New factors in nucleotide excision repair : a study in saccharomyces cerevisiae

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Chapter

3

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Obviously, a crucial step in NER is the decision where in the genome it is appropriate to incise the DNA. Although the damage recognition step is extensively studied it is still unknown how NER is able to make this decision and how it detects the damaged nucleotides in the genome. Damage recognition involves several aspects. The basis of recognition is to distinguish a damaged nucleotide from the undamaged ones. Enzymes involved in this step must somehow be able to sense certain features of the DNA that reveal whether it is damaged or not. This is especially a puzzling ability since NER is able to recognize a large number of chemically and structurally unrelated lesions. Apart from this feature, damage recognition entails additional aspects. Before a specific DNA fragment is examined by the NER damage sensors, the location of the lesion must be determined; enzymes have to search the genome for damaged nucleotides. How the NER factors search the genome for lesions is currently not known. The recognition factors may be constantly binding and dissociating, or may scan along the DNA until an injury is detected. Furthermore, the NER damage sensors may continuously probe for lesions, or alternatively, the search might only be started in the case lesions are present. How damage recognition is regulated is not known in detail, but various regulating mechanisms appear to be present that might activate, or increase the activity of, NER proteins once the presence of DNA damage is detected. Of these three different phases of recognition the final step, the actual detection of a lesion, is decisive for the incision. The topic of this chapter is the mechanism by which the GGR sub-pathway is able to determine the presence of a lesion in the DNA.

An important challenge faced by the NER damage recognition factors is the relative tiny number of lesions compared to the amount of undamaged DNA. Amidst the more than 12 million base pairs in yeast, or an overwhelming 3.3 billion base pairs in humans, NER must be able to discriminate a damaged from an undamaged base. Several NER proteins exhibit specific affinity for DNA lesions, but the preference for damaged DNA over undamaged DNA of these factors is typically only around a 1000 fold. None of the proposed damage sensors possess the extraordinary specificity required to accomplish lesion-detection in the context of the genome. In fact, it is hard to imagine that such a protein exists at all. This suggests that NER factors must cooperate to accomplish efficient recognition of lesions. One possibility is that a pre-assembled damage sensor, consisting of multiple NER proteins with affinity for damaged DNA, provides higher specificity. However, such a complex could only possess enhanced specificity when its individual components would recognize different aspects of the damaged DNA. It is doubtfull whether such complexes exist, as analysis of the diffusion rate of NER proteins indicates that the NER damage recognition proteins operate separately before engaging the DNA (Houtsmuller *et al.*, 1999; Rademakers *et al.*, 2003).

Alternatively, the incision reaction may only be initiated when two or more independently probing damage sensors are bound to the same DNA region. In this case, the chance that the bound region actually does contain a lesion will be synergistically higher compared to DNA bound by a single factor. However, as NER factors operate in a predetermined order (see 2.2) it seems more likely that the factor binding initially will recruit proteins that verify whether the bound DNA actually contains a lesion. When this double check method will be applied, the first encounter with a lesion is still depend-

ent on the search by the first factor. Considering the low specificity of the single NER factors, this factor should be present in very large quantities and verification by additional factor(s) should occur fast to achieve efficient recognition. The NER damage sensor(s) may also apply a different approach. A NER factor may 'slide' along the DNA in search for damaged nucleotides, as recently demonstrated for damage binding factors of the mismatch repair system (Gorman *et al.*, 2007) and previously for photolyase (van Noort *et al.*, 1998). In theory this can be an efficient method to locate the lesion, searching the DNA in a more systematic manner rather than random binding and dissociation. Yet, such a scanning mechanism will almost certainly require the remodeling of the chromatin structure. Indeed, chromatin remodeling is thought to be an important part of GGR, but it has yet to be explained how NER copes with chromatin during the search for DNA lesions.

