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Integration of the DNA Damage Response with Innate Immune Pathways

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1. Introduction

Genotoxic or replicative stress triggers a DNA damage response (DDR) that induces cell cycle arrest, DNA repair or – if the damage is too severe – apoptosis. The DDR has been suggested to represent a barrier against tumorigenesis by preventing the uncontrolled proliferation of cells with genomic instability or harmful mutations. Recent studies have uncovered novel links of the DDR to innate immune signaling pathways. The activation of NF-κB in response to DNA damage is mediated by ATM (ataxia telangiectasia mutated)-dependent phosphorylation of NEMO, resulting in the induction of the classical NF-κB pathways. Furthermore links between the DDR and various members of the type I interferon (IFN) pathway have been uncovered. The DDR also increases the sensitivity of cells to immune cell-mediated killing by inducing the expression of surface ligands for activating immune receptors. Here, we review how the DDR links to innate immune pathways and the potential role of these interactions in cancer and viral infection.

2. The DNA damage response (DDR)

The genome integrity is constantly challenged by environmental genotoxic agents (chemicals, ultra-violet, viral infection etc.) and endogenous genotoxic stress (replication, oxidative stress, etc.) (Lindahl, 1993; Nyberg et al., 2002; Kunkel, 2004). DNA damage may also be caused by reactive oxygen species and nitrogen compounds produced by neutrophils and macrophages at sites of inflammation (deRojas-Walker T et al., 1995; Kawanishi et al., 2006). These DNA lesions or aberrations can block transcription and genome replication, and if not repaired, lead to mutations or large-scale genome aberrations that threaten the survival of the individual cells and the whole organism (Jackson & Bartek, 2009). To cope with genomic DNA damage, organisms have evolved a repertoire of surveillance and repair mechanisms to detect and combat the deleterious effects of damaged DNA (Zhou & Elledge, 2000). The DDR is composed of sensor protein kinases that are recruited to the sites of DNA damage, the signal transducer proteins that propagate the signal downstream, and the effector proteins which activate the appropriate responses such as DNA repair, cell cycle arrest and apoptosis (Gasser et al., 2007) (Figure 1).

2.1 ATM and ATR

The diversity in the types of DNA lesions necessitates specific protein complexes to detect and initiate the correct repair programme. Studies on the biochemistry of specific DNA

