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DNA repair mechanisms protect our genome from carcinogenesis

Maria Carolina Strano Moraes[1], Januario Bispo Cabral Neto[1,2], Carlos Frederico Martins Menck[1]

[1]Department of Microbiology, Institute of Biomedical Sciences, University of Sao Paulo, Av. Prof. Lineu Prestes, 1374, Sao Paulo, SP, Brazil, [2]Institute of Biophysics Carlos Chagas Filho, Federal University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil

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1. ABSTRACT

Human cells are constantly exposed to DNA damage. Without repair, damage can result in genetic instability and eventually cancer. The strong association between the lack of DNA damage repair, mutations and cancer is dramatically demonstrated by a number of cancer-prone human syndromes, such as *xeroderma pigmentosum* (XP), *ataxia-telangiectasia* (AT) and *Fanconi anemia* (FA). This review focuses on the historical discoveries related with these three diseases and describes their impact on the understanding of DNA repair mechanisms and the causes of human cancer. As deficiencies in DNA repair are also often related with progeria symptoms, unrepaired damage and aging are somehow related. Several other pathologies associated with DNA repair defects, genetic instability and increased cancer risk are also discussed. In fact, studies with cells from these many syndromes have helped in understanding important levels of protection against cancer and aging, although little help has actually been conferred to the patients in terms of therapy. Finally, the recent advances in combined basic and translational research on DNA repair and chemotherapy are presented.

2. INTRODUCTION

The integrity of the DNA molecule is absolutely essential for guaranteeing the correct inheritance of genetic information. Damage to DNA can impair essential cellular processes, such as DNA replication or RNA transcription, possibly leading to cell death, although mutations might also occur. For multicellular organisms, when this happens in the germline, genetic transmission may be blocked by cell death. However, when somatic cells die as a result of DNA lesions, their renewal is sometimes impossible, this conceivably inducing tissue degeneration in the organism. Occasionally, the cell is not killed, although the lesions may leave a scarlike vestige, that is an alteration of the genetic information, or a mutation. Mutations can change cell metabolism, and when they occur in the germlines they may be transmitted to the progeny, thereby providing, in certain rare cases, the genetic variability necessary for evolution, although this may also affect the survival of the mutated progeny. In humans, these mutations may give rise to genetic diseases. When mutations affect somatic cells, deleterious consequences are also liable to occur, this including carcinogenesis. In the case of cancer cells, cell-

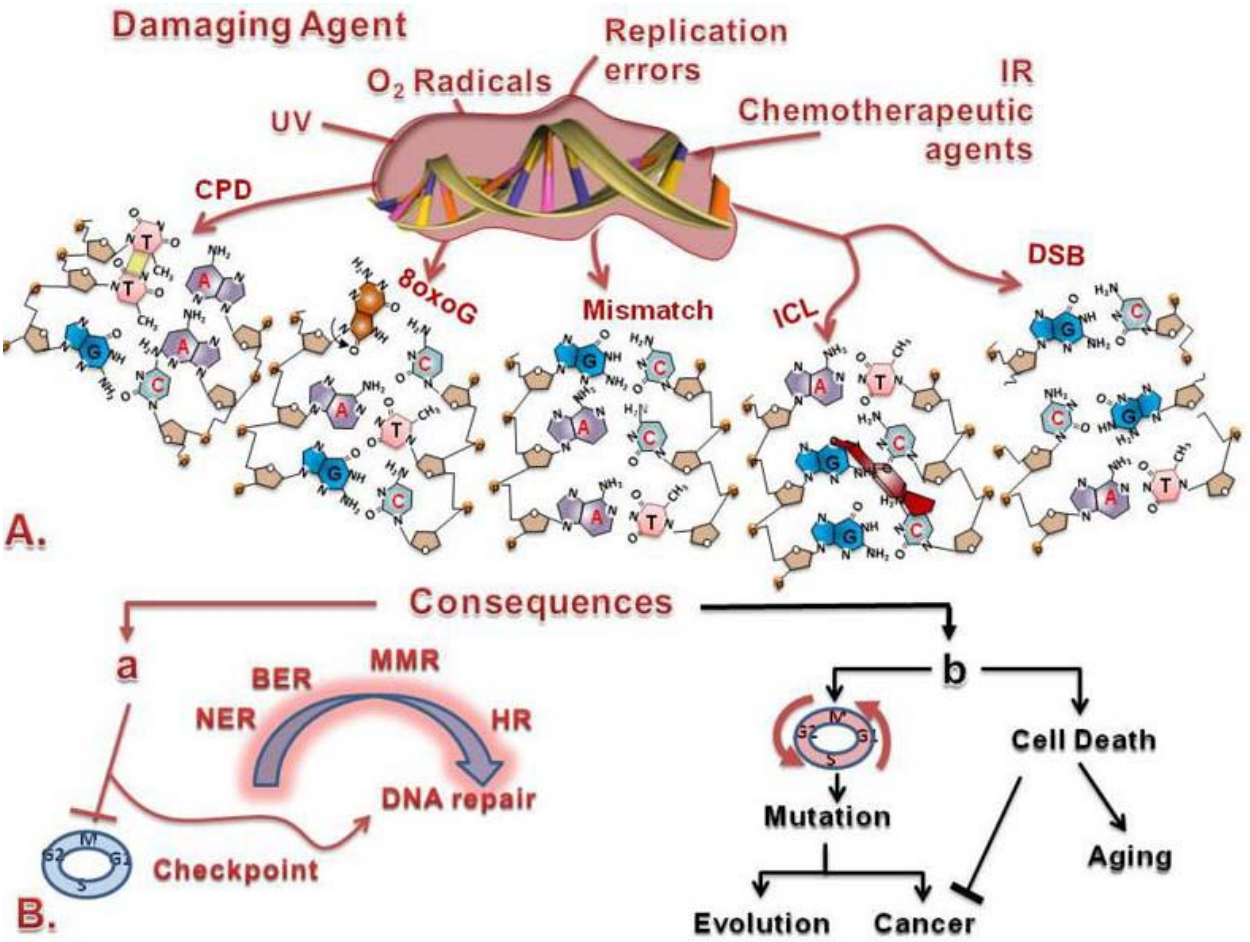

Figure 1. The induction of DNA damage and biological consequences in mammalian cells. A. Ordinary DNA damaging agents produce a spectrum of DNA lesions; B. DNA damage induces consequences in both cells and organisms: (a) Under normal conditions, DNA damage leads to transient arrest of the cell cycle (checkpoints), and activation of DNA repair mechanisms. (b) Long-term consequences of DNA lesions include different forms of mutations and genomic instability, which, although constituting the driving forces that give rise to evolution, also significantly contribute to carcinogenesis. Furthermore, unrepaired DNA damage promotes cell death, which, although directly coupled with the process of aging, also protects organisms by exterminating cancer cells.

killing promoted by DNA lesions may be positive for the organism, as dead cells are incapable of causing cancer. Figure 1 illustrates the effects of several DNA damaging agents, the lesions themselves, as well as the direct consequences on cells and organisms.

However, in order to avoid genetic instability, cells have evolved several mechanisms for protecting DNA molecules from damage, either by direct damage-removal, or by providing enzymes as an aid in cell-tolerance, as is the case of specific DNA polymerases that bypass the lesions. These mechanisms, first discovered in the 1950's in bacteria (*1*), are generally known as DNA repair mechanisms. Their discovery was almost concomitant with the proposal of the double-helix model by Watson and Crick, who inferred how DNA replication and RNA transcription should occur (*2*), although in the proposal, they omitted discussion on the importance of DNA stability. Later, Crick recognized that they "had totally missed the possible role of ... [DNA] repair although … I later came to realize that DNA is so precious that probably many distinct repair mechanisms would exist." (*3*). And several of these mechanisms have indeed been described over latter decades. Depending on the type of lesion, the known DNA repair pathways are normally classified according to the mechanisms involved. For example, nucleotide excision repair (NER) removes DNA lesions that cause helix distortions, whereas base excision repair (BER) removes altered bases. Another type of excision mechanism, mismatch repair (MMR), monitors and removes faulty base-pairing in DNA, and breaks in DNA (single and double-stranded) are normally repaired by homologous recombination repair (HR) or non-homologous end joining (NHEJ). Some lesions may be removed by simple reversion, whereat three types of direct repair are known, viz., photorepair (photolyase enzymes use light to revert pyrimidine dimers induced by ultraviolet - UV), methyl-transferase repair (alkylation adducts may be

removed by proteins that are instead themselves alkylated), and a more recently described type of oxidative DNA repair (where alkylation adducts are removed by oxidation). Although these repair pathways are classified independently, they exist in the cell as a network of proteins that aids in protecting the genome from DNA damage. Several examples of these interactions have already been demonstrated, with some proteins shown to be involved in more than one DNA repair pathway, but most probably there are many others to be discovered. With the exception of photorepair, all these repair pathways are found in human cells, and help to protect against cancer.

The intention of this work is not to describe the various detailed mechanisms of DNA repair (excellent reviews are referred to in the text), but rather, together with a historical view-point, to discuss how the lack of these mechanisms affects the human organism. More specifically, focus will be placed on the close relationship between genetic instability and cancer, dramatically demonstrated by the discovery of human syndromes in which the genetic instability has proved to be mainly caused by various deficiencies in cell DNA repair/ tolerance mechanisms. The association of the lack of DNA repair with syndromes of accelerated aging and neurodegeneration will also be discussed. Finally, how the modulation of such repair mechanisms may potentially be used in order to treat several diseases, from cancer to atherosclerosis, will be addressed.

3. XERODERMA PIGMENTOSUM AND OTHER NER-RELATED DISORDERS: NER DEFECTS PROMOTE CANCER PRONE AND PROGERIA SYNDROMES

Defects in DNA repair pathways give rise to several human disorders. The first cancer-prone syndrome, for which the DNA metabolism defect was described, was *xeroderma pigmentosum* (XP; from the Greek, *xero*, dry and *derma*, skin, and the Latin, *pigmentosum*, paint, pigmented). The first clinical description of this syndrome, issued by the dermatologists Moritz Kaposi (Hungarian) and Ferdinand Ritter von Hebra (Austrian) (*4*), appeared in 1874. By the year 1889, there were already 44 cases of XP recorded. At the time, the syndrome was also known as "dermatosis Kaposi", "liodermia cum melanosi et telangiectasia", "melanosis lenticularis progressiva", "angioma pigmentosum et atrophicum" and "atrophoderma pigmentosum". Then, however, the disease was surrounded by doubts, and XP patients were commonly diagnosed as either suffering from measles (in the early stages) or lupus. Even though XP was already recognized as an inherited disease that could afflict both males and females, it was believed that mainly one gender was sick in each family, or, in the words of H. Crocker, XP was "equally liable to attack both boys and girls, yet habitually selects only one sex in a family" (*5*). Another misconception was that the lesions appeared prevalently upon the right side of the patient's face. Sun exposure, on the other hand, was already correctly considered to be involved in the development of the disease (*5-7*). Later, the association of neurological defects with the dermatological features of XP was described for some patients in the DeSanctis-Cacchione syndrome (*8*), as will be seen below.

However, it was only almost a century later that the etiology of XP became clearer, when, in 1968, James Cleaver first demonstrated that a DNA repair pathway in XP cells is defective (*9, 10*). Following Cleaver's reports, Setlow and colleagues published their work confirming nucleotide excision repair (NER) deficiency in XP cells (*11*). Subsequently, research on both XP and NER underwent rapid growth, with many new discoveries, some of which outstanding, as the definition of XP complementation groups by cell fusion studies, the identification of the XP variant group (XPV), the cloning of XP genes, the understanding of the mechanism of NER, including determination of the two NER subpathways, TCR (transcription coupled repair) and GGR (global genomic repair), and the identification of other NER related syndromes, such as the Cockayne syndrome (CS), trichothiodystrophy (TTD), the cerebro oculofacial skeletal syndrome (COFS), the UV-sensitive syndrome (UVSS), and the XPF-ERCC1 progeroid (XFE) syndrome. Curiously, these syndromes mainly present clinical features related to premature aging, developmental problems and neurodegeneration, without increased cancer frequency. An interesting and personal account of the historical aspects of XP and NER was recently written by Cleaver (*12*).

