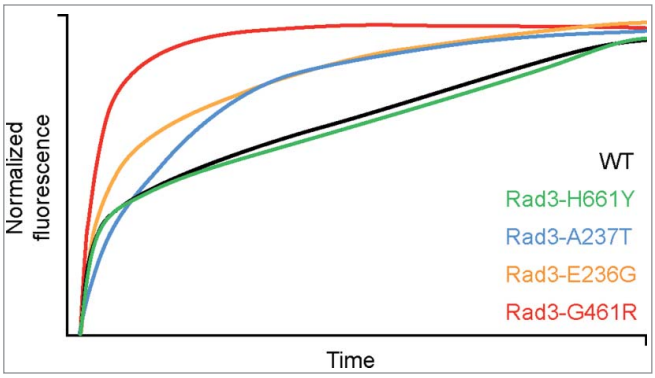

Figure 2. TFIIH dynamics in *Rad3* ATP-binding groove mutants. Representation of FRAP curves normalized to a global maximum of Tfb4-yGFP strains after 80 J/m^2 UV-C irradiation. Recovery curves of the normalized fluorescence in wild-type (WT) and *rad3* mutants affected in the ATP-binding groove of Rad3 (*rad3–102* [Rad3-H661Y], *rad3–101* [Rad3-A237T], *rad3–107* [Rad3-E236G] and *rad3–2* [Rad3-G461R]) are displayed (adapted from data in ref.[9]). The different steepness of the linear part of the curves shows the average molecular weight of the TFIIH complex under measurement.

An alternative molecular defect for the XP/CS condition

Despite all previous considerations, some observations were noted in the past that do not fit the proposal that excess free CAK is the molecular hallmark of XP/CS.[22] First, an XP-B/CS-causing mutation (XPCS1BA patient) was not seen to induce a relevant increase in free CAK[24] and, second, mutations in the C-terminus of XPD (XPD-R683W) weakening the association of the CAK to TFIIH were at the base of an XP, but not of an XP/CS, condition.[26] One simple way of resolving these inconsistencies would be that the excess of free CAK might just be one possible outcome in certain XP/CS conditions, though not the molecular, causative hallmark at the base of this pathology.

In order to solve these apparent conflicts, and sustain our proposal on the available molecular characterizations,[9,13,14] we propose that the molecular feature common to all XP/CS conditions is the persistence of bound TFIIH at an open bubble and the inability to recruit the DNA synthesis factors, which in turn extends the permanence of an unfinished NER intermediate (**Fig. 3**). This would impair accurate completion of damage repair and sequester TFIIH away from transcription sites impairing transcription resumption, which could explain the XP and CS clinical manifestations.

Our model thus provides a uniform explanation compatible with the role during NER not only of XPD (see above), but also of XPB, XPF and XPG.