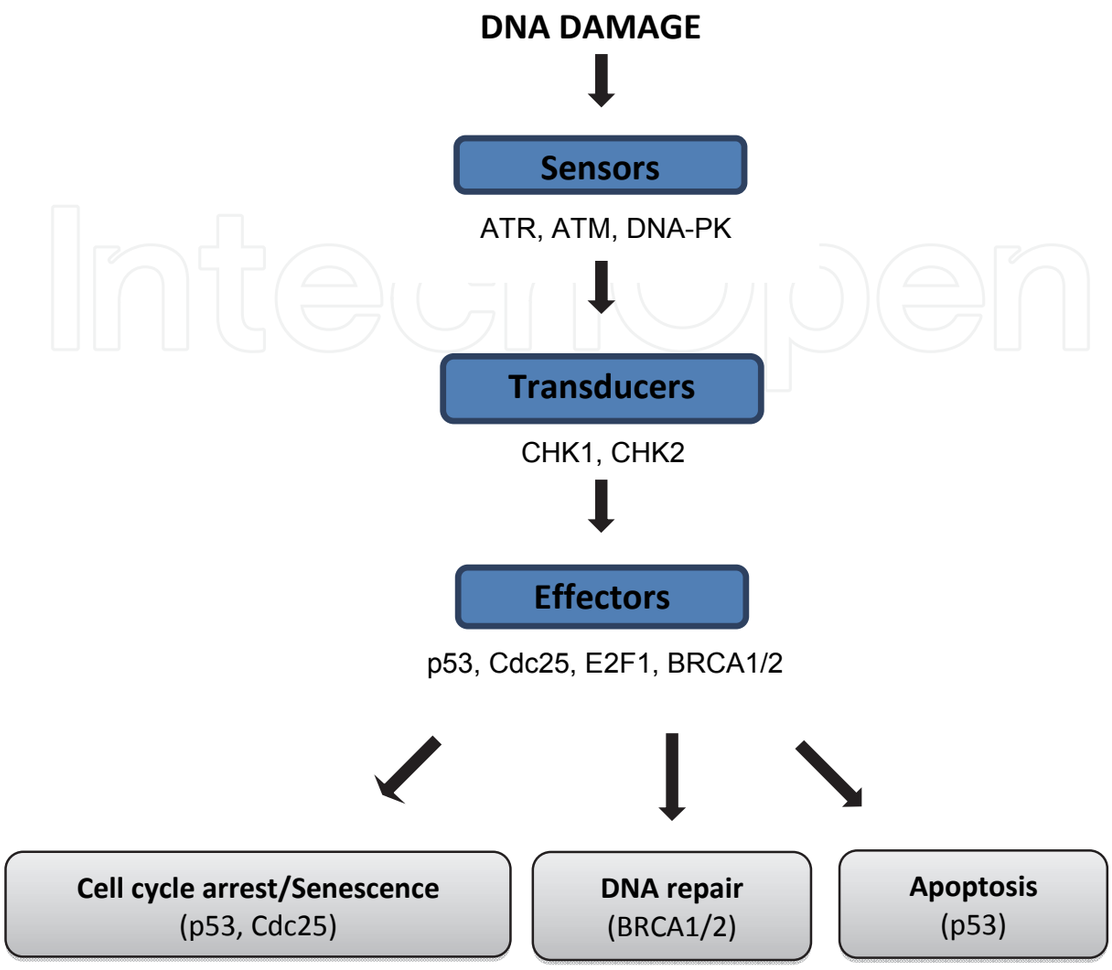

Fig. 1. Schematic diagram of the DNA damage response (DDR). The DDR is initiated by the sensors ATM and/or ATR depending of the nature of the DNA damage inducing cell cycle arrest and DNA repair or apoptosis if the damage is beyond repair.

lesions are complicated by the fact that the DNA damaging agents or ionizing radiation may each generate multiple types of DNA damage, and possibly recruiting several DNA damage sensors (Zhou & Elledge, 2000). The chemotherapeutic drug doxorubicin, for example, is a DNA topoisomerase II inhibitor that not only creates DNA strand-breaks, but also forms doxorubicin-DNA adducts, which induce torsional stress in the DNA structure (Swift et al., 2006). The different types of DNA damage eventually induce the activation of the phosphoinositide-3-kinase (PI3K)-related protein kinases (PIKKs) ATM and ATR (ATM- and Rad3-related) (Yang et al., 2003). Single-stranded DNA resulting from various types of genotoxic stress is bound by ssDNA-binding proteins such as RPA (replication protein A) (Wold, 1997). ATR and the ATR-interacting protein (ATRIP) then localizes to the RPA-coated ssDNA (Zou & Elledge, 2003). ATR also responds to stalled DNA replication forks in humans and mice (Cortez et al., 2001; Brown & Baltimore, 2000). On the other hand, ATM is recruited by double-stranded (ds) DNA breaks resulting primarily from ionizing radiation and oxidative stress (Zhou & Elledge, 2000; Shiloh, 2003). ATM is also activated by programmed dsDNA breaks during V(D)J recombination, an important process in the

generation of the diverse repertoire of immunoglobulins and T-cell receptors in B and T lymphocytes (Perkins et al., 2002; Dujka et al., 2009). It is currently not clear how ATM and ATR initiate the correct repair programmes for the wide variety of DNA lesions. Most likely different types of DNA damage recruit specific proteins (e.g. BRCA-1, H2AX, Nbs1, 53BP1 etc.) that interact with ATM and ATR thereby initiating a DNA damage-specific repair programme (Yang et al., 2003; Matsuoka et al., 2007).