The NER pathway removes several types of DNA double-helix distorting lesions, such as UV-generated lesions cyclobutane pyrimidine dimers (CPD) and 6-4 photoproducts (6-4 PP). The general scheme is presented in Figure 2, and basically comprises three steps, i.e., recognition of DNA damage, excision of the damage, and resynthesis and ligation of the excised patch. TCR and GGR differ only in the first step, for while GGR depends on the activity of proteins such as XPC-HR23B and XPE (DDB2), TCR relies on the blockage of RNA polymerase II to recognize the lesion itself. Two proteins participate in the recognition step of TCR, namely CSA and CSB. Once the lesion is detected, both subpathways converge, the actual process of damage removal involving a different set of proteins, namely XPA, RPA, the helicases XPB and XPD (components of the transcription factor TFIIH), and the endonucleases XPF-ERCC1 and XPG. XPB and XPD act to unwind the DNA, while XPA interacts with other NER proteins to direct the endonucleases XPF-ERCC1 (responsible for the 5' incision) and XPG (3' incision) to the damage site. Once the damaged region is excised, the new DNA fragment is synthesized by the DNA polymerases delta and epsilon, with DNA ligase I ending up the process by catalyzing the ligation of the new fragment to the original sequence. Mutations in seven of these proteins (XPA to XPG) can cause XP, the mutated protein defining the complementation group to which the XP patient belongs (respectively, XP-A to XP-G). For further details, see reviews (*13-15*).

XP is characterized by an approximate 1,000 to 2,000-fold increase in the incidence of skin cancer, with eye-damage also as a common feature. The early cutaneous symptoms, such as sun sensitivity and freckling, first

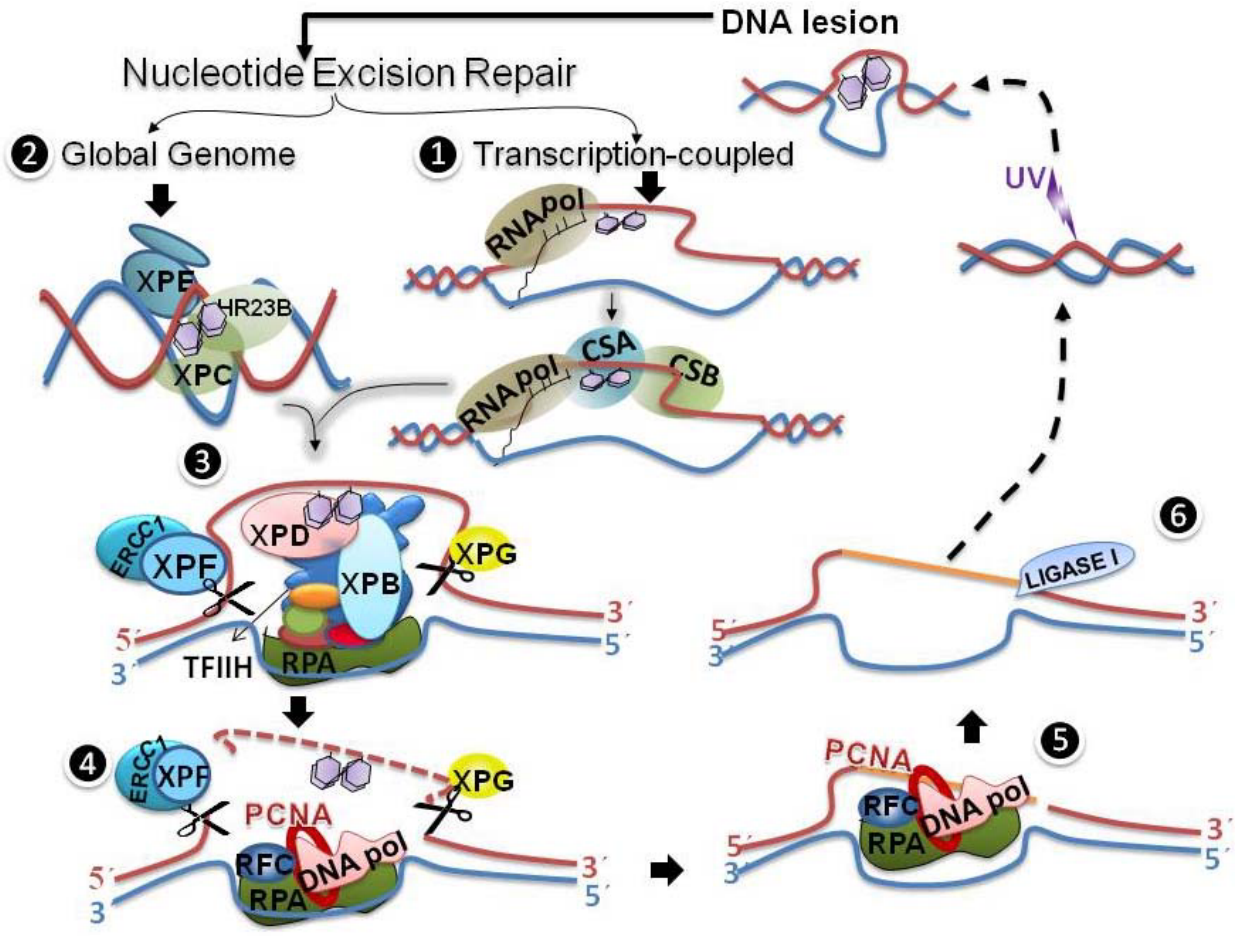

Figure 2. Schematic representation of Nucleotide Excision Repair in mammalian cells. Two NER subpathways are capable of working in concert in the removal of a wide variety of lesions from the genome, viz., (1) transcription-coupled repair (TCR), through the efficient recognition of lesions blocking transcription (mainly mediated by the TCR-specific proteins, CSA and CSB), and (2) global genome repair (GGR), in which the primary elements XPC-HR23B and XPE (DDB2) are involved in lesion recognition. (3) After the lesion is detected, both subpathways converge through the recruitment of the TFIIH transcription factor. (4) The nucleases XPF-ERCC1 and XPG make 5' and 3' incisions, respectively. Finally, (5) a new DNA fragment is synthesized by DNA polymerases epsilon and delta, and (6) DNA ligase I ends up the process by catalyzing the ligation of the new DNA fragment to the original sequence.

appear when the patient is around 1-2 years old, and are considered to be clinical markers of the disease, whereas skin cancer itself usually develops before the patient reaches 10 years old (see reviews *16* and *17*). However, at the end of the 19th century, there were already reports of patients with late onset of the disease, with one showing the initial symptoms of XP in the early teens (16 years old), and another who developed tumors only during adulthood (39 years old) (*5*). In 1970, E. Jung reported two female cases with late-onset symptoms (35 and 40 years of age) and normal repair capability. Since the clinical symptoms resembled a mild form of XP, he called the disease "pigmented xerodermoid" (*18*). Two years later, J. Cleaver reported three cases of XP with normal levels of repair (*19*), whereas later still, Lehmann and colleagues discovered that these so called "XP variants" (XP-V) with normal excision repair, were, in fact, deficient in DNA synthesis after UV irradiation (*20*). Further studies revealed that the defective gene in XP-V patients is that which codifies for DNA polymerase eta (pol eta) (Figure 3), a protein that acts in translesion synthesis (TLS) to bypass unrepaired DNA lesions, thereby allowing the continuity of the replication process (reviewed in *16*). Characteristically, XP-V cells have higher than normal mutagenicity rates following UV irradiation (*21*) and cisplatin treatment (*22*). In the case of lesions caused by UV irradiation, TLS across CPDs, but not 6-4 PPs, is less efficient and more mutagenic in XP-V than in pol eta-proficient cells, probably because an alternative translesion polymerase functions in pol eta-deficient cells to bypass the CPD in an error-prone manner, thereby enhancing error frequency and, consequently, increasing mutagenicity (*23*).

As a reflection of XP genetic heterogeneity, the clinical features of XP vary according to the complementation group to which the patient belongs. For

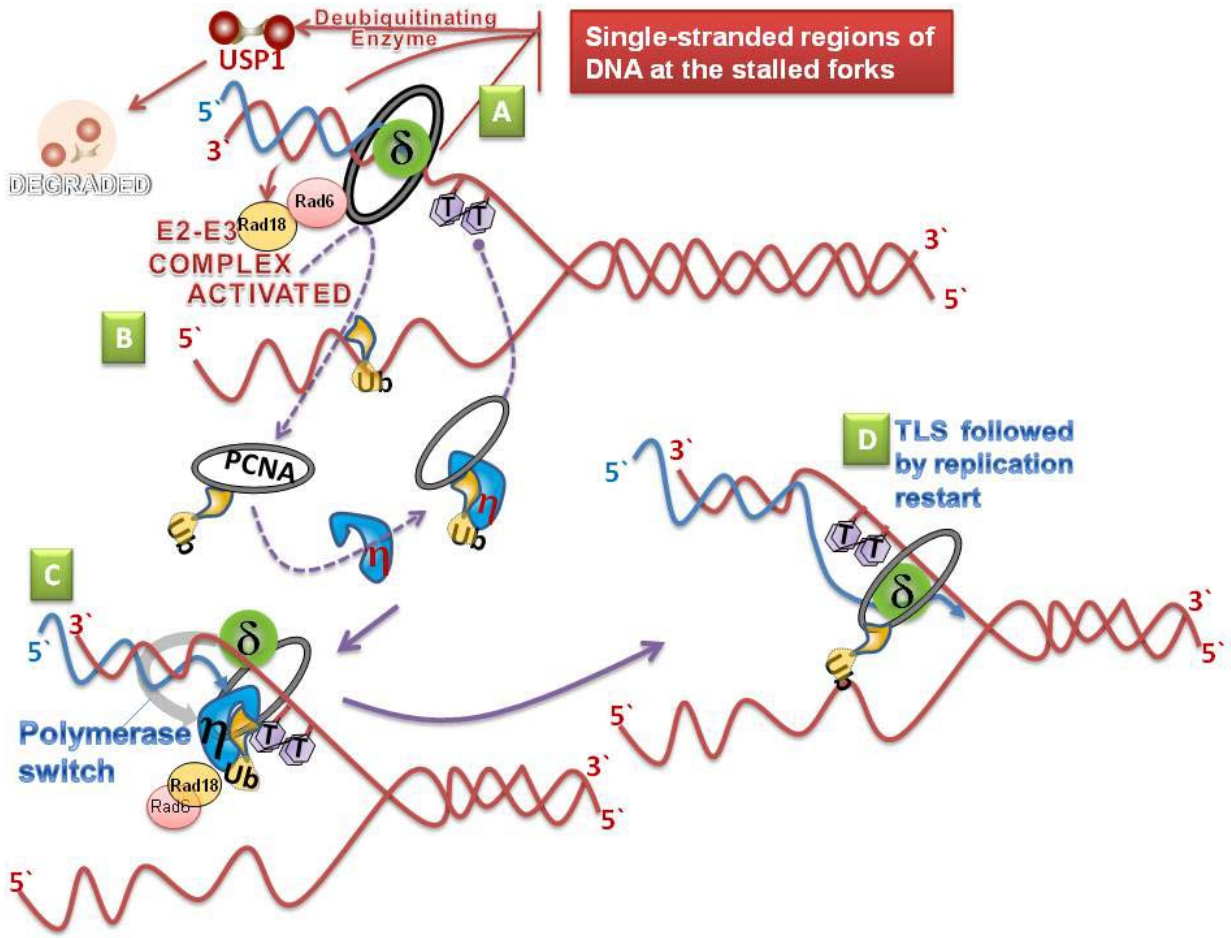

Figure 3. Defective translesion synthesis is the hallmark of XPV. Upon encountering a UV-induced DNA lesion, the error-free replicative polymerase (Pol delta) stalls, through the inability to insert a nucleotide opposite the lesion, thereby inducing PCNA (ring) monoubiquitination (UB). This increases the affinity for Pol eta, which inserts correct nucleotides opposite the thymidine dimers induced by UV light. Functional Pol eta is absent in XPV patients, whereat another error prone TLS DNA polymerase inserts the incorrect nucleotide opposite the lesion, thereby leading to the clinical pathological changes observed in XPV patients, mainly sunlight-induced skin cancer.

instance, XP-V and XP-C are clinically alike, with moderate to severe symptoms and generally no neurological abnormalities. These two complementation groups, along with XP-A, are the most frequent, corresponding to approximately 70% of XP cases worldwide (*24*). The other complementation group with only GGR deficiency is composed of XP-E patients, with almost normal levels of NER (up to 60%), and only mild symptoms of XP. In fact, cells from both XP-V and XP-E patients are only slightly sensitive to UV light, whereas cells from XP-A patients are extremely so, the patients generally presenting a severe form of XP with neurological symptoms (the DeSanctis-Cacchione syndrome – DS-C). As to patients with helicase defects, XP-B patients are very rare (until 2005, only 3 families had been recorded), whereas XP-D patients, besides being more common, are more prone to developing malignant melanomas and neurological disorders. Nevertheless, various mutations in *XPD* and *XPB* genes cause not only XP, but also other NER-related disorders, namely TTD, as well as a disease with the combined symptoms of XP/CS, which will be discussed below. The same occurs with mutations in XPG, which can cause a severe form of XP (XP-G), or XP/CS, depending on the existent mutation. XP-F patients present a mild form of the disease, with median cellular sensitivity to UV and rare cases of neurodegeneration (see reviews *14, 25* and *26*).

