DNA repair: Disorders

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Abstract

Deoxyribonucleic acid inside cells is being damaged continually. Cells have evolved a series of complex mechanisms to repair all types of damage. Deficiencies in these repair pathways can result in several different genetic disorders. In many cases these are associated with a greatly elevated incidence of specific cancers. Other disorders do not show increased cancer susceptibility, but instead they present with neurological abnormalities or immune defects. Features of premature ageing also often result. These disorders indicate that DNA repair and damage response processes protect us from cancer and are important for the maintenance of a healthy condition.

Keywords: UV light; xeroderma pigmentosum; ataxia telangiectasia; cancer; immunodeficiency; DNA repair.

Key concepts

- DNA is damaged continually from both endogenous and exogenous sources.

- Cells have evolved many different ways for repairing different types of damage

- Genetic defects in these pathways result in different disorders

- Defective DNA repair often results in an increased mutation frequency and consequent elevated incidence of cancer. Many of the DNA repair disorders are highly cancer-prone.

- The central nervous system appears to be particularly sensitive to DNA breaks. Several disorders caused by defective break repair are associated with neurological abnormalities including mental retardation, ataxia and microcephaly.

- Development of immunological diversity uses some of the enzymes required to repair double-strand breaks. Disorders caused by defects in this process are associated with immune deficiencies.

1. Introduction

Deoxyribonucleic acid (DNA) inside all cells is continually being damaged, both from endogenous reactions, such as hydrolysis and oxidation, and by exogenous agents, like ultraviolet light and chemical carcinogens. In order to survive this potentially devastating loss of genetic information, cells have evolved a variety of repair and response pathways for either removing the damage or coping with unrepaired damage. If any of these processes is faulty, the result is either a genetic disorder or death if the defect is not compatible with life. More than twenty distinct disorders, representing about 50 genes, are known to be associated with such defects, and more are being revealed each year.

2. Ultraviolet Sensitivity: Disorders of Nucleotide Excision Repair

Ultraviolet light (UV) and many chemical carcinogens produce alterations in the DNA that result in bulky distortions. This damage is removed by a complex pathway designated nucleotide excision repair (NER), a process involving many proteins (Figure 1) (Nouspikel, 2009). A defect in any one of seven of these proteins (XPA to XPG) results in the disorder xeroderma pigmentosum (XP) (Figure 2a). XP is characterized by sensitivity of the skin to sunlight, various pigmentation changes and multiple skin cancers on sun-exposed areas. In a minority of cases there are associated neurological abnormalities (Kraemer et al., 1987). The XP proteins are involved in recognition of DNA damage (XPC, XPE), opening out of the damaged structure (XPB, XPD helicases), verification of the damage (XPA) and cutting the DNA strand on either side of the damage (XPG, XPF nucleases) (Nouspikel, 2009). See also DNA Repair, and Skin: Hereditary Disorders

[figure 1 here]

[figure 2 here]

XPB and XPD are two of the subunits of TFIIH, a protein complex with two distinct functions. Before its role in NER was discovered, it had been found to be a basal transcription factor required for initiation of all transcription mediated by RNA polymerase II. In both repair and transcription functions, it carries out a similar but not identical role of opening out the DNA structure. Both XPB and XPD are helicases (of opposite polarity). The helicase activity of XPB is required for transcription initiation, but not NER, whereas the XPD helicase activity is required for NER but not for initiation of transcription (Hashimoto and Egly, 2009). See also DNA Helicases

Mutations in *XPB* and especially *XPD* can result not only in XP, but also in trichothiodystrophy (TTD) or rarely in the combined features of XP and Cockayne syndrome (CS). TTD (Figure 2b) is a multisystem disorder characterized by sulfur-deficient brittle hair, ichthyotic skin, beta thalassemia trait, physical and mental retardation and sun sensitivity, but, in contrast to XP, no pigmentation changes or increase in skin cancers (Hashimoto and Egly, 2009; Stefanini et al., 2010). Different mutations in the gene encoding the XPD protein cause the different clinical disorders, and it is widely accepted that the features of XP result from defective repair, while TTD features are caused by subtle abnormalities in transcription (Lehmann, 2001).