3.1 The composition of NER substrates

It is hard to imagine that there is a common feature shared by all the different lesions that are removed by NER. It is therefore conceivable that the NER damage recognition factor(s) are able to detect a deviation in one or more of the characteristics of undamaged DNA brought about by the presence of the lesion. All NER substrates invoke changes to the standard Watson-Crick geometry of the DNA (Dip *et al.*, 2004), alterations commonly referred to as 'helix distortion'. The efficiency by which the different NER substrates are repaired via the GGR pathway increases proportionately with the degree of helix distortion imposed by the lesions (Gunz *et al.*, 1996). For example, the deformation of the DNA helix induced by (6-4)PPs is more severe than that caused by CPDs (Kim *et al.*, 1995; McAteer *et al.*, 1998), accordingly, both Rad4 and XPC bind to (6-4)PPs with a strong preference over CPDs (Batty *et al.*, 2000; Guzder *et al.*, 1998b; Kusumoto *et al.*, 2001).

Intra-strand crosslinks caused by *cis*-diamminedichloroplatinum (cisplatin) induce helix distortion in a variable degree, dependent on the type of crosslink (Bellon *et al.*, 1991). Consistent with the notion described above, a 1,3 GTG cisplatin crosslink is removed more efficiently than the less helix distorting 1,2-GG and 1,2-AG variants (Moggs *et al.*, 1997). Furthermore, the positioning of one or two non-complementary bases opposite a 1,2-GG-cisplatin crosslink or a CPD also improves the repair of these lesions (Moggs *et al.*, 1997; Mu *et al.*, 1997a; Sugasawa *et al.*, 2001). The observations above suggest that deviation from the Watson-Crick geometry is the determining factor that allows recognition of the various lesions by the NER damage recognition proteins. Indeed, lesions that do not perturb the DNA helix, like C4' backbone modifications, are not detected by NER (Hess *et al.*, 1997b). Since mismatches and small DNA loops however are extremely poor NER substrates it seems that disturbances of the DNA helix alone are also not sufficient to meet the criteria of NER recognition (Hess *et al.*, 1997a; Hess *et al.*, 1997b; Moggs *et al.*, 1997; Mu *et al.*, 1997a). Work from the group of Hanspeter Naegeli demonstrated that sites exhibiting disturbed base pairing are only repaired in the presence of a modified nucleotide (Hess *et al.*, 1997b), even when these two features are positioned 15 nucleotides apart (Buschta-Hedayat *et al.*, 1999). These observations show that NER recognizes two aspects of damaged DNA, and may possibly indicate that the recognition of these two features occurs by

separate subunits of the NER machinery.

In later experiments from the same group the excision of a non-distorting pivaloyl adduct was monitored strand specifically. By insertion of additional nucleotides the effect of a one-sided DNA bulge on the incision reaction was examined (Buterin *et al.*, 2005). In agreement with earlier results, a pivaloyl adduct that does not interfere with normal base pairing was only recognized by the NER machinery in the presence of the DNA bulge in the undamaged strand (Buterin *et al.*, 2005). Interestingly, the DNA was not incised when this bulge was located in the same strand as the adduct. Moreover, DNA fragments in which the inserted nucleotides in the opposite strand also contained a pivaloyl adduct were also not incised (Buterin *et al.*, 2005), suggesting that NER senses DNA damage via deformations in the undamaged strand of the damaged DNA. Consistent with this assumption, XPC-hHR23B binding to photoreactive damages was inhibited when a modified base was positioned in the opposite strand (Maltseva *et al.*, 2008) and the affinity of XPC for UV treated ssDNA is lower than that for undamaged ssDNA (Maillard *et al.*, 2007a).