2.2 DNA-PK

The DNA-dependent protein kinase (DNA-PK), a member of the PI3K superfamily, is a nuclear serine/threonine kinase composed of the catalytic subunit (DNA-PKcs) and the DNA-binding Ku70/80 subunit (Carter et al., 1990; Kurimasa et al., 1999). Similar to ATM, DNA-PK is involved in the detection of dsDNA breaks and is activated by DNA damage following ionizing radiation, UV radiation and V(D)J recombination events (Kurimasa et al., 1999; Yang et al., 2003). The binding of Ku70/Ku80 to dsDNA breaks is required for the activation of DNA-PKcs and the subsequent ligation of the double-stranded DNA ends by other protein components of the NHEJ (non-homologous end-joining) machinery (Kurimasa et al., 1999; Walker et al., 2001). Recent data suggest that DNA-PK and ATM are partially redundant in their function (Stiff et al., 2004). DNA-PK has been reported to be able to phosphorylate H2AX in ATM-deficient cells after treatment with ionizing radiation (Stiff et al., 2004). Furthermore, association of ATR and DNA-PK is observed during UV irradiation and the activation of DNA-PK is impaired when ATR is inhibited (Yajima et al., 2006). Taken together, DNA-PK appears to co-operate with ATM and ATR to initiate the DDR.

2.3 CHK1 and CHK2

ATM and ATR partially coordinate the DDR through the signal transducers CHK1 and CHK2 (Zhou & Elledge, 2000; Gasser 2007). CHK1 and CHK2 contain conserved kinase domains but differ in their function and structure (reviewed in Bartek et al., 2001; McGowan 2002). The main functions of CHK1 and CHK2 are to reinforce signals from ATM and ATR (Matsuoka et al., 1998; Abraham, 2001; Shiloh, 2003). CHK1 is an unstable protein that is specifically expressed during the S and G2 phases of cell cycle (Lukas et al., 2001). Interestingly, while CHK1 is expressed and activated in unperturbed cell cycles, stalled replication forks and ssDNA breaks enhance its activity further (Kaneko et al., 1999; Zhao et al., 2002; Sørensen et al., 2003). In contrast, CHK2 is expressed throughout the cell cycle (Lukas et al., 2001) but is activated specifically in response to dsDNA breaks. Similar to ATM, CHK2 activation depends on its dimerization and autophosphorylation (Cai et al., 2009). Historically, it was thought that ATR specifically activates CHK1, while CHK2 activation depends on ATM, but recent data suggests that a certain degree of redundancy exists in the ability of ATR and ATM to activate the signal transducers. For example it was reported that the phosphorylation of CHK1 in response to ionizing radiation depends on ATM (Gatei et al., 2003; Sørensen et al., 2003). CHK1 and CHK2 share many overlapping substrates and are therefore often found to be functionally redundant (Bartek et al., 2001; McGowan, 2002). The targets of CHK1 and CHK2 regulate many fundamental cellular functions such as cell cycle, DNA repair and apoptosis (Figure 1). For example, both CHK2 and CHK1 reduce the activity of cyclin-dependent kinases (CDKs) such as CDK2 and CDK1. The resulting inhibition of these G1/S- and G2/M-promoting CDKs results in cell cycle delays (Falck et al, 2001; Zhao & Piwnica-Worms, 2001). Despite their functional redundancy, mouse studies have revealed striking differences for CHK1 and CHK2 during

development (Liu et al., 2000; Takai et al., 2000). CHK1-deficient mice are embryonic lethal in contrast to CHK2-deficient mice (Liu et al., 2000; Takai et al., 2000; Hirao et al., 2000; Takai et al., 2002). CHK2 is required for radiation-induced, p53-dependent apoptosis and the stability of p53 is reduced in mice lacking CHK2 (Hirao et al., 2000; Takai et al., 2002). Nevertheless both CHK1 and CHK2 have been shown to be able to phosphorylate p53 on several sites in response to DNA damage (Hirao et al., 2000; Shieh et al., 2000; Ou et al., 2005).