The initial damage-recognition step of NER differs if the damage is on the transcribed strand of an active gene. In this case the XPC protein is dispensable, and the recognition signal in this 'transcription-coupled repair' is thought to derive from ribonucleic acid (RNA) polymerase molecules stalled at damaged sites (Figure 1) (Fousteri and Mullenders, 2008). The two proteins defective in patients with CS, namely CSA and CSB, are required to displace the stalled RNA polymerase and recruit the proteins involved in the later steps of NER (Fousteri et al., 2006). The clinical features of CS (Figure 2c) include dwarfism with severe physical and mental retardation, progressive neurological and retinal degeneration, ataxic gait, deafness and sun sensitivity, but again no pigmentation changes or skin cancer (Nance and Berry, 1992). The CS proteins are required for transcription-coupled repair, not only of UV damage but also for repair of some types of oxidative damage. It is thought that the clinical features of the disorder may result from the accumulation of oxidative damage. The CS proteins are also thought to have a nonessential role in transcription. Combined features of XP and CS are found in rare individuals with mutations in the genes encoding the XPB, XPD and XPG proteins. See also Transcription-coupled DNA Repair

3. Disorders of Replication of Deoxyribonucleic acid damaged by ultraviolet light

Although DNA damage is normally removed by NER, it is a relatively slow and incomplete process, and cells need to replicate past unrepaired DNA damage (translesion synthesis (TLS)). Replicative DNA polymerases are unable to carry out TLS, and so the cell employs low-fidelity distributive polymerases, which are able to carry out TLS past different types of damage. About 20% of XP patients have normal NER but are defective in DNA polymerase η, a specialised DNA polymerase that is able to carry out TLS past UV photoproducts and other types of DNA adducts (Masutani et al., 2000; McCulloch et al., 2004). Both NER-defective and TLS-defective XP cells are highly mutable by UV light, and it is this hypermutability that gives rise to the skin cancers that are associated with the disease. See also DNA Polymerases: Eukaryotic, **DNA Mismatch Repair: Eukaryotic** and DNA Replication Fidelity

4. Abnormal Responses to Damage by Ionizing Radiation

Unlike UV, the most important damage generated in DNA by ionising radiation are double strand breaks (DSB's). At least two mechanisms are available to repair these breaks, nonhomologous end joining (NHEJ) and homologous recombination (HR). NHEJ is essentially a DSB re-sealing pathway but often involves loss of genetic material at the DSB termini so is regarded as an 'error-prone' type of repair. HR, on the other hand, copies the identical sister DNA molecule and consequently is an 'error free' type of repair. Sister chromatids are, however, only available at certain stages of the cell cycle after DNA replication (S/G2), so that HR is limited to these periods of the cell cycle. Several genetic disorders are associated with abnormal responses to ionizing radiation.

4.1 Disorders of Nonhomologous end joining (NHEJ)

The major pathway for repairing DSB in human cells is NHEJ (Figure 3). In this process, the Ku 70-80 heterodimer binds to the ends of the DSB and recruits the catalytic subunit of DNA-dependent protein kinase (DNA-PK$_{CS}$), resulting in activation of its kinase activity. The breaks are subsequently joined by DNA ligase IV which exists in a tight complex with XRCC4 and XLF (XRCC4-like factor)/Cernnunos (Lieber, 2010). The same set of proteins are required to rejoin programmed breaks generated in the V(D)J recombination process during development of immunoglobulins and T cell receptors. Thus there is a strong link between repair of ionising radiation damage and development of the immune response. The severe combined immunodeficient (SCID) mouse is mutated in DNA-PK$_{CS}$ and is radiation sensitive and immunodeficient and a single immunocompromised individual with point mutations in *DNA-PK* has been described (van der Burg et al., 2009). As yet no human disorder has been associated with defects in Ku. However several immunodeficient individuals with deficient DSB-repair have been identified as having mutations in the gene for DNA ligase IV and for XLF/Cernnunos (O'Driscoll et al., 2001). Both sets of patients exhibit overlapping clinical features of pancytopenia, microcephaly, and developmental delay. Other immunodeficient and radiation-sensitive individuals were found to be defective in a protein designated Artemis (Moshous et al., 2001). This protein is found in a complex with DNA-PK$_{CS}$, and is a substrate for its kinase activity. When phosphorylated by DNA-PK$_{CS}$, Artemis is able to open hairpin structures generated as intermediates in V(D)J recombination thereby explaining their SCID phenotype (Ma et al., 2002). Nevertheless, whilst the exact role of

Artemis in DSB-repair is unclear, Artemis-defective cells exhibit ionising radiation sensitivity and and DSB repair defect epistatic to that of A-T cells.