The data above show that NER senses DNA that exhibits helical distortion and contains a chemically modified nucleotide. Of these two, helical distortion appears the more conspicuous feature and hence a better target for the initial search for DNA damage. Indeed, binding of the initiator of NER, Rad4-Rad23/XPC-hHR23B, is not dependent on the presence of a chemical modification (Sugasawa *et al.*, 2001), suggesting that NER initially recognizes helical distortion. As mentioned earlier, helix distortion refers to the deviation from standard, undamaged DNA. But what constitutes the deviation recognized by NER? One model assumes that thermodynamic destabilization of the damaged helix facilitates binding of the NER damage sensors (Geacintov *et al.*, 2002; Gunz *et al.*, 1996). Thermodynamic destabilization is associated with the lowering of the melting temperature of damaged DNA compared to that of undamaged molecules. The presence of certain lesions however, such as psoralen crosslinks, increase the thermodynamic stability of the DNA rather than destabilize it, and still are recognized by NER (Shi and Hearst, 1986; Thoma *et al.*, 2005). Moreover, a perfectly normal TAT/ATA trimer is thermodynamically even less stable than a GGC/CGG mismatch. Therefore it seems that thermodynamic destabilization alone can not explain how NER initially identifies damages within the DNA. In view of this, Isaac and Spielmann (2004) proposed an alternative model, in which an increase in local flexibility in damaged DNA is a determining factor in damage recognition. This model is based on the observation that conformational alterations in the DNA caused by covalent modifications decrease the energy required to bend the DNA. It was proposed that the NER damage sensors search for DNA that exhibit increased flexibility. While probing the DNA for lesions, the NER damage sensors will attempt to force the DNA into a deformed conformation. The energy required to induce bending of the damaged DNA must be sufficiently small to (temporarily) trap the sensor protein as it scans the DNA (Isaacs and Spielmann, 2004). The observation that binding of XPC-hHR23B induces a strong bend in the DNA, which is fixed at the position of a lesion supports this hypothesis (Janicijevic *et al.*, 2003).

An alternative, though not intrinsically different, view on damage recognition arose from mathematical analysis of the double helix (Blagoev *et al.*, 2006; Maillard *et al.*, 2007a). Mathematical models describing the dynamics of double stranded DNA show

that thermal fluctuations constantly cause the DNA strands to oscillate with respect to each other, creating short lived bubble structures (Alexandrov *et al.*, 2006). In undamaged DNA the oscillations are assumed to be too fast (on the pico to nanosecond scale) to allow detection by the NER machinery. However, even the presence of a relatively non-distorting CPD dimer leads to a 3 fold increase of the average distance between the two strands and 25 times increased occurrence of longer lived, larger bubble structures (Blagoev *et al.*, 2006). This model postulates that NER detects the single stranded nature of the DNA in the close vicinity of the lesion. An important aspect of this model is that the oscillations are most pronounced in the undamaged strand, which is in concord which several damage binding features of Rad4-Rad23/XPC-hHR23B (Maillard *et al.*, 2007a; Maltseva *et al.*, 2008; Min and Pavletich, 2007).

Summarizing, the exact nature of the 'helix distortion' that is required to catch the attention of the NER machinery is not known, but it is clear that NER recognizes DNA that deviates from standard B-DNA. It seems that the NER damage sensors force the DNA into a different conformation, a transaction that is only possible, or more stable, in the presence of DNA damage. This identification of an aberration in the structure of the DNA helix might also represent a method by which NER searches the genome. A NER factor may scan along the DNA, searching for regions that are susceptible to the conformational change it is trying to inflict. Once the DNA can be forced into a certain changed conformation, the NER factor traps itself, thereby forming a signal for downstream NER factors to further inspect the bend region. The receptiveness of the DNA to this transaction signifies that a lesion may be present, but does not yet confirm the presence or precise location of a chemically modified nucleotide. It is likely that the initial damage sensor, stably in complex with the conformationally changed DNA, is bound by subsequent NER factors that verify the presence of an adducted nucleotide.

3.2 The prokaryotic damage recognition model

To get a better understanding of eukaryotic damage recognition the mechanism in the prokaryotic system, which is elucidated in considerably detail, is discussed here. The number of proteins involved in the NER reaction in prokaryotes is limited; just three proteins are required for the basic incision reaction whereas eukaryotic NER employs at least 16 proteins. The three prokaryotic players UvrA, UvrB and UvrC (collectively known as the UvrABC system) can nevertheless cope with a similar diversity of substrates and the lesions are removed in a similar fashion.

Two of the three proteins required for the incision reaction are involved in damage recognition, while the third, UvrC, is required for the incision. Damage recognition is not separated from 'downstream' NER events but is in fact intertwined with the construction of the pre-incision complex. In line with the 'bipartite recognition model' (Hess *et al.*, 1997a) two steps can be discerned in prokaryotic damage recognition, initial detection of helical distortion (by $UvrA_2$ and UvrB) and subsequent recognition of the base modification (by UvrB). For detailed reviews on prokaryotic NER see Truglio *et al.* (2006a) and Van Houten *et al.* (2005). A summary of the damage recognition mechanism is described below.