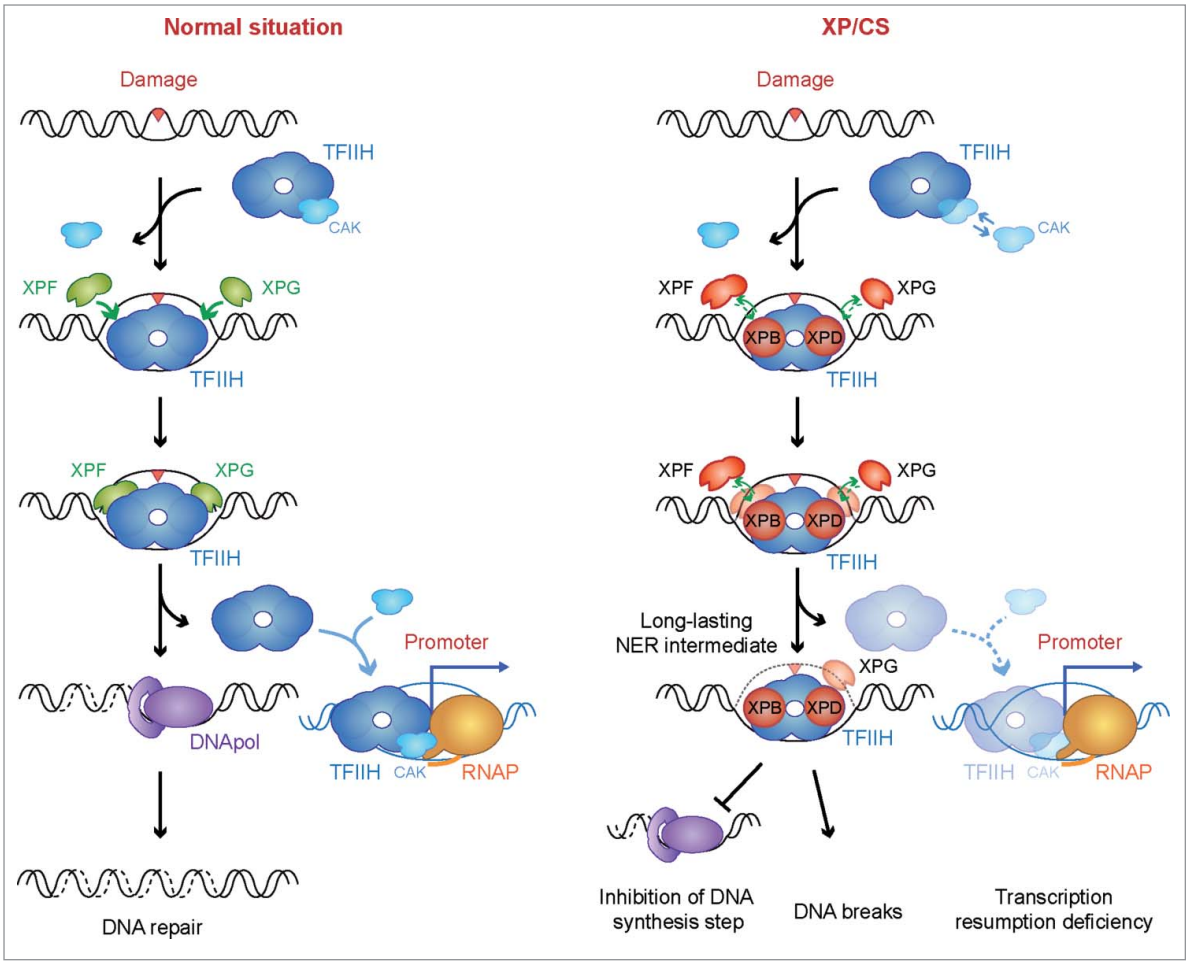

Figure 3. A possible unified model to explain the XP/CS molecular defect. In a normal situation, TFIIH is recruited to the damaged site, releasing the CAK subcomplex and allowing DNA unwinding and excision of the DNA containing the lesion by the XPF and XPG endonucleases. After DNA repair completion, TFIIH is relocated to the promoter sites, thus allowing transcription resumption. In XP/CS cells, TFIIH is also recruited to the damaged site and performs bubble opening. Incision by XPF or XPG nucleases could be prevented. In all cases, TFIIH could be retained in the DNA as a long-lasting NER intermediate. As a consequence, DNA synthesis would be impaired and DNA break formation may occur whenever incision has happened. TFIIH retention would provoke a delay in transcription resumption. In this scenario, an excess of free CAK is a possible outcome of some XP/CS mutations. Proteins whose deficiencies can cause an XP/CS condition are highlighted in red: XPB, XPD, XPF and XPG.

XPB-associated ATPase activity needs to be exerted for NER.[27] In analogy with XPD, any loss of ATPase activity in context of a functional TFIIH may cause a gain of affinity for DNA.[28] The recently uncovered patient whose XP/CS condition was associated with an XPF deficiency[29] can also be described on the basis of an opened NER bubble without further incision. As for XP-G/CS-causing mutations, it has been shown that they prevent the XPG interaction with TFIIH and may even cause CAK and XPD dissociation.[24] TFIIH association with the lesion may therefore occur, but the inability to recruit XPG halts incision by both XPF-ERCC1 and XPG at the 5′ side or at the 3′ side of the lesion, respectively,[22,30] and may even cause late XPD and CAK dissociation, leaving an aberrant repair bubble without further processing.[24] There is evidence supporting this hypothesis. First, XPB mutations leading to XP/CS have been shown to fully allow TFIIH recruitment and subsequent assembly of the incision nucleases,[11] which is accompanied by bubble opening and XPG incision. Since this XPB mutation impairs XPF incision,[31] the NER intermediate is long lasting[32] and DNA synthesis does not take place.[11] Second, XPG mutations leading to XP/CS are as well able to promote TFIIH assembly and bubble establishment, but recruitment of DNA synthesis factors is prevented.[11] Altogether, we propose the long-lasting NER intermediate as the general molecular defect underlying all XP/CS deficiencies, irrespective of whether it is XPD, XPB, XPF or XPG being mutated (**Fig. 3**). As a consequence, and only in some circumstances, this may lead to an excess of free CAK.

Therapeutic possibilities of the model

Some therapeutic considerations could be derived from our proposal. If

the mutations at the base of XP/CS are causing the molecular defect we have described here, namely a long-lasting NER intermediate, this could be exploited for XP/CS-associated cancer treatment. As previously explained, the impact of these mutations would be different in non-dividing *versus* cycling cells. The latter would present an acute dependency on HR functions in order to tolerate the unfinished NER. In the absence of HR, DSBs would accumulate in their genomes, eventually leading to cell death. Given that cancer cells cycle more frequently than most body cells, inhibition of HR could be explored as a therapeutic approach to XP/CS-associated cancers. Moreover, not only the spontaneous damage that is a substrate of NER would generate DSBs in an XP/CS-like context, but also their production could be exacerbated if cells are directly challenged with UV light-mimetic drugs.[9] Thus, if the local delivery of such drugs in combination with HR inhibitors is feasible, this could be investigated as a way to hyper-sensitize XP/CS cancer cells.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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