[figure 3 here]

4.2 Disorders of Homologous recombination (HR)

The alternative mechanism for repairing DSB involves homologous recombination to restore the genetic information lost at the site of the break. This process requires several human homologues of the *Saccharomyces cerevisiae* Rad51 protein, as well as homologues of the Rad52 and Rad54 proteins. Recently, mutations in *RAD51C* a gene encoding a RAD51 paralogue have been associated with breast and ovarian cancer pedigrees as well as in a single family exhibiting a developmental disorder (with multiple congenital abnormalities and with cellular features reminiscent of Fanconi anaemia-derived cell lines) (Meindl et al., 2010; Vaz et al., 2010).

The majority of familial breast cancers result from mutations in the breast cancer 1 (*BRCA1*, early onset) or breast cancer 2, early onset (*BRCA2*) genes. These individuals are heterozygous for the defective gene, and the tumours result when the second allele is also lost or mutated. Cell lines derived from these tumours have been tested for their ability to carry out homologous recombination and were found to be defective. Furthermore both BRCA1 and BRCA2 proteins interact with RAD51 (Gudmundsdottir and Ashworth, 2006). Both genes are essential, but cells with hypomorphic mutations are sensitive to ionizing radiation and exhibit chromosome instability. Taken together, these findings implicate *BRCA1* and *BRCA2* in homologous recombination, although they undoubtedly have other functions as well. *BRCA1* mutants are also defective in some of the ionizing radiation-induced cell-cycle checkpoints (see below). See also DNA Recombination

5. Detecting and responding to DNA strand discontinuities

The signal transduction cascade enacted upon DNA breakage (Figure 4) is controlled by two functionally overlapping protein kinases, ATM (ataxia telangiectasia mutated) and ATR (ataxia telangiectasia and Rad3-related). This cascade coordinates the activation of downstream events including cell cycle checkpoint arrest mechanisms, DNA repair pathways and even when appropriate, apoptosis. ATM is activated rapidly upon DSB formation, whilst ATR is activated by single stranded regions of DNA (ssDNA), which can occur, for example, following DNA replication fork stalling or after resection of DSB ends to facilitate recombination/repair. One of the earliest detectable events at a DNA strand break is the phosphorylation of the histone H2A variant H2AX. This helps to recruit various 'mediator' proteins such as 53BP1 and MDC1 which are important facilitators of these downstream events. Emerging evidence indicates that other post-translational modifications aside from phosphorylation such as ubiquitylation and sumoylation are vitally important for cellular responses to DSBs (Zlatanou and Stewart).

[figure 4 here]

5.1 Ataxia-telangiectasia, Ataxia telangiectasia-like Disorder and Nijmegen breakage syndrome

Patients with ataxia-telangiectasia (A-T) have progressive cerebellar ataxia, telangiectases in the eyes and face and various immune deficiencies. Their blood cells have a variety of chromosome aberrations, particularly translocations between chromosomes 7 and 14, which is where the immunoglobin and T cell receptor coding genes reside. Affected individuals are also very susceptible to developing lymphoid tumors and carcinomas. Importantly, A-T patients have an extreme overreaction to radiotherapy treatment. This is reflected in the hypersensitivity of A-T cells to ionizing radiation, likely resulting from a deficiency in repair of DSB in heterochromatin. In addition they are deficient in many of the ionizing radiation damage-induced cell-cycle checkpoints. Since ATM regulates many signal transduction pathways that are elicited by ionizing radiation damage, phosphorylating substrates including p53, CHK2 and MDM2, deficiencies in these pathways likely contribute the pleiotropic nature of the disorder (Lavin, 2008). See also Cell Cycle Checkpoint Genes and Cancer

A heterotrimeric complex of proteins, RAD50/MRE11/NBS1 (the 'MRN' complex) has an important role in recognition of DSB's and recruits ATM to the sites of damage (Stracker et al., 2004). An A-T-like disorder (A-T-LD) was found to be caused by hypomorphic mutations in the gene encoding the MRE11 protein. These patients present with an attenuated/less severe, later onset form of A-T (Stewart et al., 1999). Interestingly no cancer predisposition has been reported in A-T-LD to date, unlike in A-T. Defects in the gene encoding the NBS1 protein component of the MRN complex result in the Nijmegen breakage syndrome (NBS). In contrast to A-T and A-T-LD the principal features are microcephaly, mental and growth retardation, but also with immune deficiencies and cancer predisposition (Taylor et al., 2004). NBS cells are, like A-T and A-T-LD cells, deficient in most of the cell-cycle checkpoints and also have similar defects in repair of DSB's following ionizing radiation (Digweed and Sperling, 2004). Interestingly, in response to ionizing radiation, both MRE11 and NBS1 proteins are phosphorylated by ATM.