UvrA and UvrB reside in a $UvrA_2UvrB_2$ complex (Malta *et al.*, 2007). The initial contact with (damaged) DNA is made by the $UvrA_2$ subunit, which exhibits roughly

1000 fold preference for binding to damaged DNA over undamaged DNA (Seeberg and Steinum, 1982). The affinity of $UvrA_2$ for (damaged) DNA appears to be largely based on electrostatic interactions (Pakotiprapha *et al.*, 2008) and the $UvrA_2$ subunit is therefore expected to bind helical distorted DNA in general and to be insufficient for determining the true nature of the deformed DNA region.

The decision whether to abort or continue the NER reaction is made by UvrB, the protein that can be considered to be the central damage recognition factor of the UvrABC system. The UvrB protein contains several domains required for interactions with $UvrA_2$ and UvrC, but the key features in UvrB that enable damage recognition are a *ß*-hairpin and six helicase motifs that are dispersed throughout the protein. The crystal structure confirms that UvrB meets the requirements of a *bona fide* helicase, suggesting that UvrB functions in the separation of the DNA strands, similar to the role of TFIIH in eukaryotic NER.

After the $UvrA_2$-DNA interaction positioned the $UvrA_2$-$UvrB_2$ complex at a potential lesion, the DNA is transferred from the UvrA dimer to $UvrB_2$, initiating the actual recognition of the lesion. Once the DNA is bound by UvrB, the *ß*-hairpin is inserted in between the DNA strands, clamping one of the two strand behind the *ß*-hairpin. Several aromatic residues at the base of the *ß*-hairpin interact with the DNA via hydrophobic interactions. Two specific residues (Tyr92 and Tyr93) are thought to force the base out of the helix, a mechanism referred to as 'base flipping' (Malta *et al.*, 2006; Moolenaar *et al.*, 2001). The insertion of the *ß*-hairpin and the subsequent flipping of bases is presumed to be only possible when base stacking interactions are loosened, a property that is shared by all the lesions repaired by NER (Van Houten and Snowden, 1993).

Based on the crystal structure of UvrB bound to a ssDNA loop it was suggested that, once one of the strands is clamped behind the *ß*-hairpin, ATPase driven 3' > 5' translocation of a few nucleotides facilitates a mechanism to pinpoint the precise location of the lesion (Truglio *et al.*, 2006b). During the translocation the nucleotides are proposed to be flipped out one by one into a hydrophobic pocket of UvrB. When a damaged nucleotide is encountered, the translocation will be arrested as it will not fit in the hydrophobic pocket (Truglio *et al.*, 2006b). In this model, the damaged base will always be located directly 5' of the flipped-out nucleotide. These results are supported by the notion of Malta *et al.* that flipping of the base 3' adjacent to the lesion may be the general mechanism for damage recognition (Malta *et al.*, 2006).

Summarizing, in prokaryotic NER high specificity is achieved by combining a general scanning for sites that display helical distortion followed by a more detailed detection of the damaged nucleotide. The search for DNA exhibiting helical distortion is initially performed by UvrA but also involves UvrB, which uses its *ß*-hairpin to detect regions of disturbed basepairing or basestacking. In both the $UvrA_2$-UvrB-DNA and UvrB-DNA complexes the DNA is wrapped around the UvrB protein, causing a sharp kink in the DNA (Shi *et al.*, 1992; Verhoeven *et al.*, 2001). In line with the general mechanism to probe for helix distortion suggested in the previous paragraph, the $UvrA_2$-$UvrB_2$ complex may probe for DNA regions that are stable in this forced conformation. However, it appears more likely that the wrapping of DNA facilitates the possibility to place the *ß*-hairpin in between the strands when destabilized DNA is encountered. Successful insertion will trap the complex and trigger ATP driven translo-

cation to localize the damaged nucleotide. UvrB can only examine one strand and at this stage UvrB does not 'know' which strand contains the lesion. However, the presence of two UvrB molecules in the $UvrA_2$-$UvrB_2$ complex might enable the inspection of both strands of the DNA; when no damage is detected in the first search, the DNA might be transferred to the second UvrB protein to inspect the other strand (Verhoeven *et al.*, 2002).