As mentioned previously, defects in the NER pathway cause other autosomal recessive disorders besides XP, those most studied being the segmental progerias TTD and CS. Photosensitivity is a clinical feature of CS, first described as a syndrome by Cockayne in 1936 (*27*). Besides photosensitivity, other CS-features are cachectic dwarfism, microcephaly, postnatal growth failure and growth retardation, immature sexual development, lack of subcutaneous fat, progressive sensorineural deafness, brain dysmyelination, pigmentary retinopathy and a characteristic "bird-like" face. Although the link with NER was not at first apparent, cells from CS patients were shown to be

sensitive to UV-light and unable to recover from RNA synthesis inhibition after UV irradiation (*28*). This feature has been used to identify the complementation groups, thereby leading to the cloning of *CSA* and *CSB* genes. Furthermore, these effects in RNA synthesis were suggested to be related to a defect in the preferential repair of actively transcribing genes, this representing a small proportion of total NER. In fact, CS mutations were shown to affect the TCR subpathway of NER, and CSA and CSB proteins action in the first steps of DNA damage recognition (mainly CPD) on the transcribed strand of actively expressed genes.

CS presents a very heterogeneous picture, with distinct mutations in the very same genes involved in the development of a number of syndromes, these varying from mild to extremely severe. It has been reported, for example, that a unique inactivating mutation in *CSB* is capable of causing two severe pathologically distinct disorders, either CS or a severe form of XP (DS-C syndrome) (*29, 30*). In contrast, a null mutation in the same *CSB* gene can give rise to a milder disease, UVSS, characterized mainly by photosensitivity (*31*), which can alternatively be caused by mutation in *CSA* (*32*). Furthermore, there are reports of patients bearing the complex syndrome XP/CS, with somatic and neurological abnormalities similar to CS and the skin problems observed in XP patients, caused by mutations in *XPB*, *XPD* or *XPG*. The neonatal lethal syndrome COFS, the result of various mutations in *XPD* (*33*), *XPG* and *CSB* genes (reviewed in *14, 17, 34* and *35*), is another severe disorder through NER deficiency. Nevertheless, to date the most severe clinical case of NER deficiency is a recently reported patient bearing a mutated *ERCC1* gene. This, the first report of a mutation in ERCC1, was therefore considered as a new NER complementation group. The patient, who was diagnosed as a severe case of COFS, died during early childhood (14 months old) (*36*). There was, however, a certain relationship with the progeroid syndrome, recently described in a 15-year-old boy with a severe mutation in the *XPF* gene (the XPF protein acting in NER in partnership with ERCC1). This patient presented several clinical features of progressive neurodegeneration (including dwarfism, cachexia, and microcephaly). Interestingly, although he also presented skin sunlight sensitivity, there was no development of skin tumor, and dermatological symptoms were inconsistent with XP. The progeroid syndrome, which probably affected the two latter patients, was named XFE (for the XPF-ERCC1 progeroid syndrome) (*37*).

First proposed by Price and colleagues in 1980, the name trichothiodystrophy (TTD) describes one of the clinical markers of this disease, viz., sulphur-deficient brittle hair (from Greek: *tricho* – hair; *thio* – sulfur; *dys* – faulty; *trophe* – nourishment) (*38*). In fact, hair abnormalities, such as tiger-tail banding of hair analyzed by way of polarized microscopy, are diagnostic hallmarks of this syndrome. Other clinical features include developmental delay, intellectual impairment, short stature, proneness to infections, decreased fertility, and nail and ocular abnormalities. Symptoms can vary from mild to extremely severe, the most severely affected patients often dying during early childhood. There are two forms of TTD, with and without photosensitivity. The non-photosensitive form is caused by mutations in TTDN1, a protein codified by *C7orf11*, and which possibly participates in regulating mitosis and cytokinesis (*39*). The photosensitive form is caused by mutations in three different subunits of TFIIH, namely TTDA (*40*), XPB and XPD. Once again, XP-B patients are rarer, probably because XPB activity is essential for transcription. Besides TTD and XP, distinct mutations in *XPB* and *XPD* are liable to cause a disease with overlapping features of both syndromes, namely XP/TTD (reviewed in *41* and *42*).

Even though they share diverse deficiencies in the same repair pathway (NER), and all are marked by photosensitivity, of all the syndromes discussed in this topic, only XP is linked to an increase in the incidence of cancer, most of the remainder presenting progressive neurodegeneration and features of premature aging. A summary of the several NER related syndromes with the genes affected is presented in Figure 4. However, it should be noted that the diagnosis of these syndromes, especially as regards to aspects related to neurodegeneration, may be difficult, some even misleading. For example, clinical diagnosis in CS or XP/CS patients presents features related to demyelination of the central nervous system, together with the calcification of certain brain areas, whereas the DS-C syndrome is associated with neuronal loss in specific cell populations (*43*). There is, as yet, no plausible explanation of the apparent paradox of the absence of cancer in many of the NER syndromes. In general, patients with impaired GGR do not present clinical effects involving either the nervous system or development, whereas this is clearly observed in patients, such as CS, with TCR impairment. It has been proposed that CS cells, probably mediated by transcription blockage, are strongly signaled to cell death by DNA damage (*44*), which is in agreement with the cell-killing effect in the progressive degeneration and aging in these patients, as well as a reverse effect in cancer development, based on the idea that dead cells do not result in cancer. Nevertheless, XP-A cells are also highly sensitive to DNA damage, XP-A patients themselves always presenting skin cancer. On the other hand, since TCR affects only CPD repair, but not 6-4 PPs, there could be a possible relationship with the origin of UV-induced cancer (*45*). However, repair of 6-4 PP lesions in the cells of TTD patients, not prone to skin cancer if unassociated with XP, was also shown to be deficient (*46*). Another important aspect is that the characteristically short lifetimes in most of the severely affected CS, COFS, XFE and TTD patients, are insufficient for cancer development. Independently of why there is no tumor development in certain NER syndromes, it should be noted that the existence of such a diverse spectrum of diseases with NER deficiencies could be viewed as a reflection of the importance of this repair pathway in the maintenance of genome stability in human cells.

4. ATAXIA-TELANGIECTASIA: STARTING POINT FOR UNDERSTANDING THE DNA DAMAGE-RESPONSE NETWORK

Ataxia-telangiectasia (AT), an inherited autosomal recessive disease, affecting 1 in 40,000 births, is

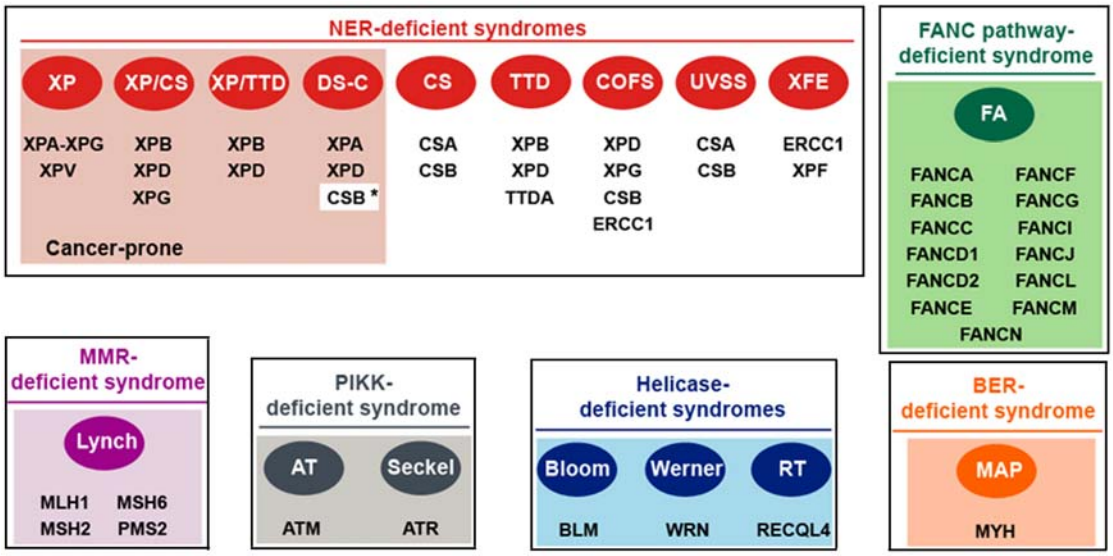

Figure 4. Representative scheme of the DNA repair-deficient syndromes and genes found to be mutated in related patients. Each box represents either a pathway or an enzyme family possibly impaired by a germline mutation, thereby giving rise to a human syndrome. The white box represents syndromes not related to increased cancer frequency, whereas those in colored boxes represent cancer-prone disorders, with the exception of the complementation group CSB originating the DeSanctis-Cacchione syndrome, indicated by (*). Abbreviations used: XP, xeroderma pigmentosum; CS, Cockayne syndrome; TTD, trichothiodystrophy; DS-C, DeSanctis-Cacchione syndrome; COFS, cerebro oculofacial skeletal syndrome; UVSS, UV-sensitive syndrome; XFE, XPF-ERCC1 progeroid syndrome; FA, Fanconi anemia; AT, ataxia-telangiectasia; Seckel, Seckel syndrome; Bloom, Bloom syndrome; Werner, Werner syndrome; RT, Rothmund-Thomson syndrome; MAP, MYH-associated polyposis; Lynch, Lynch syndrome; NER, nucleotide excision repair; PIKK, phosphoinositide 3-kinase (PI3K)-related protein kinase family; BER, base excision repair; MMR, mismatch repair.

initially characterized by progressive neurodegeneration, especially in the cerebellum, as well as oculo-cutaneous telangiectasia, immunodeficiency and recurrent sino-pulmonary infections. In fact, the term ataxia (from the Greek *ataxis*, disordered) derives from the severe cerebellar *ataxia* observed in these patients, this leading to a lack of motor coordination and progressive mental retardation. *Telangiectasia* (from Greek *telos* end, *angeion* vessel, *ektasis* dilation) refers to the marked dilatation of small blood vessels, especially in the skin and eyes. The condition was first mentioned by several authors early in the twentieth century, although AT itself was not distinctly recognized until the late fifties, when Border and Sedgwick (*47*) published a study of 8 cases from 5 unrelated families, 6 akin, thereby coining the term ataxia-telangiectasia syndrome to describe the disorder clinicopathologically. Soon after, in the early sixties, a striking cancer susceptibility increase of approximately 100 times higher when compared to the general population, was reported as a clinical hallmark feature of AT patients, with the most common tumors affecting the lymphoreticular system, including Hodgkin and non-Hodgkin lymphoma (*48*). An important consideration is that, different from XP, heterozygous relatives of AT patients are more prone to developing breast cancer (*46*).

The most striking feature of AT cells is their hypersensitivity to ionizing radiation (*49*), discovered soon after the observation that AT patients suffered severe and fatal reactions when submitted to cancer radiation therapy (*50*). Later, it was shown that AT cells were also sensitive to X-ray mimetic chemicals, but not to UV-light, thus forging the idea that AT cells were for ionizing radiation what XP cells, described above, were for UV radiation. Although indicated in early reports (*51-53*), there is no clear indication of defective repair of DNA damages induced by ionizing radiation in cells from AT patients.