5.2 Defective ATR-function and human syndromes

Despite the functional overlap between ATM and ATR, mutation in *ATR* is associated with a clinically distinct disorder from that of A-T. A hypomorphic mutation that impacts on correct splicing of *ATR* has been found to cause Seckel syndrome, a severe form of microcephalic proportionate dwarfism (O'Driscoll et al., 2003). Cells from these patients exhibit increased DNA replication fork stalling and defective checkpoint activation in response to UV and not ionising radiation. Interestingly, other disorders that superficially exhibit clinical overlap with Seckel syndrome, such as NBS and MCPH1-associated Primary Microcephaly, phenocopy ATR-defective Seckel syndrome cells. In fact, mutations in the gene encoding Pericentrin (PCNT), a core centrosomal protein, which are also associated with Seckel syndrome and a related condition, Microcephalic osteodysplastic primordial dwarfism type II, are also associated with defective ATR-dependent checkpoint activation. A recent 'humanised' mouse model of ATR-Seckel syndrome (i.e. modelling the human *ATR* mutation) suggests ATR-deficiency results in embryonic replicative stress, reinforcing the concept of 'intrauterine' programming, the notion that events occurring in utero can result in overt, irreversible clinical outcomes post-natally (O'Driscoll, 2009).

6. Disorders of Deoxyribonucleic acid Interstrand Cross-link Repair

DNA interstrand cross-links are produced in DNA by bifunctional chemicals such as mitomycin C, nitrogen mustard and psoralens in combination with UV-A treatment. Patients with Fanconi anemia (FA) exhibit progressive aplastic anaemia, skeletal abnormalities (hypoplastic radii) and lymphoid malignancy (Moldovan and D'Andrea, 2009). As with A-T, chromosome abnormalities are found in lymphoid cells, but the type of aberration differs from those found in A-T. Curiously, cells from FA patients are specifically hypersensitive to killing by cross-linking agents, implying a defect in the repair of this kind of lesion. The exact mechanism of DNA interstrand cross-link repair has not been determined, although elements of HR, NER and other DNA repair pathways are co-opted or combine to facilitate repair in this context (Moldovan and D'Andrea, 2009). FA cells are also slightly sensitive to ionizing radiation. FA can result from a mutation in any of 13 FANC genes. Eight of the FANC proteins form a nuclear complex which binds to DNA via the FANCM protein and forms a ubiquitin ligase via the FANCL E3 ligase. In response to DNA damage, this ligase is activated and ubiquitylates the FANCD2/FANCI heterodimer. This modified heterodimer colocalizes with HR proteins in nuclear foci. The functional link between FA-pathway and HR is further illustrated by the fact that the FANCD1-complementation group of FA patients are mutated in the *BRCA2* gene and the FANCN gene encodes the BRCA2 partner PALB2(Moldovan and D'Andrea, 2009). Thus there are important links between FA and both genes involved in familial breast cancer. The way in which the FANC proteins facilitate repair of crosslinks and the relationship between defective FANC proteins and the specific clinical spectrum of this disorder is currently unclear. See also **DNA Interstrand Crosslink Repair** 10.1002/9780470015902.a0000575.pub2

7. Disorders of Mismatch Repair

Although DNA replication is very accurate, mistakes are occasionally made, resulting in either mismatched bases or small insertions or deletions. These errors are repaired by the mismatch repair system, in which the mismatch is first recognized by one of two heterodimers, MSH2/MSH6 (for mismatched bases or small insertion/deletions) or MSH2/MSH3 (larger insertion/deletions). A second heterodimeric protein MLH1/PMS2 is then recruited, and a complex mechanism for removing and repairing the mismatched base(s) ensues (Jiricny, 2006). Hereditary nonpolyposis colon carcinoma (HNPCC) is caused in nearly all cases by defective mismatch repair. In this autosomal dominant condition, patients inherit a heterozygous mutation in a mismatch repair gene, and in tumor cells the second allele is mutated or lost. The majority of cases result from mutations in the genes encoding the MSH2 or MLH1 proteins, with rare cases mutated in the genes coding for PMS2 and MSH6. Since mismatch repair is a vital mutation avoidance mechanism in all cells, the reason for the specificity of the tumor type remains a matter of speculation. See also Colorectal Cancer: Genetics, and Mismatch Repair Genes

8. Disorders of base excision and single-strand break repair

Lesions that produce minor distortions in DNA, like some types of oxidative and methylated lesions, are removed by base-excision repair (BER) (Figure 5). The first step in BER is the removal of the damaged base by a glycosylase, which cleaves the bond between the damaged base and the deoxyribose sugar. The resulting "AP site" where the base is lost is cleaved by an endonuclease to generate a single-strand break, which is further processed and repaired. 8-oxoguanine is the most common base alteration

generated by oxidative damage. It can adopt a different configuration such that it can base pair with adenine. Subsequently this erroneous pairing is recognised and the misincorporated adenine is removed by a glycosylase designated Myh. Biallelic mutations in the *MYH* gene result in a predisposition to multiple colorectal adenomas and carcinoma.