3.3 Damage recognition in eukaryotic NER

Sensing helical distortion

Assuming that the principle of damage recognition in eukaryotes is comparable with that in the prokaryotic system, a two step mechanism will also be applied in eukaryotes. In the core-NER reaction Rad4-Rad23/XPC-hHR23B is the initial damage recognition factor and hence the primary candidate to function as a sensor for helical aberrations. Rad4/XPC indeed displays a general affinity for distorted DNA. XPC-hHR23B binds mismatch bubble structures regardless of the presence of a modified base (Sugasawa *et al.*, 2001). The crystal structure of CPD-bound Rad4 (discussed in section 2.3) implicates that Rad4 has affinity for DNA that is destabilized such that it allows insertion of the Rad4 ß-hairpin in between the strands of the DNA. In addition, a predicted conformational change of the DNA bound Rad4 is postulated to introduce a kink in the DNA (Min and Pavletich, 2007). Binding of XPC-hHR23B is observed to kink DNA fragments regardless of the presence of a lesion. When the DNA fragment contains a lesion, XPC-hHR23B is fixed at the site of the injury (Janicijevic *et al.*, 2003). Similar to what has been suggested above for $UvrA_2$-$UvrB_2$, the kinking of the DNA might be required to allow inspection of basepairing by the ß-hairpin. Possibly, Rad4-Rad23/XPC-hHR23B may actively scan along the DNA for regions that are susceptible to insertion of the ß-hairpin. The domain in Rad4 that binds undamaged DNA adjacent to the lesion (Min and Pavletich, 2007) might function to anchor the DNA while attempting to place the hairpin between the strands of the DNA. The crystal structure shows no direct contact between Rad4 and the damaged nucleotides (Min and Pavletich, 2007), indicating that a chemical modification is not required in order to facilitate the Rad4-DNA interaction. This strongly suggests that Rad4-Rad23/XPC-hHR23B recognizes the consequences of the presence of the lesion and that the lesion itself has to be detected by a different factor.

Recognition of the damaged nucleotide

In prokaryotes, ATP driven helicase activity of UvrB confirms the presence and the precise location of the damaged nucleotide, utilizing the ß-hairpin to flip out nucleotides one by one, until it arrests when the damaged nucleotide is encountered (see 3.2). In eukaryotes a similar mechanism may be applied. Here, a ß-hairpin is already inserted through the DNA by Rad4. Rad4 lacks helicase or ATPase activity and can therefore not employ an UvrB-like damage-localization mechanism by itself. Yet, a second NER factor might translocate the DNA while the Rad4 ß-hairpin is kept in place in between the DNA strands. The only core-NER factor possessing helicase activity is TFIIH, which is indeed the first factor that is recruited after Rad4-Rad23/XPC-hHR23B binding (Volker *et al.*, 2001; Yokoi *et al.*, 2000). Rad4-Rad23/XPC-hHR23B and TFIIH could

cooperate to locate the damaged nucleotide, and consequently confirm that the DNA bound by Rad4/XPC is actually damaged. As Rad4 binds the undamaged strand and the flipped out thymine dimer is exposed towards the solvent (Min and Pavletich, 2007), it must be assumed that TFIIH not only provides the helicase activity, but also the equivalent of the UvrB hydrophobic pocket that arrests the translocation once a damaged nucleotide will not fit into the pocket. Very recently, analysis of the crystal structure of an archeal XPD protein (a helicase subunit of TFIIH) showed the presence of a narrow pocket that could hold non-adducted bases but would reject damaged substrates, prompting the suggestion that this pocket may enable XPD to verify the presence of damaged nucleotides (Wolski *et al.*, 2008).