Molecular defects in AT cells affect DNA replication (mainly replication-origin firing) and DNA damage checkpoint. Surprisingly, this was first perceived through the discovery of their radioresistant DNA synthesis capacity. In fact, in human cells, and as a consequence of DNA damage from UV or ionizing radiation, there is an almost immediate response in DNA synthesis inhibition. From previous observations, it was found that in XP cells, this inhibition is much stronger after UV-radiation, with similar expectations when considering AT cells and ionizing radiation. However, on the contrary, three different laboratories almost simultaneously reported that DNA synthesis in AT cells, when compared to normal fibroblasts, was barely inhibited after gamma-ray irradiation (*54-56*). This radioresistant DNA synthesis, later also observed after DNA damage induced by radiomimetic drugs, such as bleomycin (*57*), is a hallmark of AT cells. It was correctly interpreted to be responsible for the high sensitivity of AT cells to DNA damage induced by these agents, as there was no cease in either cellular DNA synthesis or the cell cycle, with the consequential loss in the crucial time necessary for lesion removal. The

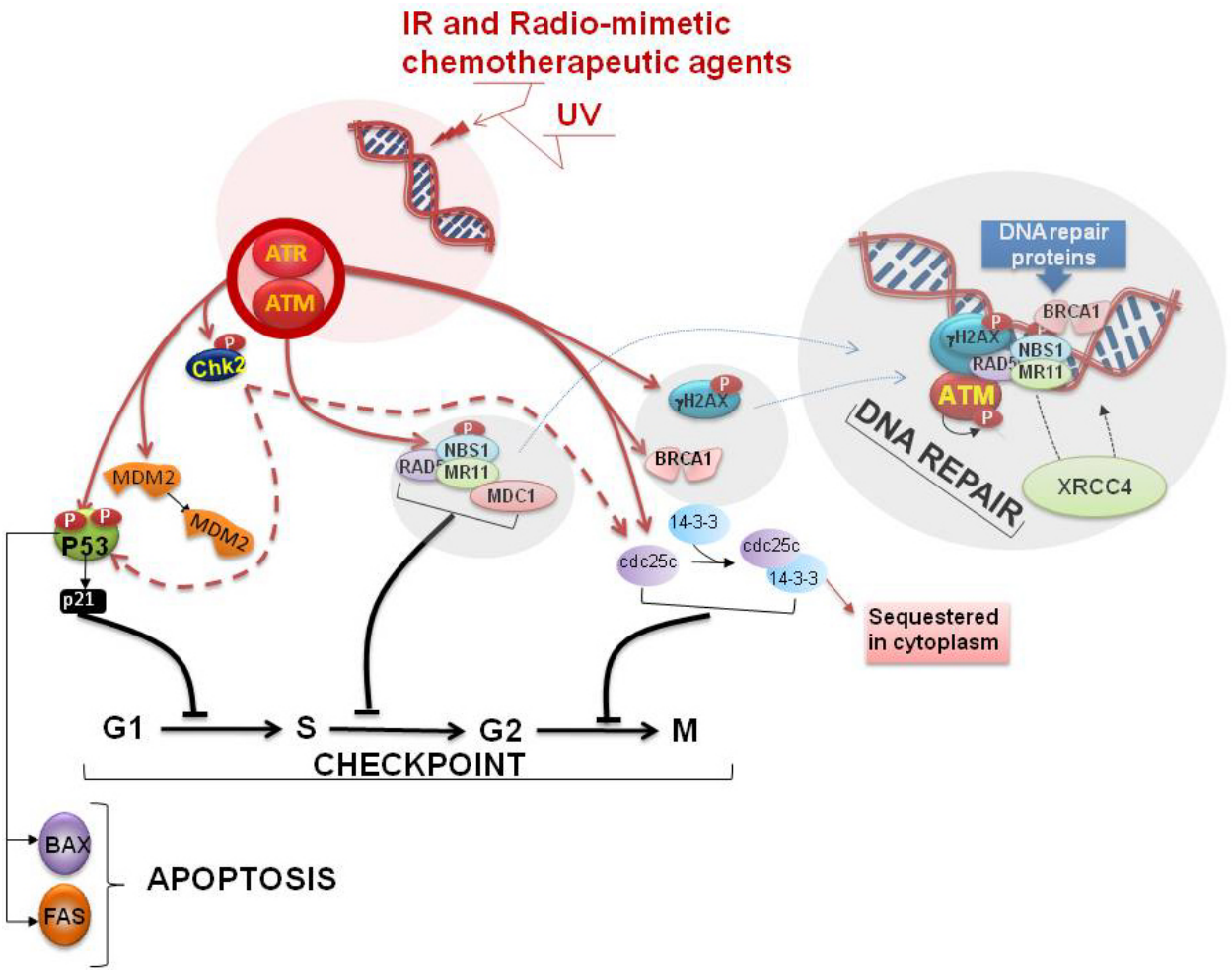

Figure 5. Summary of ATM/ATR network of cellular responses to DNA damage. After DNA damage, and depending on the type of damage, ATM or ATR act as kinases in different substrates, exemplified here by p53, Chk2, Nbs1 and H2AX, thereby triggering DDR. DDR is based on complex networks of signaling pathways that activate cellular processes, such as cell cycle arrest (checkpoint), cellular survival coupled with DNA repair, and apoptosis.

continuous replication of damaged DNA thereby leads to an increase in cell-killing in AT cells.

Radioresistant DNA synthesis has provided the basis for detecting complementation groups of the defect in cell hybrids, culminating in the identification of four groups (*58*). This genetic heterogeneity was in agreement with the concept of AT as a clinically pleiotropic disorder. A complex multigenic inheritance model, in which at least four different genes were involved in the pathology, was thus proposed. Notwithstanding, the sequence of just one gene (*ATM*, for AT mutated) was identified as being impaired in all the AT patients, thereby showing that mutations in this gene alone were indeed responsible for the various manifestations of the disease (*59*). The *ATM* gene, located in the human chromosome 11q22-23, encodes a Ser/Thr protein kinase member of the phosphoinositide 3-kinase (PI3K)-related protein kinase (PIKK) family (*60*), which includes ATR (AT and Rad3-related protein), SMG1 (required for nonsense-mediated decay of mRNA harboring premature terminator codons and DNA-damage responses), as well as the catalytic subunit of DNA-dependent protein kinase (DNA-PKcs). Since identification, the functional role of ATM became a paradigm in cancer research, providing valuable information on how DNA damage response (DDR) pathways lead to cell cycle arrest, DNA repair, or the death of cells exposed to genotoxic agents. A general scheme of ATM/ATR-mediated DDR signaling is presented in Figure 5.

It is well established that, in mammalian cells, DNA damage initiates an interacting signaling transduction pathway, orchestrated by several proteins working as sensors, transducers and effectors. Both ATM and ATR kinases are supposed to be prototype transducers of DNA-damage signaling to a multitude of cellular pathways. For example, p53, a tumor suppressor protein involved in the multiple processes implicated in the maintenance of genomic stability, including DNA damage checkpoints, DNA repair and apoptosis, was the first ATM substrate to be identified by several groups almost simultaneously (*61-63*). ATM and ATR have, through working in a central

signal transducer system, in response to a wide range of DNA lesions in eukaryotic cells, the appropriate flexibility for successfully operating on a very large number of similarly shaped substrates (*64, 65*). The activation of numerous cellular processes and pathways, as diverse as DNA damage repair coupled with accurate cellular survival or cellular inactivation by apoptosis, is carefully coordinated to mediate genome stability (*66, 67*). In general, ATM is considered to be responsible for the activation of G1, S, and G2/M checkpoints following ionizing-radiation-induced DNA lesions (*68*), whereas S phase checkpoint activation by UVC, hydroxyurea or DNA interstrand cross links follows a branched pathway, under the control of ATR (*69*). Interestingly, mutations in the *ATR* gene were found in some patients diagnosed with the Seckel syndrome, characterized by severe developmental, and even intrauterus, problems (*70*). Interestingly, even cells from patients not mutated in this gene are defective in the ATR-pathway function (*71*).

In addition to p53, ATM also phosphorylates the checkpoint kinase Chk2, Cdc25C (the tyrosine phosphatase involved in cell cycle control) and BRCA1 (a protein linked to DNA repair and breast cancer), thereby exerting control over the G1/S and G2/M checkpoints, H2AX (one of a set of histone H2A proteins), Nbs1 (a component of the MRN complex, Mre11-Rad50-Nbs1, involved in double strand break – DSB – repair and activation of the S phase checkpoint), and FANCD2 (also necessary for activation of the DNA damage-induced S phase checkpoint). In fact, radioresistant DNA synthesis in AT cells, described above, resulting from a specific defect in the S phase checkpoint, is also observed in other human cancer prone genetic syndromes, such as the Nijmegen breakage syndrome (NBS, mutated in *NBS1*), the AT-like disorder (ATLD, mutated in *MRE11*) and Fanconi anemia (*72-75*).

Following exposure to DSB-inducing agents, such as ionizing radiation or radiomimetic drugs, the ATM dimer dissociates into active monomers, a process mediated by the MRN complex, whereupon ATM kinase activity is enhanced, thereby activating a signal transduction pathway to initiate DNA repair via HR. Andegeko and colleagues (*76*) proposed a novel methodology to detect the abundance and subcellular distribution of ATM in response to DSB-induced lesions. They successfully showed that, immediately following DSB induction, a fraction of the ATM pool becomes extraction resistant and detectable in nuclear aggregates. Moreover, ATM was found in the same nuclear foci with the phosphorylated form of histone H2AX (gamma-H2AX) and Nbs1, thereby implying ATM association with DSB sites.

4.1. Which comes first: sensors or transducers?

The role of ATM and ATR in DDR pathways is partially mediated by the effector proteins Chk1 and Chk2. Once activated, these checkpoint kinases cause the phosphorylation and consequent inactivation of Cdc25 (cell division cycle 25) tyrosine phosphatases, thereby creating a binding site for 14-3-3 proteins, which promote nuclear export and accumulation of Cdc25 in the cytoplasm (*77*). The cell cycle will remain quiescent, as long as Cyclin-dependent kinase 1 (Cdk1)/Cdc2 complexes remain phosphorylated through the absence of Cdc25 phosphatases. It is now widely accepted that the MRN complex acts as a DNA damage sensor in mammalian cells, although it also possesses the evident end-bridging and endonucleolytic activities required for initiating HR repair of DSBs (*78*). Assembly of the MRN complex is mediated by the Mre11 protein itself, this binding Nbs1, DNA and the SMC (structural chromosome related) protein Rad50, thereby facilitating the establishment of the chromatin bridging scaffold structure required for stabilizing the DNA ends at the break (reviewed in *79*).

Nbs1, one of the three components of the sensor MRN complex, is presumably properly phosphorylated by ATM in response to DSB lesions, although somewhat contrary to reason, thus constituting a paradox in which the transducer may precede, to some extent, the sensor. Over the past decade, ATM and ATR were recognized by several authors by their potential roles as DNA-damage sensors and initiators of subsequent protein kinase cascades. More recently, Guo and colleagues (*80*) reported that oxidation of ATM by H_2O_2 also increased its affinity for GST-p53, thereby inferring that conformational changes occur during the process. *In vitro* studies have shown that H_2O_2 appears to induce the stabilization of covalent dimers of phosphorylated ATM, as observed with ATM immunoprecipitated from human cells exposed to H_2O_2. Thus, this original set of data contains a plausible explanation regarding the activation of ATM under conditions of oxidative stress, besides showing it to be an important sensor of reactive oxygen species in human cells. Nevertheless, queries as to the precise mechanism by which damaged DNA activates ATM, the meaning of ATM autophosphorylation and how the gene itself can be deactivated, are, as yet, incompletely understood. Whatever the mechanism, it is by no means an easy pathway, given the chemical diversity of damaged DNA and the complexity of the cellular response to DNA lesions. Thus, this fundamental biological process can hardly proceed at the expense of a single class of proteins. It is more likely that several independent molecular complexes are involved in sensing and signaling different types of DNA damage (see reviews *81* and *82*).

ATM also phosphorylates the histone H2AX C-terminal in the vicinity of DSBs, to so generate the necessary gamma-H2AX for chromatin remodelation (*83-85*). In mammalian cells, the so-called checkpoint mediate protein (MDC1) binds to gamma-H2AX, thereby connecting the MRN-ATM complexes through phosphorylation-dependent interactions with Nbs1 FHA-BRCT1-BRCT2 domains, these serving to further amplify or sustain checkpoint signals. ATM and ATR are thus activated during the initial stages of the DNA damage response signal transduction pathway, whereby the reasonable deduction of their double function, transduction of the message to other transducers or effectors and stereospecific recognition, together with other proteins operating in DNA sensing, of certain DNA lesions (*86-90*).

5. THE MANY FACETS OF FANCONI ANEMIA

Progress in cancer research is often slow, sometimes originating from unexpected findings associated

with substantial intuition. Thanks to the Swiss pediatrician Guido Fanconi, the existence of a rare genetic disease, known as Fanconi anemia (FA), and displaying susceptibility for childhood cancers, was reported as early as 1927 (*91*). As the symptoms may be varied and complex, pathological diagnosis was complicated, and Guido Fanconi intuitively realized that the syndrome might be the result of chromosomal translocation instead of a defect in a single gene. This rationale became the keystone in diagnosis established on the basis of both spontaneous and increased chromosomal breakage in the presence of DNA interstrand cross-linking agents, as observed in cells from FA patients.

FA is a rare multigenic disorder, its major clinical aspects including various birth defects (eg, dangling thumbs, microcephaly, radial-ray abnormalities), as well as renal, ocular, genital and cardiac deformities. Short stature and pigmented birthmarks (*cafe au lait spots*) are also commonly observed at an early age. The onset of impaired hematopoiesis probably takes place from the very early stages in development. Thus, deficiencies in embryonic hematopoiesis may underlie the progression to bone-marrow failure (*92*). Nevertheless, the most relevant (and certainly most devastating) clinical features are acute and progressive aplastic anemia (deficiency of all bone-marrow derived hematopoietic lineages), and the high incidence of cancer (especially myeloid leukemia and squamous cell carcinoma). In leukemia, the increase in risk, when compared to the general population, is close to 1,000-fold (*93*).