Uracil can be generated in DNA by hydrolytic deamination of cytosine or by misincorporation of dUTP. In cells of the immune system, uracil is an intermediate in the generation of immune diversity by hypermutation and class switching. It is produced by the action of AID (activation-induced cytidine deaminase) and is then cleaved from the DNA by uracil-DNA glycosylase (*UNG)*. Some patients with hyper-IgM syndrome are mutated in the *UNG* gene (Figure 5) and this results in defective class switch recombination and hypermutation.

[figure 5 here]

Spinocerebellar ataxia with axonal neuropathy (SCAN1) results from mutations in the *TDP1* gene. Topoisomerases are enzymes that are able to alter the degree of topological twisting of DNA molecules. An intermediate in this process is the formation of a complex in which a tyrosine residue in the topoisomerase is covalently bound to the end of a cleaved DNA molecule. Anti-cancer drugs like camptothecin block the topoisomerase reaction at the stage of this so-called cleavable complex. Tdp1 catalyzes the hydrolysis of the tyrosyl-3' phosphate linkage found in these topoisomerase I–DNA covalent complexes (Figure 5). Inside cells this is manifested as a reduced ability to repair single-strand breaks, and possibly double strand breaks. Persisting DNA breaks in the cerebellum may lead to the neurodegeneration associated with this disorder. (Caldecott, 2008)

Another neurological disorder, ataxia-oculomotor apraxia type 1 (AOA-1), is characterized by cerebellar atrophy and sensorimotor neuropathy. Clinical manifestations include disturbances in motor coordination from an early age, oculomotor apraxia, loss of reflexes, and progressive disability. The *APTX* gene defective in this disorder encodes ataxin, whose function again appears to involve the removal of abortive intermediates in the repair of DNA breaks. In this case the intermediate is formed during DNA ligation. An intermediate of DNA ligase reactions involves the addition of an adenylate group to the 5' end of the break, which is usually removed during the final step of DNA ligation by nucleophilic attack by the 3'-OH group. If the break does not have a clean 3'-OH, however, the adenyl group can persist on the 5'-end of the break and require aprataxin for its removal (Figure 5) (Rass et al., 2007). In AOA1 it is possible that defective aprataxin results in the gradual build up of breaks in the cerebellar DNA.

9. Disorders of RecQ Helicases (Chu and Hickson, 2009)

The RecQ helicase of *Escherichia coli* is a multifunctional protein involved in the initiation of homologous recombination and suppression of illegitimate recombination. There are five human homologues of *RECQ*, and mutations in three of them result in genetic disorders. Bloom syndrome (BLM) is characterized by reduced stature, a high incidence of many types of cancers, especially of the lymphoreticular system, reduced fertility and

chromosome abnormalities. A hallmark is a very high frequency of sister chromatid exchanges in Bloom cells. A major function of BLM protein is the dissolution of recombination intermediates (Wu and Hickson, 2003). See also DNA Helicase-deficiency Disorders

Werner syndrome (WRN) patients have many features of premature aging, such as loss of skin elasticity, graying hair, cataracts, loss of adipose tissue, atherosclerosis and increased risk of soft tissue sarcomas. They do not, however, develop dementia. Chromosome instability is manifested differently from that in BLM. There is a high frequency of illegitimate recombination. Both the BLM and WRN proteins are RecQ-like helicases with 3' to 5' polarity. In addition, WRN, uniquely in the RecQ family, has 3'–5' exonuclease activity. The substrate specificities of the two helicases are very similar, and the exact roles of these helicases are not yet understood. The properties of the cells and the proteins are consistent with a role in resolving topological or structural abnormalities that arise during DNA replication.

Individuals with Rothmund–Thompson syndrome have various abnormalities of the skin and skeleton, and some increase in cancer incidence, especially of skin cancers and osteosarcomas. Patients are mutated in the RecQ protein-like 4 (*RECQL4*) gene, but little is known about its function.