Alternatively, the TFIIH helicase activity may be involved in the verification of the lesion separately from base flipping by the Rad4/XPC *ß*-hairpin. Since the Rad3 helicase activity is inhibited in the presence of DNA damage, it has previously been proposed that Rad3/XPD will arrest when processing a damaged nucleotide (Naegeli *et al.*, 1992, , 1993a) and that by this feature TFIIH might determine the presence and location of a chemical modification to the nucleotide (Wood, 1999).

Rad3/XPD will inspect one strand of the potentially damaged DNA, but it is not clear how NER proceeds when no lesion is identified in the examined strand. Will the complex disassemble or does TFIIH somehow check the second strand? Possibly, initial binding of Rad4/XPC already notifies in which strand the lesion is present. Although Rad4 also binds DNA regions that do not contain a damaged nucleotide, when a lesion *is* present, binding of Rad4 may confer strand specificity. The Rad4-CPD crystal structure shows that the CPD is approached from the side of the undamaged strand and in fact predicts that Rad4 will be unable to approach the DNA from the strand that contains the CPD (Min and Pavletich, 2007). In concord, It has been shown that binding of XPC-hHR23B to ssDNA is inhibited by the presence of DNA damage (Maillard *et al.*, 2007b; Trego and Turchi, 2006) and experiments by Maltseva *et al.* (2008) show that XPC-hHR23B requires an undamaged strand opposite the adducted strand in order to bind. These results strongly suggest that Rad4/XPC recognizes deviations in the undamaged strand of damaged DNA, in support of the model postulating that the presence of a NER substrate leads to an increase in oscillation of primarily the undamaged DNA strand (Blagoev *et al.*, 2006; Maillard *et al.*, 2007a).

In eukaryotes an additional protein, Rad14/XPA, is implicated in damage recognition. The role of Rad14/XPA is not clarified, but since the protein acts after TFIIH and preferentially binds to damaged DNA *in vitro* it was assumed that Rad14/XPA functions as a damage verification factor. Nevertheless, Rad14/XPA does not appear to examine the damaged DNA in more detail than Rad4/XPC does in the initial probing. A detailed examination of the DNA binding characteristics of XPA demonstrated that the affinity of XPA for damaged DNA is entirely based on the presence of deformations in the DNA helix and does not require any chemical modification of nucleotides (Missura *et al.*, 2001). Also the binding of the XPA-RPA complex, which was reported to possess superior damage specificity compared to XPA or RPA alone, is dependent on helix distortion only (Missura *et al.*, 2001). Based on the affinity of XPA for certain DNA structures the authors concluded that rigid bending of the deoxyribose-phosphate backbone is the predominant factor that determines the high affinity interaction of XPA with DNA (Missura *et al.*, 2001). These data implicate Rad14/XPA in the recognition

of specific structural features of the developing open complex, not in the direct sensing of the lesion. As the inclusion of XPA in the XPC-hHR23B-TFIIH-DNA complex is reported to stimulate strand separation by TFIIH (Coin *et al.*, 2006; Winkler *et al.*, 2001) it seems that lesion-verification by TFIIH is initiated only after recruitment of XPA, implicating the protein in indirect verification of the lesion. In general XPA appears mainly involved in the architecture of the pre-incision complex. The DNA binding properties of Rad14/XPA and its interactions with most of the core-NER proteins likely enables the coordination of the NER complex in relation to the damaged DNA.

The data discussed here strongly suggest that Rad4-Rad23/XPC-hHR23B and TFIIH are the key players in damage sensing in eukaryotes (Figure 3). The heart of the damage recognition is performed by the TFIIH helicase subunit Rad3/XPD. Arrest of helicase activity serves as a signal to proceed with the reaction; when TFIIH is not obstructed it may dissociate from the substrate along with Rad4-Rad23/XPC-hHR23B. The true nature of the helicase-arrest is not essentially relevant for this model of damage recognition; it may require 'active' base-flipping by the ß-hairpin (as suggested for prokaryotic NER), but may also be an intrinsic characteristic of the Rad3/XPD (or perhaps all) helicase(s). Importantly, the central enzyme in damage recognition, TFIIH, does not require affinity for damaged DNA, a property that was the basis to implicate certain NER proteins in the damage recognition process.