In one of the most relevant discoveries in the early 1960's, it was noted that cultured cells from FA patients are most frequently associated with chromosomal fragility. Later, it was observed that the increased rates of chromosome breaks could be specifically induced by DNA cross-linking agents, such as mitomycin C (MMC) or diepoxybutane (DEB). Since then, these features, in conjunction with clinical data, became common place in confirming diagnosis. In addition to spontaneous and induced chromosomal aberrations, cells from FA patients show hypersensitivity to cross-linking agents, altered homologous recombination, abnormal induced apoptosis and defects in S/G2 phase checkpoint activation in response to DNA interstrand crosslinks (ICL).

Based on the supposition that phenotypic heterogeneity, both clinical and cellular, in FA patients, is related to defects in various genes, a series of ingenious experiments were carried out in the early 1980's to check the hypothesis of genetic heterogeneity. This involved the search for complementation in somatic cell hybrids constructed by fusing together lymphoblast cell lines from unrelated FA patients. The complementation of cellular defects was achieved by analyzing sensitivity to growth inhibition induced by MMC, as well as spontaneous and MMC-induced chromosome breakage in the hybrid cells. Initial studies provided evidence of at least two complementation groups, FANCA and FANCB, the latter capable of complementing the FA phenotype of a standard FANCA cell-line (*94*). Complementation studies led to the identification of other groups, as well as to the cloning of most of the involved genes. Until recently, 13 mutated genes had been associated to known complementation groups, namely FANC-A, B, C, D1, D2, E, F, G, I, J, L, M, N. Recently, two individuals with clinical features of FA were found to be mutated in the gene coding the SLX4 protein, which was renamed *FANCP* (*95*). They were, thus, the first patients assigned to the fourteenth FA complementation group, FANC-P. With the exception of the *FANCB* gene, located on the X chromosome (Xp22.33) (*96*), all the remainders were found in autosomal chromosomes, thereby underlying a recessive inheritance pattern. The *BRCA* gene, implicated in breast cancer susceptibility, was surprisingly identified as the *FANCD1* complementing gene (*97*). Thus, in the light of these remarkable findings, FA can be defined as a multigenic autosomal and X-linked recessive disorder, resulting from deleterious mutations in those related FA genes controlling the FA/BRCA pathway. Many of the protein products of these genes (FANCA, -B, -C, -E, -F, -G, -L and -M) interact both with each other and with three other non-FA proteins, FAAP100, FAAP24 and HES1, to form a multisubunit nuclear complex, the FA core complex, indispensable for monoubiquitination of the FANCI-FANCD2 heterodimer (also called the ID complex), either in response to DNA damage or during S phase of the cell cycle. Ubiquitination of FANCD2 is catalyzed by the E3 ubiquitin-ligase FANCL, and this post-translational modification of FANCD2 is required for its appropriate recruitment to the DNA repair nuclear foci, together with other proteins, such as BRCA1, BRCA2, gamma-H2AX, Mre11, Rad51 and RPA (*98*). The three remaining FA proteins, FANCD1/BRCA2, FANCJ/BRIPI/BACH1 and FANCN/PALB2, act downstream from FANCD2, in this pathway (*99*). Despite remarkable progress in research on the molecular features affecting FA deficient cells, there are still some cell lines from patients with positive clinical and molecular FA diagnosis in which the affected gene is still unknown.

To a certain extent, FA is known to share overlapping phenotypes, as abnormal DNA repair and cancer predisposition, with other genetic disorders, such as XP, the Bloom Syndrome (BS) and AT, thereby implying their mutual linkage through a complex criss-cross biochemical pathway. XPF cells, for instance, are also sensitive to ICL inducers, which could be reasonably explained by the participation of XPF-ERCC1 endonuclease in the FA pathway of cross link repair (*100*). On the other hand, FA cells are exquisitely refractory to DNA damage checkpoints, as it occurs in AT cells, understandable in the light of DNA damage recognition and the remodeling activities of FANCM/FAAP24, apparently critical for efficient activation of DNA damage checkpoint response, even though this process is ATR instead of ATM-dependent (*101, 102*). As regards BS, Deans and West *(103*) recently published a very informative article showing that FANCM works as a scaffold protein, thus bringing together key components of the FA and BS pathways to stalled replisome. Therefore, at least in part, their results can clarify overlapping clinical features affecting these two disorders.

5.1. ICLs: a huge challenge for DNA replication countered by a criss-cross pathway

ICLs result from the covalent linkage of two DNA strands, thereby preventing replication and transcription. Although ICLs may be repaired within normal cells, these kinds of lesions pose the most difficult challenge for DNA repair systems, since the information encoded by the complementary strand cannot be used while DNA strands remain cross-linked. ICLs can be induced by natural products, such as photoactivated psoralens, malondialdehyde (a highly toxic endogenous by-product formed in part by lipid-oxidation-derived free radicals), as well as from exposure to a wide range of therapeutic anticancer drugs, mainly bifunctional alkylating agents, such as cisplatin, MMC, cyclophosphamide and methotrexate (*104*).

When considering the functionality of FA genes and FA disease cancer proneness, the hypersensitivity of FA cells to cross-linking agents has given rise to the hypothesis of their involvement with ICL DNA repair mechanisms. Experiments in the early 1990's using an *in vitro* DNA repair assay with extracts from FA cell lines have failed to demonstrate any deficiency in NER. Furthermore, extracts from cell lines belonging to the two different complementation groups of FA known at that time, revealed normal DNA repair synthesis in plasmids containing *cis*-DDP or UV adducts (*105*).

Evidence of DNA cross link repair deficiency in FA cells has been reported since the early 1970's (*106, 107*). However, even experiments designed to examine the extent of FA-cell sensitivity to DNA damage induced by various cross-linking agents have proved to be somewhat controversial, probably because most of these studies involved comparisons of structurally different adducts formed by various types of compounds (*108*). Nevertheless, previous research by Averbeck and colleagues (*109*) has shown that the repair of monoadducts and ICLs is truly impaired in FA cells. Their results were conspicuous enough to ensure that by increasing the proportion of DNA ICLs over monoadducts, the differential sensitivity between FA and normal cells increases. Since then, this particular FA-cell sensitivity has been widely confirmed.

Recently, the significance of the FA/BRCA pathway for DDR during the S phase of the cell cycle, especially implicated in the repair of ICLs, has became increasingly evident, although it is not clear whether FA proteins become committed to the repair of ICL DNA lesions at an early or late stage, and what their precise role in the DNA damage signal transduction pathway. Hence, the findings of Kumaresan and Lambert were very informative (*110*). They noted that chromatin-associated protein extracts from FANCA cells are defective in their ability to produce dual incisions in DNA at ICL sites. Curiously, in another almost simultaneous study, it was indicated that the endonuclease XPF-ERCC1 has an unexpected capacity for cleaving DNA on both sides of a psoralen cross link, thereby presupposing a mechanism for initiating ICL repair, in no way supporting any relationship with the genetic and molecular basis of FA. Subsequent studies by Qiao and colleagues (*111*) have demonstrated that FA proteins associate with chromatin and the nuclear matrix in an inducible fashion after treatment with MMC, thus elucidating the linkage of the FA pathway to DNA repair of ICLs.

In another study, Pichierri and colleagues (*112*) reported interesting results indicating a direct role for FANCC in RMN complex focus assembly in response to ICL inducers. They also reported that the unhooking of MMC-induced ICL is normally achieved in FA deficient cells, an indication that the MMC sensitivity of FANCC cells is not beholden to a defect in ICL incision. Moreover, it was demonstrated that FA pathway components promote homology-directed repair of chromosomal DSBs (*113*). Furthermore, Hanada and colleagues (*114*) proposed the involvement of Mus81–Eme1 and Rad54-mediated HR in the same DNA replication-dependent ICL repair pathway. Soon after, Zhang and colleagues (*115*) investigated the effect of a site-specific psoralen ICL on HR *in vivo*, by way of an ingenious plasmid-based assay containing a site-specific ICL. Although HR is inhibited by ICLs, on introducing a DSB adjacent to the site, ICL removal can be enhanced and the substrate funneled into an HR repair pathway. This process is largely dependent on the activity of the XPF-ERCC1 endonuclease, REV3, a specialized DNA polymerase, the FA pathway, and the MMR protein MSH2, also required for recombination repair processing of the ICL.

Thus, practically all reports suggest a crucial role for FA proteins in the maintenance of genome stability during the S phase. Notwithstanding, the FA/BRCA pathway still remains an enigma, in that almost none of these proteins contain known sequence motifs for DNA repair. By inference, there is still much to be unraveled as to how FA/BRCA confers ICL resistance to normal cells. In this connection, the identification of FANCM, a component of the FA core complex that, besides incorporating DNA-dependent ATPase activity, also activates the dissociation of DNA triplexes *in vitro* (*116, 117*), represents a breakthrough in understanding the functional meaning of the FA pathway itself, although alone it is incapable of binding DNA. More recently, Smogorzewska and colleagues (*118*) were able to identify two nucleases required for ICL repair. One, FAN1, possesses both endonuclease and exonuclease activities and is recruited to the lesions after ubiquitination of FANCD2.

FANCJ is another noteworthy gene, also possibly involved in convergence of the FA/BRCA pathway with the DDR network. This tumor-suppressor gene is involved in the multiple processes implicated in maintaining genomic stability, such as DNA damage checkpoints (*119*) and DNA repair (*120, 121*). The product of this gene is a DNA helicase that binds directly to BRCA1 (*122*), whereby the initial nomenclature of BACH1 (BRCA1-Associated C-terminal Helicase1) or BRIPI (BRCA1 Interacting Protein C-terminal Helicase1). More recently, it was renamed FANCJ, following its identification as a component of the FA/BRCA pathway (*123*). According to Cantor and colleagues (*122*), germline FANCJ mutation carriers are