10. Cohesinopathies

After cells have replicated their DNA, the two sister chromatids of each chromosome are held together by a protein complex called cohesin, which is thought to form a ring-like structure that embraces the two sister chromatids. Cohesin contains four components, Smc1, Smc3, Scc1 and Scc3. This complex is loaded onto chromatin by Scc2/Nipbl-Scc4, and establishment of cohesion involves the acetylation of Smc3 by Esco2 acetyltransferase. When double-strand breaks are introduced into a chromatid, cohesin accumulates at the break site and assists in repairing the break by recombination with the intact sister. Cornelia de Lange Syndrome and Roberts syndrome, conditions characterised by multiple congenital abnormalities result from defects in the cohesion pathway. Interestingly Cornelia de Lange syndrome cells have been shown to be defective in HR. More than 60% of the former are mutated in Scc2, Smc1 or Smc3, whereas the latter is caused by mutations in Esco2 (Bose and Gerton, 2010).

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Cockayne syndrome Type A MIM 216400

Cockayne syndrome Type B; MIM 133540.

Xeroderma pigmentosum Group A MIM 278700

Xeroderma pigmentosum Group B MIM 610651

Xeroderma pigmentosum Group C MIM 278720

Xeroderma pigmentosum Group D MIM 278730

Xeroderma pigmentosum Group E MIM 278740

Xeroderma pigmentosum Group F MIM 278760

Xeroderma pigmentosum Group G MIM 278780

Xeroderma pigmentosum variant MIM 278750

Ataxia-telangiectasia MIM 208900

Nijmegen Breakage Syndrome MIM 251260

Ataxia-telangiectasia like disorder MIM 604391

Seckel syndrome MIM 210600

Fanconi Anemia MIM 227650

Spinocerebellar ataxia with axonal neuropathy;SCAN1 MIM 607250

Ataxia, oculomotor apraxia type 1 MIM 208920

Bloom Syndrome MIM 210900

Werner Syndrome MIM 277700

Rothmund-Thomson Syndrome MIM 268400

Cornelia de Lange syndrome MIM 122470

Roberts syndrome MIM 268300

See also

[DNA Damage Response](), [DNA Repair](), [DNA Repair: Evolution](), [Mismatch Repair Genes](), and [Transcription-coupled DNA Repair]()

Figure 1. Different steps in nucleotide excision repair (NER), showing the involvement of the different xeroderma pigmentosum (XP) and Cockayne syndrome (CS) proteins. (Modified from Volker *et al.* 2001)
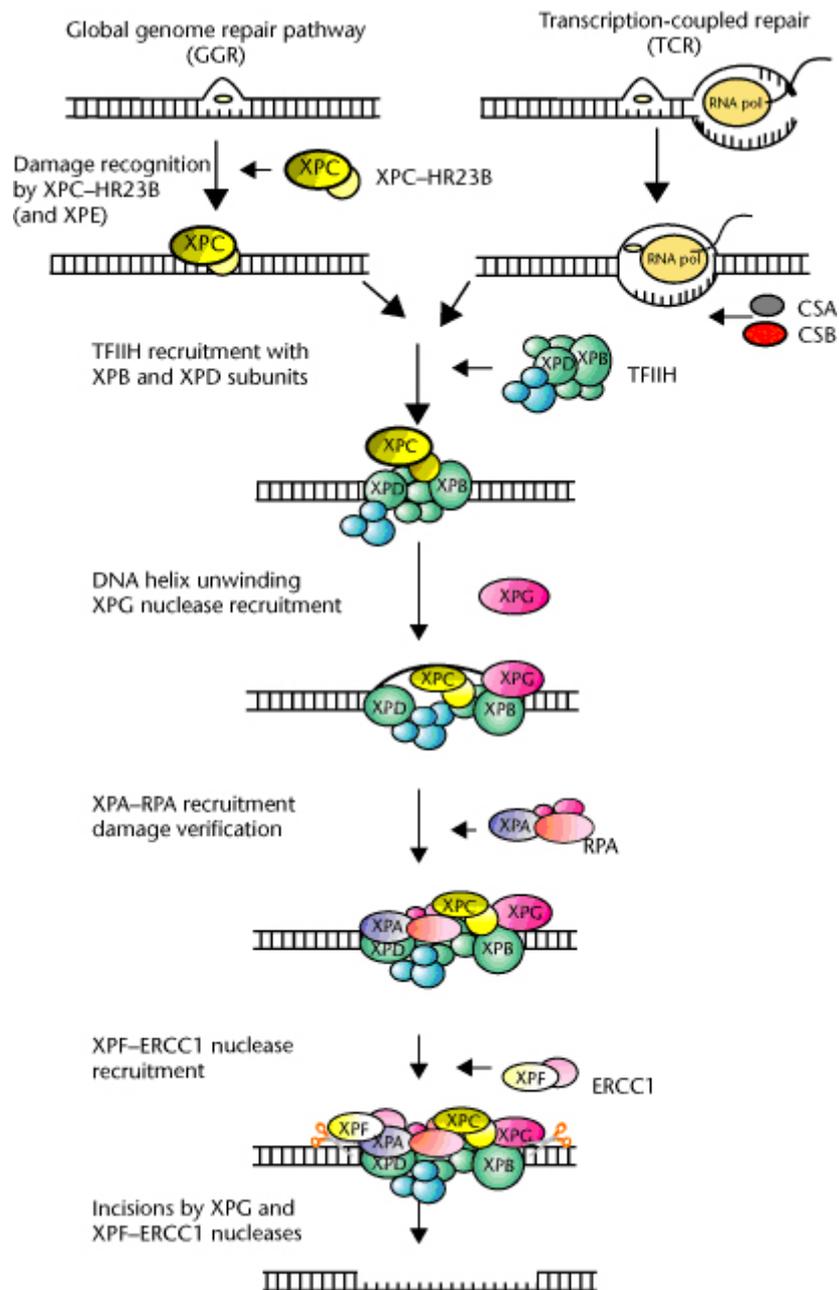
**Figure 2.** Patients with (a) xeroderma pigmentosum, (b) trichothiodystrophy and (c) Cockayne syndrome.