2.4 p53

Whether the DNA repair machinery or cellular apoptosis is initiated as a consequence of DNA damage is a crucial decision of the DDR. Although not fully understood, a large body of evidence hints at p53 playing a critical role in this important decision (reviewed in Vousden & Lu, 2002; Das et al., 2008). Depending on the nature of the DNA damage, p53 is phosphorylated on several serine residues by ATM (Banin et al., 1998; Khanna et al., 1998), ATR (Tibbetts et al., 1999) or DNA-PK (Shieh et al., 1997; Achanta et al., 2001). In addition the signal transducers CHK1 and CHK2 directly bind and phosphorylate p53 (Hirao et al., 2000; Ou et al., 2005, Dumaz & Meek, 1999). The phosphorylation of p53 at Ser20 is known to be important for destabilizing the interaction of p53 with its inhibitor MDM2 (Shieh et al., 1997; Unger et al., 1999). In addition, studies have demonstrated that p53 function is modulated by acetylation in response to DNA damage (Ou et al., 2005). These posttranslational modifications allow p53 to induce the expression of its target genes such as p21, a CDK2 inhibitor implicated in G1/S transition (Wade Harper et al., 1993; Chen et al., 1995). In case of irreparable DNA damage, p53 induces a differential set of target genes leading to the activation of both the mitochondrial and CD95-FasL apoptotic pathways (Kastan et al., 1991; Lowe et al., 1993b; Bennett et al., 1998; Chipuk et al., 2003; Mihara et al., 2003).

Recent studies demonstrated that p53 is activated early in tumorigenesis as a result of oncogene expression. Oncogene activation is thought to induce “replication stress” leading to the collapse of DNA replication forks and the formation of dsDNA breaks (Halazonetis et al., 2008). It has been suggested that p53 acts as an anti-cancer barrier in precancerous lesions. In support of this hypothesis, functional inactivation of p53 has been observed in 50% of all human cancers (Hanahan & Weinberg, 2000). Thus, oncogene-induced DNA damage may explain two key features of cancer: the high frequency of p53 mutations and the resulting genomic instability, which is often observed in cells lacking p53 (reviewed in Jackson & Bartek, 2009).

3. DDR and the immune system

As early as the 19th century it was recognized that some tumors are infiltrated by innate and adaptive immune cells (reviewed in Dvorak, 1986). In recent years new data suggests that DDR can initiate an immune response. As discussed below in more detail, the DDR directly activates a variety of transcription factors such as NF-κB and interferon regulatory factors (IRFs). These transcription factors induce the expression of various immune genes, including inflammatory cytokines and chemokines. In addition, the DDR and oxidative stress induce the expression of a number of ligands for activating immune receptors such as NKG2D and DNAM-1, which are mainly expressed by cytotoxic immune cells such as T cells and NK cells.