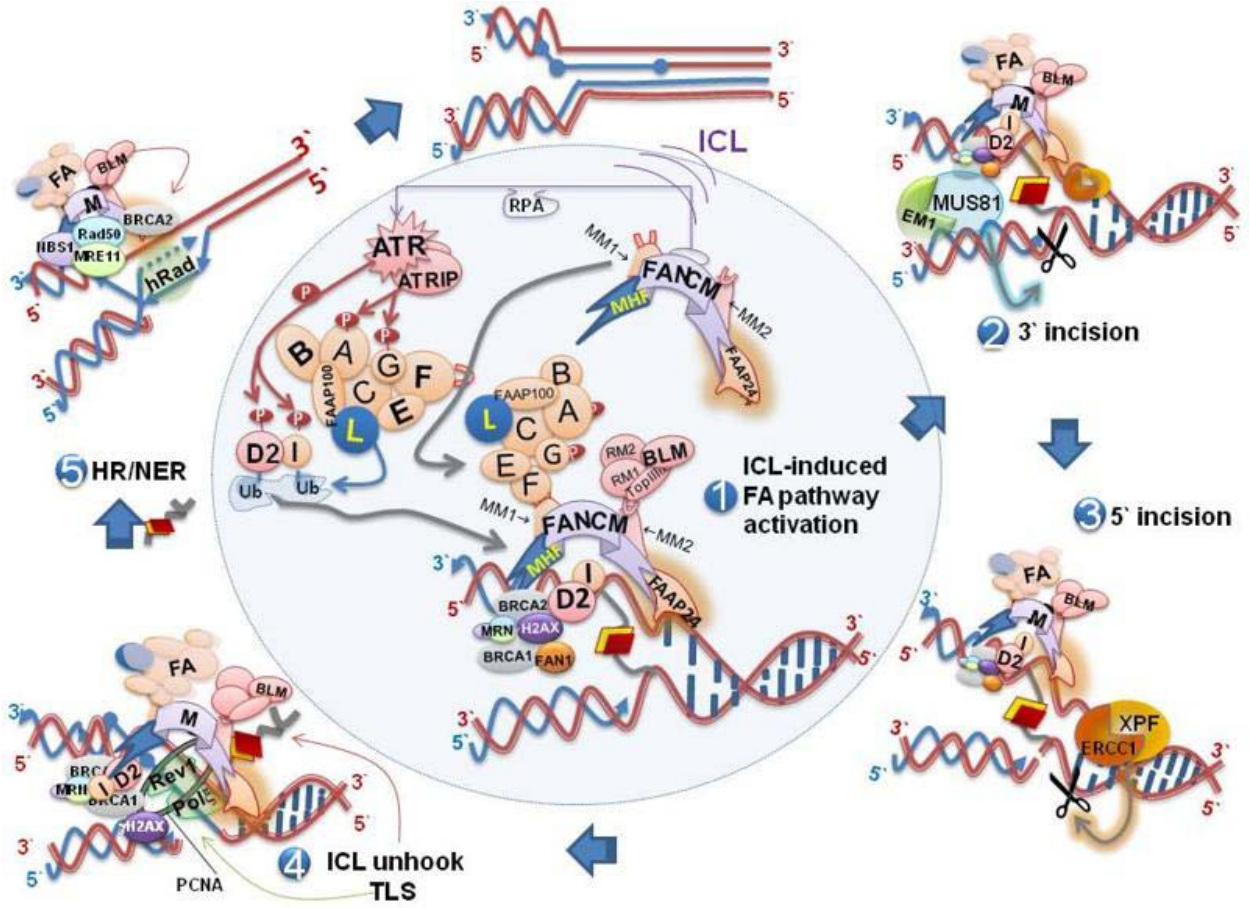

Figure 6. Scheme of replication-coupled ICL repair. The FA/BRCA pathway is involved in the repair of ICLs in a cell cycle-dependent process. The repair of ICL requires the coordinated and hierarchical action of three classical pathways, namely NER, TLS and HR. (1) ICL-induced replication arrest during the S phase activates assembly of the FA core complex, as well as the monoubiquitynation of FANCD2/FANCI, which is translocated to the chromatin, where it becomes set together with repair factors, such as BRCA1, gamma-H2AX, BRACA1, BRACA2, Rad51, PCNA. Replication fork stalling is also recognized by the FANCM–FAAP24–MHF complex, which recruits the FA core and Bloom complex to chromatin and activates ATR/ATRIP signaling, through the binding of RPA to single stranded DNA. (2) The first incision is accomplished by active Mus81-Eme1 endonuclease, thus converting the stalled replication fork to a DSB. (3) Unhooking of the cross link from DNA after the 5` incision carried out by XPF-ERCC1. (4) The unhooked lesion is by-passed by translesion polymerases. (5) HR and NER systems are involved in the repair of broken sister chromatid and removal of the adduct remaining hooked onto the parental strand.

prone to breast-cancer. A further observation was that FANCJ-deficient cells harboring a deleterious mutation in a residue, essential for catalytic activity in other helicases, interfered with normal DSB repair, through a mechanism partially dependent on the ability of the helicase (FANCJ) to bind the so called BRCT (BRAC1 C-terminal) region of BRCA1.

Thus, in the light of current knowledge, it has been proposed that repair of a cross link in mammalian cells involves dual incisions in the DNA backbone flanking the lesion, followed by bypass synthesis over the lesion on the remaining intact strand, by means of a specialized DNA polymerase. In short, the sequence of events involves recruitment of at least two endonucleases, Mus81-Eme1 and XPF-ERCC1, after collision of the DNA replication fork with the tethered lesion. The active Mus81-Eme1 endonuclease is supposedly responsible for the first incision, thereby converting the stalled replication fork into a DSB. The ICL can be completely unhooked after the second incision on the part of the other endonuclease, XPF-ERCC1, thereby facilitating TLS beyond the ICL, in a DNA polymerase zeta-dependent manner. After bypass synthesis, strand invasion initiates reformation of the replication fork via HR, prior to re-starting replication. Alternatively, FAN1 can also be recruited to the damage site by monoubiquitinated FANCD2–FANCI, to thereat mediate nucleolytic incision and induce unhooking of the cross link, allowing lesion bypass by TLS polymerases (for further details, see review *124*). A general scheme illustrating the activation of the FA pathway for ICL-repair during DNA replication is depicted in Figure 6.

5.2. FA/BRCA pathway and iPS cells technique: a hope in gene/cell therapy

It is acknowledged that effective cancer therapy depends on early diagnosis and intervention. FA patients may benefit from bone-marrow transplantation or immunosuppressive therapy with a reasonable chance of recovery during the early-onset of the disease. Unfortunately, despite remarkable progress concerning these therapeutic protocols, and even after successful bone-marrow transplantation to correct hematological problems, the cancer risk still remains high. In this respect, Raya and colleagues (*125*) recently published interesting and promising results when working with somatic cells from patients with FA. By using a gene-therapy protocol, they corrected the defective gene in the patients' cells, and then, by making use of a combination of transcription factors, OCT4, SOX2, KLF4 and cMYC, they successfully reprogrammed the repaired cells into induced pluripotent stem (iPS) cells. The resulting FA-corrected iPS cells were indistinguishable from human embryonic stem cells and iPS cells generated from healthy donors, and thus could be used for bone-marrow repopulation. Curiously, non-corrected FA cells do not generate iPS cells, a possible indication of the essential role of this DNA repair pathway in stem cell genome reprogramming. This work thus meticulously exemplifies the potential utility of iPS cells as a new promising and robust technology that cannot be ignored. It brings together gene therapy and the iPS cell technique for the design of individualized therapy, tailored to the genetic profile of a particular disorder.

6. OTHER GENOME INSTABILITY SYNDROMES RELATED TO DNA REPAIR DEFECTS

As already discussed, mutations in genes that encode DNA repair proteins give rise to various genomic instability syndromes, often characterized by an increase in cancer predisposition. Genomic instability is also a characteristic of almost all sporadic human cancers, its two most well-known forms being the chromosome instability (CIN) and microsatellite instability (MSI). Whereas the former is characterized by gross chromosomal abnormalities, such as the gain or loss of whole chromosomes or simply fractions, the latter is characterized by changes in the number of oligonucleotide repeats present in microsatellite sequences. As mentioned, the presence of both in hereditary cancers has been linked to mutations in DNA repair genes. For instance, mutations in MMR genes lead to MSI in the Lynch syndrome, whereas CIN can result in syndromes caused by other DNA repair defects, such as germline mutations in Nbs1 (Nijmegen breakage syndrome), ATM (ataxia-telangiectasia), WRN (Werner syndrome), BLM (Bloom syndrome), RECQL4 (Rothmund-Thomson syndrome), FANC genes (Fanconi anaemia) and XP genes (xeroderma pigmentosum). A third form of genetic instability is characterized by an increase in base-pair mutation frequency. This is a feature of hereditary MYH-associated polyposis (MAP), which predisposes to colorectal cancer, and is caused by germline mutations in the BER MYH gene (see reviews *126* and *127*).

Notwithstanding, the link between sporadic cancers and DNA repair defects is not so clear. There are reports of mutations or polymorphisms in the BER gene *XRCC1* being associated with lung cancer, head and neck squamous cell carcinoma, differentiated thyroid cancer and sporadic breast cancer. Polymorphism in another BER gene, *APE1*, is also predictive for lung cancer, whereas in *ERCC1*, *XPA*, *RAD23B* and *XPD* (NER), it is associated with esophageal cancer risk. *ERCC5* (*XPG*) and ERCC6 (*CSB*) (NER) reduced expression levels or *ERCC6* polymorphisms are also associated with elevated lung cancer risk. And polymorphisms in *XPC* (NER) may be linked with susceptibility to several solid cancers (*128*), whereas *XPC* inactivation has been associated with squamous cell carcinomas ((*129-132*), reviewed in (*126*)). According to other reports, the very low frequency of these and other mutations indicated that genomic instability in several sporadic human cancers might not be due to inactivation of DNA repair genes, as this feature could appear later in a tumor, instead of in initial development (for a more detailed discussion on this topic, see review *127*). Accordingly, some as yet unaddressed genomic instability syndromes will be focused.

6.1. MYH-associated polyposis (MAP) and Lynch syndromes

Most colorectal cancers (CRC) are sporadic, although approximately 10 to 30% of all cases are associated with familial predisposition. The most prevalent, the Lynch syndrome of dominant inheritance, accounts for approximately 3% of all CRC cases (reviewed in *133* and *134*), and is caused by germline mutations in one of four MMR genes, namely MLH1 (*135, 136*), MSH2 (*137, 138*), MSH6 (*139*) or PMS2 (*140*), the mutated gene being directly associated with the severity of the disease. Mutations in the PMS2 gene, for instance, cause a much more attenuated form of the syndrome than in the other three. Furthermore, the frequencies of the mutated genes are not the same, for while mutations in MLH1 or MSH2 account for approximately 70% of all the known Lynch syndrome mutations, MSH6 and PMS2 mutations each account for only 15%. Besides CRC, this syndrome is associated with increased risks of extra-colonic cancers, including cancer of the endometrium, ovary, pancreas, stomach, small intestine, skin, urinary tract and brain. When associated with brain cancer, the variant form of the disease is called the Turcot syndrome, and when associated with skin cancer (cutaneous sebaceous neoplasms), the Muir-Torre syndrome (*133, 134*).

Diagnosis of the Lynch syndrome can be difficult. As the family history of the patient is of extreme importance, certain guidelines have been developed for use as diagnostic tools, namely the Amsterdam Criterias I and II, and the Bethesda Guidelines. These established a few standardized selection criteria mainly related to the number of family members affected with tumors (both CRC and extra-colonic), and the young age at diagnosis (before 50 years old). Effective diagnosis also depends upon molecular testing, including immunohistochemistry tests and MSI analysis, since this type of genomic instability is a hallmark of the Lynch syndrome (*133, 134*). Nevertheless,

about half of the families that comply with the Amsterdam criteria do not present deficiencies in MMR genes, thereby indicating the absence of MSI. The hereditary disease that affects these families, described by some as "familial colorectal cancer type X", was previously known, together with the Lynch syndrome itself, as "hereditary nonpolyposis colorectal cancer" (HNPCC) (*133, 141*). The MSI phenotype, present not only in tumors from Lynch syndrome patients, but also in approximately 15 to 20% of sporadic colon cancers, is generally due to somatic hypermethylation of the MLH1 promoter which results in transcriptional silencing, instead of the MMR gene germline mutations observed in Lynch syndrome originated tumors (134, 142). Furthermore, Valeri and colleagues recently reported that MSI tumors without MMR germline defects may be the result of overexpression of microRNA miR-155 which downregulates the expression of MMR proteins, mainly by posttranslational inhibition (*143*).

MAP, a hereditary colon cancer syndrome with an autosomal recessive pattern, is the result of mutations in the BER gene MYH (or MUTYH). These mutations are responsible for approximately 1.4% of all adenomatous polyposis. Unlike the Lynch syndrome, MAP is characterized by the presence of multiple adenomatous polyps, the mean number reaching about 100, and besides it is also associated with extra-colonic tumors, such as duodenal adenomas, thyroid tumors, osteomas and brain tumors ((*144, 145*), reviewed in (*134*)).

6.2. The Bloom, Werner and Rothmund-Thomson syndromes

DNA helicases are enzymes that unwind DNA, i.e. separate the complementary strands of duplex DNA, in an ATP-dependent and directionally specific manner. The RecQ helicases are highly conserved proteins, active in the maintenance of genome stability through their involvement in various DNA metabolic processes, such as DNA recombination, replication and repair. So far, five RecQ helicases have been identified in humans, namely RECQL1, BLM, WRN, RECQL4 and RECQL5. Their cellular functions are not, as yet, fully understood (reviewed in *146* and *147*).

In DNA repair processes, they seem to be especially relevant for the efficient repair of DNA DSBs, even though their participation in other repair pathways has already been described or suggested. BLM, for instance, is important for the initiation of DSB HR repair (*148*). Furthermore, through FANCM, there is an association with the FA/BRCA pathway in repairing DNA damage caused by interstrand crosslinking agents, such as MMC (*103*). Crosstalk among FA proteins and BLM has also been shown to maintain chromosome stability during mitosis (*149*). On the other hand, WRN participates, in an ATM/Nbs1-dependent manner, as a repressive regulator in the TLS pathway (*150*), its phosphorylation, which is dependent upon ATM and ATR, being relevant for the prevention of DSB formation at stalled replication forks (151). As with WRN and BLM, RECQL4 also seems to be involved in DSB repair (*152, 153*). Finally, roles for RECQL4 in the BER (*154*) and NER (*155*) pathways have already been suggested.