The principle of damage recognition in prokaryotes and eukaryotes might be comparable since similar tools are applied (the ß-hairpin and helicase activity); however, the events that lead to recognition are organized differently in these two systems. In prokaryotes the two recognition proteins (UvrA and UvrB) exist in one complex whereas in eukaryotes Rad4/XPC and TFIIH operate as separate units, although some reports show interaction between Rad4-Rad23/XPC-hHR23B and TFIIH in absence of DNA damage (Drapkin *et al.*, 1994; Mu *et al.*, 1995). In prokaryotes, UvrB is involved both in the detection of helix distortion and in the precise localization of the lesion, i.e., it first inserts its ß-hairpin through the DNA strands and then applies helicase activity. Rad4/XPC senses helical disrupted DNA and sets the stage for the localization of the lesion in the process. However, the required ATPase/helicase activity for the damage-verification is provided by the Rad3/XPD subunit of the consequently recruited factor TFIIH.

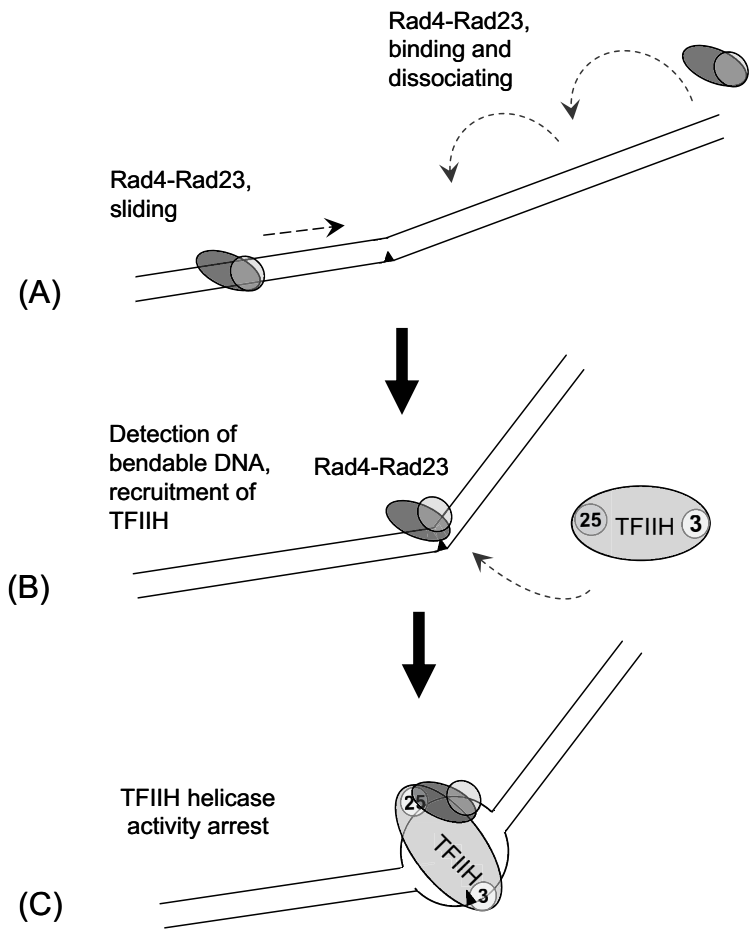

Figure 3
Possible model for damage recognition. (A) Damaged DNA is scanned by Rad4-Rad23, probing for regions that are destabilized such that the Rad4-β-hairpin can be inserted in between the DNA strands and/or DNA that can be forced into a curved conformation. How this scanning is performed is not precisely known. Rad4-Rad23 could slide along the DNA until a lesion is encountered or the Rad4-Rad23 complex may continuously bind and dissociate until a damaged region is encountered. (B) Once Rad4-Rad23 is bound to a DNA region that is bendable and/or susceptible to the insertion of the β-hairpin, Rad4-Rad23 is (temporarily) trapped, allowing the recruitment of TFIIH. (C) The helicase activity of TFIIH separates the two strands. The presence of a modified nucleotide will block the Rad3 helicase, triggering the further formation of the NER pre-incision complex. Absence of a modified nucleotide will lead to disassembly of the DNA-Rad4-Rad23-TFIIH complex.

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