3.1 NF-κB

Transcription factors belonging to the NF-κB family are mostly nuclear proteins that were initially reported to bind to the promoter of the κ immunoglobulin gene in B cells upon lipopolysaccharide (LPS) stimulation (Sen & Baltimore, 1986). It is now recognized that these transcription factors regulate many key aspects of innate immune signaling (Baeuerle & Henkel, 1994; Pahl, 1999). The NF-κB subunits are usually sequestered in the cytoplasm through their interactions with inhibitory IκB proteins. Phosphorylation of IκB proteins by the IκB kinase (IKK) complex, consisting of IKKα, IKKβ and the scaffold protein NEMO/IKKγ, leads to the degradation of IκB (Scheidereit 2006). Upon IκB degradation, NF-κB subunits subunits translocate to the nucleus (Scheidereit 2006) and modulate the expression of NF-κB target genes such as IL-6 (Libermann & Baltimore, 1990), IL-8 (Kunsch et al., 1994), and IL-1β (Cogswell et al., 199). The picture is complicated by the fact that NF-κB complexes consist of homodimers or heterodimers of five NF-κB family proteins: p65 (Rel-A), Rel-B, c-Rel, p50 and p52 (Hayden & Ghosh, 2008). The Rel subfamily of NF-κB proteins possess C-terminal transactivation domains (TADs) that promote target gene expression when bound to κB sites as heterodimers with either p50 or p52 (Ghosh et al., 1998). The p50/p65 heterodimer is the main activating NF-κB dimer in many cells, and the combinatorial diversity of heterodimers confers specificity in gene activation under specific physiological conditions (Ghosh et al., 1998). In contrast, the p52 and p50 homodimers inhibit transcription (Ghosh & Karin, 2002).

NF-κB is also activated in response to DNA damage (Brach et al., 1991; Simon et al., 1994). In ATM-deficient mice, NF-κB activation is impaired after irradiation (Li et al., 2001). Similarly, in DNA-PK-deficient cells, the activation of NF-κB was impaired upon irradiation (Basu et al., 1998). The activation of NF-κB following DNA damage mainly results in survival signals (Wang et al., 1998; Wang et al., 1999) that could provide a time window for cells to repair damaged DNA (Beg & Baltimore, 1996; Wang et al., 1996).

3.1.1 NEMO

Recent insights into the molecular mechansims leading to NF-κB activation in response to DNA damage indicate an important role for NEMO (Huang et al., 2000; Huang et al., 2002; Huang et al., 2003). The reconstitution of NEMO-deficient cells with wild-type NEMO restored NF-κB activation in response to DNA damage (Huang et al., 2002). The dsDNA breaks promote the SUMO (small ubiquitin-like modifier) modification of nuclear NEMO, which prevents its nuclear export (Huang et al., 2003; Janssens et al., 2005). At the same time, activated ATM phosphorylates SUMOylated NEMO leading to the removal of SUMO and the attachment of ubiquitin (Wu et al., 2006). These modifications allow NEMO to enter in a complex with ATM to be exported to the cytoplasm, where ATM mediates K63-linked polyubiquitination of ELKS and TRAF6 (Hinz et al., 2010; Wu et al., 2010). In addition NEMO is monoubiquitinated on lysine 285 via cIAP1 (Hinz et al., 2010). The polyubiquitinated complex activates IKKε in a TAK1-dependent manner. Activated IKKε then phosphorylates IκBα leading to K48-linked polyubiquitination and the subsequent degradation of IκBα by the proteasome (Figure 2 and Scheidereit 2006). The free NF-κB (p50/p65) dimer undergoes nuclear translocation and induces the transcription of pro-survival genes (Beg & Baltimore, 1996; Wang et al., 1998).

The activation of NF-κB in tumor cells in response to constitutive genotoxic stress has been suggested to be tumor- promoting (Annunziata et al., 2007; Grosjean-Raillard et al., 2009;

Meylan et al., 2009). The ATM-NEMO-NF-κB pathway is constitutively activated in acute myeloid leukemia (AML) cell lines, samples from high-risk myelodysplastic syndrome (MDS) and AML patients (Grosjean-Raillard et al., 2009), multiple myeloma (Annunziata et al., 2007) and lung adenocarcinomas (Meylan et al., 2009). The pharmacological inhibition or knockdown of ATM in AML cell lines ablated ATM-NEMO interactions, downregulated NF-κB and induced apoptosis (Grosjean-Raillard et al., 2009). In summary, the constitutive activation of the DDR in early cancer not only induces cell cycle arrest, thereby establishing a barrier to cancer progression, but also promotes the survival of cancer cells by the activation of NF-κB (Bartkova et al., 2005; Gorgoulis et al., 2005).