Mutations in three of the RecQ helicases are associated with rare recessive genetic disorders. The Bloom syndrome is caused by defects in BLM, the Werner in WRN, and the Rothmund-Thomson, RAPADILINO and Baller-Gerold by various defects in RECQL4 (reviewed in *146, 147, 156* and *157*). The Bloom and Werner syndromes are considered to be segmental progerias, as patients show the early onset of several, although not all, the features accompanying normal aging. Both are characterized by growth retardation, genomic instability and a predisposition for the development of cancer, but whereas Werner patients are more susceptible to the onset of mesenchymal tumors, such as sarcomas, the tumors inflicting Bloom syndrome patients have a normal distribution of tissue and type. Sunlight sensitivity is another feature of the Bloom syndrome, the hallmark feature of this disorder being a 10-fold elevation in the frequency of sister-chromatid exchanges, a clinical feature in molecular diagnosis of the syndrome (see reviews *146, 147* and *156*). There are two clinical subforms of the Rothmund-Thomson syndrome, viz., RTSI and RTSII, although only the latter is caused by mutations in RECQL4. It is characterized by skin manifestations (poikiloderma), congenital bone defects and growth retardation, as well as premature aging, with the increased risk of osteosarcoma in childhood and skin cancer later in life. As the other two RECQL4 associated-diseases are not closely associated with cancer or progeria, they will be discussed no further (reviewed in 146 and 157).

6.3. Neurodegenerative and neuromuscular diseases

Whereas defects in DDR in proliferating cells can lead to growth advantage and ultimately cancer, in non-replicating neurons these defects can result in neurodegeneration, in some of the already mentioned syndromes. Furthermore, there are indications that DNA repair defects might play a role in chronic neurodegenerative diseases of late onset, as Alzheimer and Parkinson, since these disorders also display the accumulation of DNA damage. ATM defects seem to be of relevance in this neurodegenerative process, although this is, as yet, obscure. Even so, $ATM^{-/-}$ mice display a progressive and age-dependent reduction in dopaminergic cells of the substantia nigra, a characteristic feature of Parkinson's disease (*158, 159*). Furthermore, oxidative damage is implicated in the etiology of Alzheimer's disease, a possible outcome of impaired DNA repair resulting from reduced activity of the BER gene OGG1 (*160-163*). Finally, $Ercc1^{-/-}$ mice develop age-dependent motor abnormalities, disruption of neuromuscular connectivity at the neuromuscular junction, and degeneration of motor neurons all through the lack one allele of the ERCC1 gene, whereas the protein derived from the other allele is truncated, thus with reduced activity. The complex XPF-ERCC1 acts not only in NER, but also in ICL and DSB repair, whereby the authors proposed that the accumulation of DNA damage caused by this DNA repair deficiency might be one of the age-related risk factors that contribute to the onset of degenerative disorders, such as amyotrophic lateral sclerosis (*164*).

6.4. Atherosclerosis and the Metabolic syndrome

Associated with insulin resistance and atherosclerosis, the metabolic syndrome is characterized by hypertriglyceridemia, low HDL cholesterol, hypertension, hyperglycemia, and excessive visceral adiposity. Human atherosclerotic plaques present increased levels of DSBs and basal activation of DNA repair pathways involving ATM, this increasing *in vivo* with the severity of the disease (*165*). With a view to a better understanding of the processes of metabolic and cardiovascular diseases, Schneider and colleagues proposed that ATM deficiency might contribute to development of the metabolic syndrome, since it causes insulin resistance, resembles the metabolic syndrome itself, and increases vascular disorders (*166*). This association was recently confirmed by Mercer and colleagues, who showed that ATM heterozygosity results in DNA damage in cells that comprise atherosclerotic plaques, besides promoting atherosclerosis and inducing multiple features of the metabolic syndrome (*167*).

6.5. New target partners involved in DDR and more potential DNA repair related disorders

The DDR machinery is now an essential domain in investigations for understanding the precise mechanisms at the core of carcinogenic processes. Extensive multi-discipline studies have resulted in the identification of several of the cellular components involved in the process, the nature of DNA damage sensors involved in recognition and their implication in genomic stability. In an attempt to improve current understanding of the DDR network, Hurov and colleagues (*168*) performed a genome-wide RNAi screening to identify genes required for resistance to ionizing radiation. They discovered a large set of novel genes, e.g., TTI1 (Tel two-interacting protein 1) and TTI2, two highly conserved regulators of DDR in mammals, whose depletion leads to cellular sensitivity to this radiation. Both associate physically with TEL2 to form a conserved trimeric complex called the Triple T complex. Accordingly, this complex is essential for regulating the protein levels of ATM, ATR and a group of related PIKKs. Another interesting study by Slabicki and colleagues (*169*) was designed to highlight the relevance of DNA repair genes in the maintenance of genomic stability. They described a genome-scale endoribonuclease-prepared short interfering RNA (esiRNA) screen for genes involved in DNA DSB repair. In so doing, they discovered 61 genes that influenced the frequency of HR DSB repair, besides characterizing, in detail, the gene KIAA0415, which encodes a putative helicase that interacts with two proteins mutated in hereditary spastic paraplegia.

7. DNA REPAIR AND CANCER CHEMOTHERAPY

The efficacy of DNA repair pathways is of extreme importance in the maintenance of genome stability. As described so far, the incapacity or diminished capacity to repair DNA lesions is often associated with the onset of pathological processes. Thus, components of the repair machinery become potential pivots in the prognosis and treatment of several disorders. For example, it is amply evident that the treatment of human atherosclerotic plaque vascular smooth muscle cells with atorvastatin can accelerate DNA repair in a process that requires Nbs1, this possibly leading to the reduction of DNA damage in atherosclerosis *in vivo* (*165*). It has been shown that the assessment of DNA repair characteristics can be very informative in the choice and prediction of the outcome of therapy, even though further studies with a larger number of patients are often required for confirmation of results. Polymorphisms in the NER genes *XPG* and *XPC*, for instance, are associated with the differential response of chronic myeloid leukemia patients to treatment with imatinib (*170*). The A23G polymorphism of the NER gene *XPA* is associated with increased response of non-small cell lung cancer patients to platinum-based chemotherapy (*171*). Furthermore, the survival rates in advanced CRC patients harboring *XPG* C/C (His46His) and XPA A/G or A/A (5' UTR) polymorphisms are more prolonged following treatment with oxaliplatin/fluoropyrimidine chemotherapy (*172*).

Since many chemotherapeutic drugs currently in clinical use act by damaging the DNA molecule, it is expected that the impairment of those DNA repair processes involved in the processing of such DNA damage would increase the cytotoxic effects of chemotherapy (for a historical and broad overview on the subject, see *173*). To date, numerous DNA repair inhibitors have already been studied. The compound O^6-benzylguanine (BG), for instance, is a DNA repair inhibitor that inactivates the enzyme MGMT (O^6-methylguanine-DNA methyltransferase), involved in the removal of alkyl adducts from the O^6-position of guanine (*174*). BG and its analogue O^6-benzyl-2'-deoxyguanosine (dBG) (*175*) are both capable of potentiating the cytotoxic effects of chloroethylating agents, such as BCNU and CCNU in medulloblastoma tumor xenografts (*176, 177*) and colon carcinoma cells (*174*). Another study has revealed that BG alone is capable of reducing the volume of pancreatic tumors in mice, besides sensitizing pancreatic cancer cells to gemcitabine (*178*). Other derivatives of BG, such as O^6-benzyl-N2-acetylguanosine (BNAG) and deoxyguanosine (BNAdG), were shown to increase the cytotoxicity of cystemustine in mice bearing human melanoma tumor cells with high levels of MGMT (*179*). So far, phase I/II clinical trials have been widely applied for analyzing the capacity of BG to potentiate the tumor killing effects of chemotherapeutic drugs such as temozolomide, irinotecan and BCNU (*180-184*), with many others under way.

Another class of DNA repair inhibitors consists of molecules that impair the efficient activity of BER. An example is methoxyamine (MX), whose action mechanism depends upon its binding to DNA abasic (AP) sites, as the products of such binding are not substrates for BER enzyme AP endonuclease (*185*). MX has been shown to enhance temozolomide cytotoxicity in colon (*186*) and ovarian (*187*) cancer cells. In the former, it increased both the cytotoxic effects of IdUrd (5-iodo-2'-deoxyuridine) and the radiosensitization induced by this agent (*188*). Other evidences show that MX potentiates the antitumor effects of BCNU in colon cancer xenografts, without systemic toxicity, this potentiation being further enhanced by

concomitant treatment with BG (*189*). On the contrary to MX, other BER inhibitors act by way of a distinct mechanism, i.e., inhibition of the enzyme AP endonuclease 1 (APE1). One of these, lucanthone, enhances the killing effects of temozolomide in breast cancer cells (*190*). The increase in temozolomide cytotoxicity is also achieved by the use of the small-molecule inhibitors CRT0044876 in fibrosarcoma cells (*191*), and AR03 in glioblastoma cells (*192*). Another participant of the BER process, also susceptible to inhibition, is the protein PARP, which will be discussed below.

Apart from that mentioned, many other DNA repair inhibitors have already been characterized, these including the ATM inhibitor KU-55933 (*193*); the DNA-PK inhibitor PI-103 (*194*); and the Chk1/2 inhibitor, AZD7762, the latter also capable of blocking homologous recombination through the reduction of Rad51 focus formation (*195*). These and others will no longer be discussed here due to the limited space. Readers are referred to the following reviews (*196-199*).

7.1. The PARP inhibitors

The nuclear enzyme poly (ADP-ribose) polymerase 1 (PARP1) plays a key role in the repair (BER) of DNA single-strand breaks (SSBs). In response to DNA damage, PARP, on binding to DNA SSBs, catalyzes the cleavage of NAD^+ to nicotinamide, which is then released, and ADP-ribose, which is transferred to an acceptor protein (either PARP1 itself or another acceptor protein). Nicotinamide can act as a weak PARP inhibitor, and in fact the first generation of PARP inhibitors was comprised of nicotinamide analogues, such as 3-aminobenzamide. Recently, other more potent inhibitors, such as AG14361, GPI15427 and AZD2281, have been developed. So far, many PARP inhibitors have been shown to act as chemopotentiating agents, thereby increasing the cytotoxic effects, not only of DNA-damaging agents, such as temozolomide, but irradiation as well (see reviews (*200-202*), and references therein).

A few years ago, Bryant and colleagues, and Farmer and colleagues demonstrated that PARP inhibitors also function as single agents in the killing of cells deficient in the homologous recombination repair of DSBs, more specifically BRCA mutant cells, probably due to synthetic lethality (*203, 204*). This allowed for the design of targeted therapies, to the point of monotherapy using PARP inhibitors becoming current in clinical trials (*205*). For further information on clinical trials of these and other DNA repair inhibitors, the readers are referred to the databases of "ClinicalTrials.gov" (http://clinicaltrials.gov) and "Cancer Research UK" (http://www.cancerhelp.org.uk/trials/).

7.2. Targeting the FA/BRCA pathway for cancer therapy

As described above, inherited mutations affecting FA genes are closely associated with several different kinds of cancer. However, since deleterious mutations in FA proteins render cells particularly vulnerable to chemicals widely used as chemotherapeutic agents, the genes integrating the FA/BRCA pathway may be potentially implicated in the outcome of cancer treatment. Cisplatin, for instance, is one of the most widely used anticancer drugs, although its effectiveness in many cases is limited, due to acquired or intrinsic resistance.

Taniguchi and colleagues (*206*) reported that the differential methylation status of the *FANCF* promoter could account for the refractory response to cross-linking agents, such as cisplatin. Likewise, Burkitt and Ljungman (*207*) presented interesting suggestions for prognosis and treatment optimization of cancer cells, on comparing the functional status of the FA/BRCA pathway and cisplatin sensitivity in head and neck cancer cells. It was confirmed that the defective recruitment of FANCD2 to nuclear foci was significantly correlated with higher sensitivity to cisplatin, although cisplatin-resistant cell lines became proficient in FANCD2 foci formation following cisplatin treatment. Interestingly, these authors (*208*) also demonstrated that the pretreatment of cisplatin-resistant head and neck cancer cells with phenylbutyrate sensitized these to cisplatin, while simultaneously decreasing the levels of cisplatin-induced FANCD2 foci formation, whereby the inference that the mechanism for sensitization may involve abrogation of the FA/BRCA pathway. A similar strategy, developed by Ferrer and colleagues (*209*), involved an adenoviral vector encoding a dominant-negative form of FANCA, for the expressed purpose of investigating whether the FA/BRCA pathway could be a target for sensitizing tumor cells. The disruption of this repair pathway was demonstrated by the abnormal FANCD2 monoubiquitination induced by the transduced gene. As a result, a panel of tumor cell lines, including non-small-cell lung cancer cells, could be significantly sensitized in response to cisplatin, thereby showing the FA/BRCA pathway to be a feasible target for the sensitization of solid tumor cells in chemotherapy treatment with this anticancer agent.