(a)   (b)   (c)
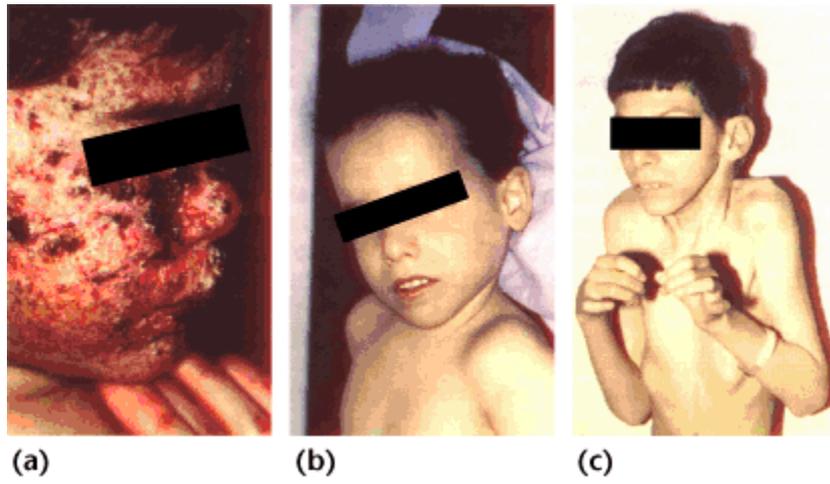
Figure 3. The steps of double-strand break repair by nonhomologous end joining.
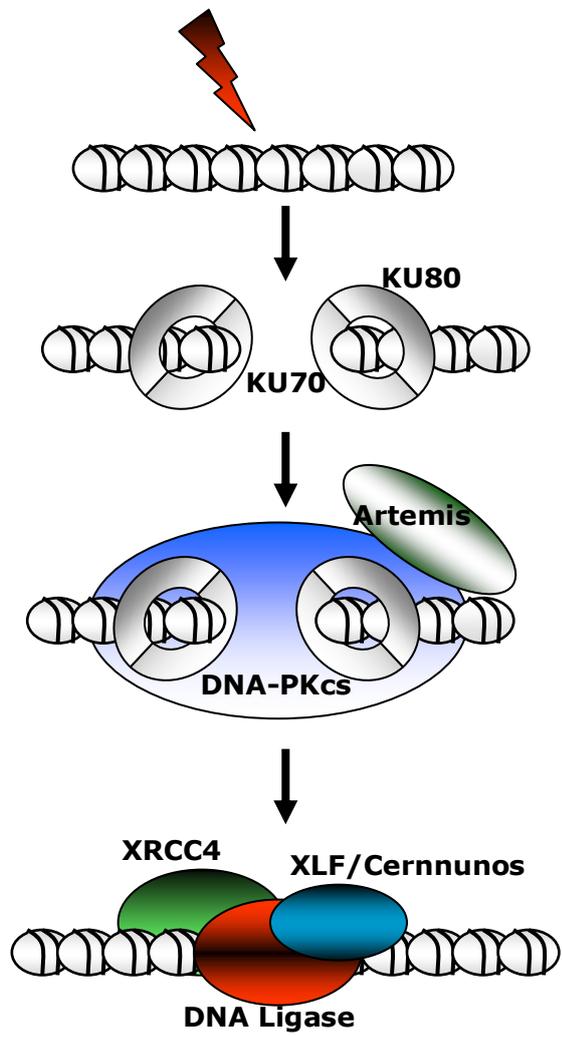
Figure 4 DNA damage signalling