The perspectives of developing alternative protocols for modulating DNA damage responses, with proposals for decreasing cancer cell-resistance to chemotherapeutic agents, are manifold. Furthermore, there are still probably many different DNA repair routes to be explored. One obvious possibility is to use siRNA molecules, together with chemotherapy drugs, to either silence or down-regulate DNA repair genes. This could be even more effective with improvements in the possibility of drug delivery nanoparticles targeting approaches. Figure 7 illustrates DNA damage response to genotoxic agents linked to downstream biological consequences, thereby identifying some of the potential for these strategies. A putative model for evidence-based clinical decisions, highlighting research evidence concerning DNA repair and the therapeutic effectiveness for reaching optimal care, is depicted in Figure 8.

8. SUMMARY AND PERSPECTIVES

8.1. Unrepaired DNA damage: a shortcut towards cancer and aging

Genetic instability seems to be the major hallmark of two quite distinct biological processes, cancer and aging. On the one hand, genomic instability induces

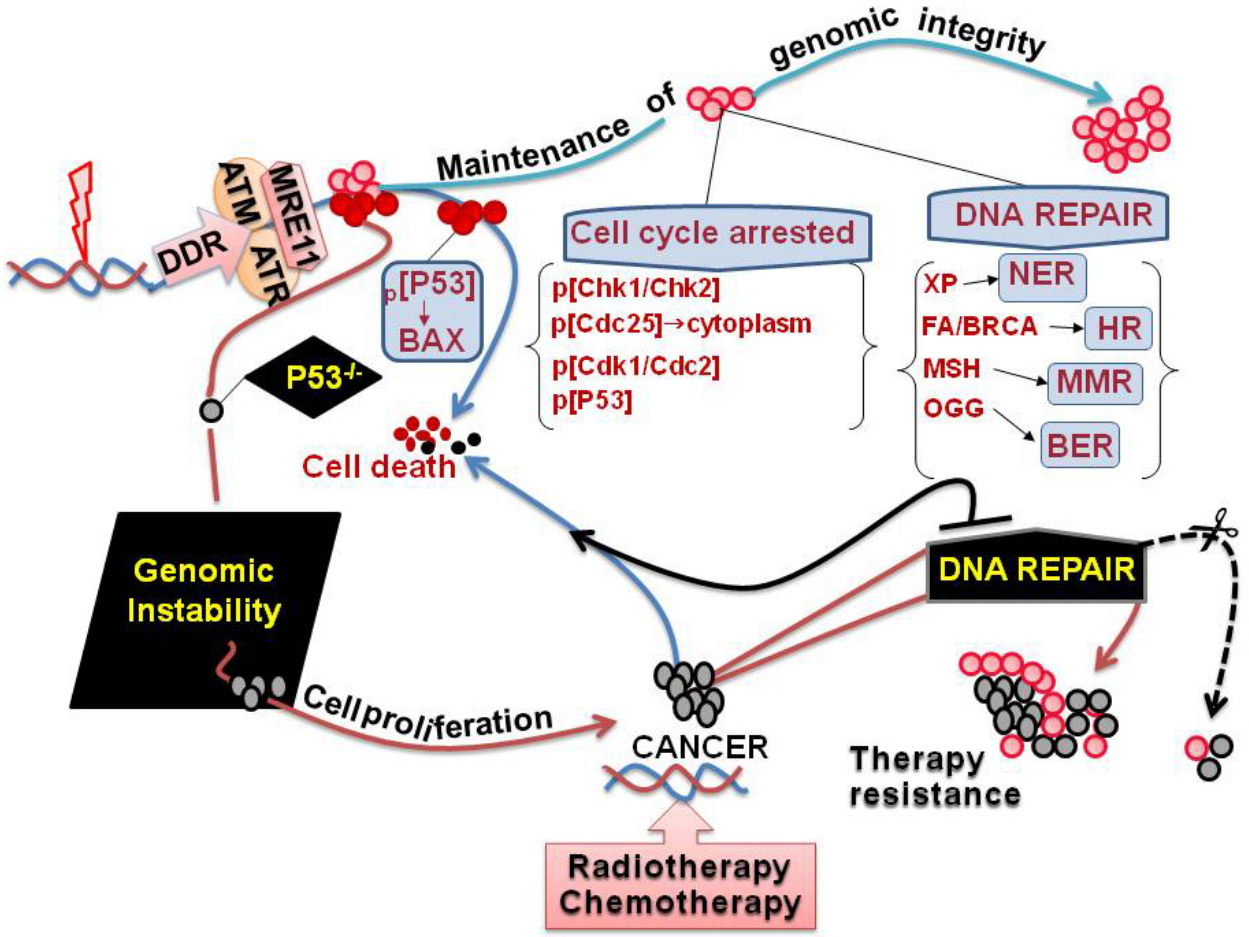

Figure 7. DNA damage response – The implications on Genomic Stability and the outcome in cancer therapy. Following damage to the DNA molecule, a series of proteins collaborate towards cell survival. Among these, several participate in various DNA repair processes and cell cycle checkpoints (as indicated). The lack of damage repair induces genomic instability, this possibly leading to the development of pathological processes, such as cancer. With the excessive accumulation of damage, cell death occurs. The increased cell death in certain tissues seems to be linked to accelerated aging. As regards cancer treatment, one currently used clinical approach is to damage cellular DNA, the accumulation of genomic lesions eventually leading to the killing of highly replicating cancer cells. Nevertheless, the repair of damaged DNA in cancer cells may permit cell survival, and thus induce resistance to genotoxic therapy. Thus, inhibiting DNA repair in these transformed cells would potentially improve the outcome of such therapies.

cells to overcome the normal restrictions to cell division and differentiation leading to cancer, whereas on the other, it compromises the capacity of regeneration of different organs due, at least in part, to cellular dysfunctions affecting stem cells (reviewed by *210*). Since unrepaired DNA is one of the most serious threats to genome stability, DNA repair can be considered a common link in carcinogenesis and aging. There is substantial evidence in the literature that cancer progression might be impelled by the accumulation of a wide spectrum of genetic and epigenetic alterations. The unavoidable rate of endogenous and exogenous DNA damage might account for the accumulation of these abnormalities over several consecutive rounds of replication in different kinds of cell, this including stem cells. Efficient DNA repair is essential for preserving genomic stability, thereby avoiding cancer and favoring the lifespan. However, it can also play the role of villain, in that it may provide acquired resistance to chemotherapeutic agents. The necessary amount of DNA damage accumulated during the lifespan of an individual to speed up pathological processes, such as cancer, or normal physiological processes, as ageing, is as yet unknown. However, it is quite informative to see that virtually all pathologies related to DNA repair defects (as described above) display a predisposition to cancer or aging, or both.

Here, the intention was to give the readers a broad overview of the importance of DNA repair mechanisms for the successful maintenance of genome stability. The consequences deriving from the disruption of one or more of these repair pathways are extremely harmful to individual health, as illustrated by both the existence of inherited syndromes characterized by defects in DNA repair, and the connection of these defects with the

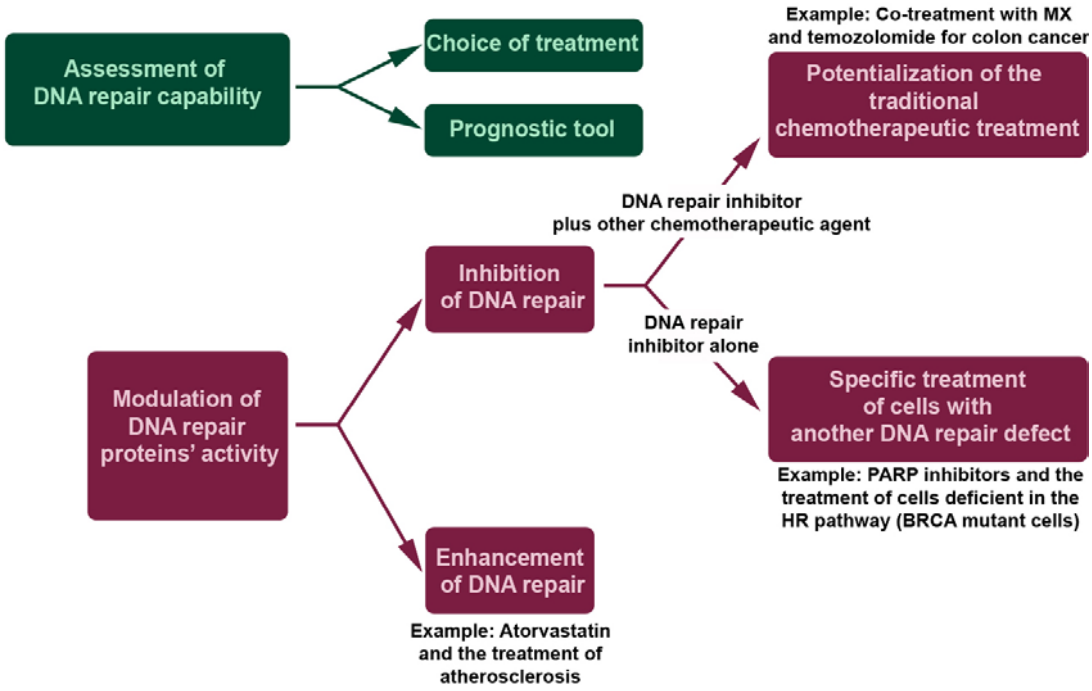

Figure 8. Clinical approaches depending upon DNA repair modulation/assessment.

development of other non-inherited diseases, whereby the possible usefulness of assessing DNA repair proteins for predicting the outcome, or even for aiding in the choice of treatment.

8.2. Targeting DNA damage responses for therapy

There is growing evidence of the potential benefits of modulating DNA repair pathways to directly treat individuals stricken by diseases as diverse as cancer, neurodegenerative disorders and atherosclerosis. DNA repair inhibitors are capable of inducing higher degrees of genomic instability in treated cells, thereby aiding in inducing cell death after treatment with other chemotherapeutic drugs. Besides the use of DNA repair inhibitor agents as chemopotentiators, recent studies have begun to demonstrate how these agents alone can be used to kill cancer cells with specific DNA repair defects. These are exciting possibilities, especially since only cancer cells appear to be sensitive to a line of treatment dependent upon synthetic lethality, since surrounding normal cells are repair-proficient. This promising approach would dramatically diminish the side effects experienced by many patients under treatment with traditional chemotherapy, worldwide.

Finally, over the latter decades, much has been learned of what is now known on the causes of cancer and, more recently, about aging, as a direct result of work with cells defective in DDR, brought about by disease, with much compensation to human society. Unfortunately however, this path has been completely one-way, as there is almost nothing that can be done to alleviate the pain of patients and their relatives. In spite of all that is already known, there remains much to learn about the components of the diverse pathways, and the possible crosstalks that exist among them. It is sincerely hoped that a more complete understanding on these topics and the development of new strategies for gene and cell therapy might bring effective help to patients that suffer from such devastating diseases and syndromes.

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Abbreviations: DDR: DNA damage response, XP: xeroderma pigmentosum, XPV: XP variant group, AT: ataxia telangiectasia, FA: Fanconi anemia, CS: Cockayne syndrome, TTD: trichothiodystrophy, COFS: cerebro oculofacial skeletal syndrome, UVSS: UV-sensitive syndrome, XFE: XPF-ERCC1 progeroid syndrome, DS-C: DeSanctis Cacchione syndrome, NBS: Nijmegen breakage syndrome, ATLD: AT-like disorder, MAP: MYH-associated polyposis syndrome, HNPCC: hereditary nonpolyposis colorectal cancer, RTS: Rothmund-Thomson syndrome, BS: Bloom syndrome, NER: nucleotide excision repair, TCR: transcription coupled repair, GGR: global genomic repair, BER: base excision repair, MMR: mismatch repair, HHR (HR): homologous recombination repair, NHEJ: non-homologous end joining, TLS: translesion synthesis, UV: ultraviolet, CPD: cyclobutane pyrimidine dimmer, 6-4 PP: 6-4 photoproduct, DSB: DNA double strand break, SSB: DNA single strand break, ICL: DNA interstrand crosslink, AP: DNA abasic sites, PIKK: phosphoinositide 3-kinase (PI3K)-related protein kinase family, CIN: chromosome instability, MSI: microsatellite instability, iPS: induced pluripotent stem cell, MMC: mitomycin C, BG: O^6-benzylguanine, dBG: O^6-benzyl-2'-deoxyguanosine, BNAG: O^6-benzyl-N2-acetylguanosine, MX: methoxyamine.

Key Words: Cancer, Xeroderma pigmentosum, DNA repair, Fanconi anemia, Ataxia telangiectasia, Genomic instability syndromes, Chemotherapy, Nucleotide excision repair, Review

Send correspondence to: Carlos Frederico Martins Menck, Ed. Biomedicas 2 ICB, USP, Av. Prof. Lineu Prestes 1374, Sao Paulo, SP, Brazil, CEP 05508-900, Tel: 55-11-3091-7499, Fax: 55-11-3091-7354, E-mail: cfmmenck@usp.br

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