The red arrows indicate ATM-dependent phosphorylation events. The mediators enhance ATM-dependent signalling. Phosphorylated H2AX is referred to as γH2AX.
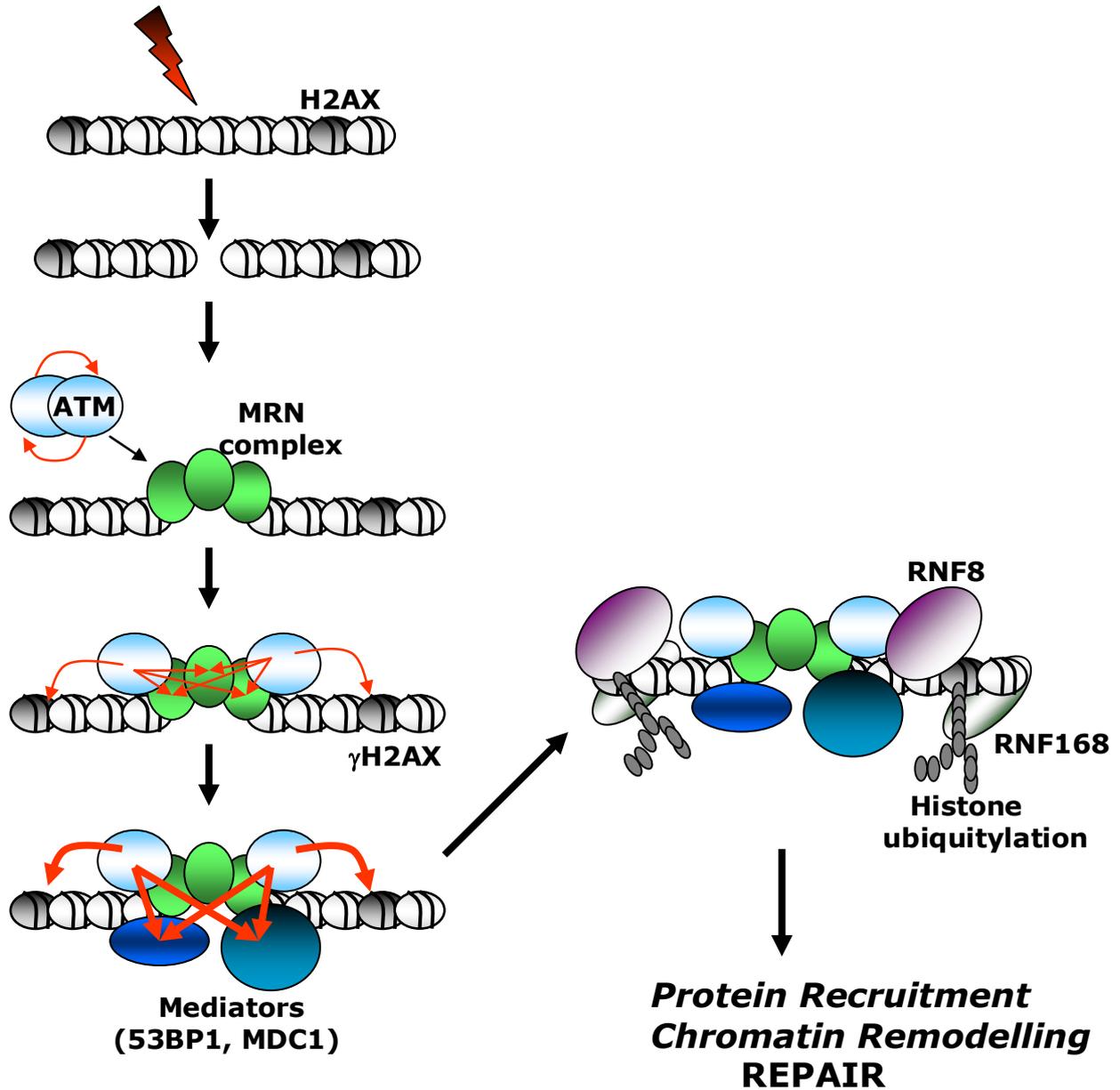
Figure 5 The steps of Base excision repair. ● represents a damaged or inappropriate base, some examples of which are shown on the following line. These bases are cleaved of the backbone by the indicated glycosylases. Disorders resulting from enzymatic defects are indicated in parentheses below the enzyme.