Apart from promoting tumorigenesis, DDR-mediated NF-κB activation also plays an important role in lymphocyte development and survival (Bredemeyer et al., 2008). DsDNA breaks are generated as result of recombinase activating gene (RAG) expression during V(D)J recombination in pre-B cells. The subsequent activation of the ATM-NEMO-NF-κB pathway is critical for the expression of genes involved in lymphocyte development, survival and function (Bredermeyer et al., 2008).

3.2 Interferon regulatory factors

IRFs are a class of transcription factors that have diverse roles in immune responses (Honda & Taniguchi, 2006). There are nine members in the mammalian IRF family. Each IRF contains a well-conserved DNA-binding domain, which recognizes a consensus DNA sequence known as the IFN-stimulated response element (ISRE) (Honda & Taniguichi, 2006). ISRE sequences are found on the promoter regions of type I interferons (IFN-α and IFN-β and other pro-inflammatory genes, thus making IRFs the essential mediators of IFN-α/β and other pro-inflammatory cytokines (Tanaka et al., 1993; Taniguchi et al., 2001). IRFs are well known to be activated upon binding of invariant microbial motifs, often referred to as pattern-associated molecular patterns (PAMPs), to pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), NOD-like receptors (NLRs) and RIG-I-like receptors (RLRs) (Akira et al., 2006; Creagh & O'Neill, 2006; Kanneganti et al., 2007; Yoneyama and Fujita, 2007). However, some IRFs are also activated in response to genotoxic stress as discussed below in more detail (Taniguchi et al., 2001).

3.2.1 IRF-1 and IRF-2

The link between IRFs and the DDR was first shown for IRF-1. IRF-1 was found to be essential for the apoptosis of T lymphocytes and embryonic fibroblasts in response to ionizing radiation or chemotherapeutic agents (Tanaka et al., 1994; Tamura et al., 1995). Recent studies have shown that the overexpression of IRF-1 results in the apoptosis of cancer cells through both cell intrinsic mitochondrial and extrinsic death ligand pathways (Strang et al., 2007; Gao et al., 2010). Furthermore, ATM-deficient cells derived from patients with ataxia telagienctasia (AT) fail to induce IRF-1 mRNA transcription in response to DNA damage (Pamment et al., 2002). The reconstitution of ATM restored IRF-1 induction in response to radiation (Pamment et al., 2002). These findings suggest that IRF-1 participates in DDR-mediated cell cycle arrest, although the precise molecular mechanisms still need to be established in more details (Tanaka et al., 1996).

3.2.2 IRF-3

IRF-3 interacts with CREB-binding protein (CBP)/p300 co-activators to form a dsDNA-activated transcription factor 1 (DRAF-1) complex which binds to the ISRE of type 1

interferons and other interferon-stimulated genes (ISGs) (Weaver et al., 1998). In contrast to other IRF members, IRF-3 is constitutively expressed in the cytoplasm of most cells (Kumar et al., 2000). IRF-3 is activated through phosphorylation by TANK-binding kinase 1 (TBK1) and/or IKKε leading to its dimerization and translocation to the nucleus (Kim et al., 1999; Fitzgerald et al., 2003). It was later discovered that IRF-3 is also a direct target of DNA-PK (Karporva et al., 2002). Our own data suggest that IRF-3 phosphorylation and activation in response to DNA damaging agents Ara-C or aphidicolin critically depends on ATM and ATR (Lam et al., submitted). Interestingly, IRF-3 may also participate in the DDR-mediated anti-cancer barrier. A dominant negative mutant of IRF-3 promoted the transformation of NIH3T3 cells and tumorigenesis *in vivo* (Kim et al., 2003). The overexpression of IRF-3 inhibited the proliferation of fibroblasts and astrocytes. Interestingly, the IRF-3 induced cell cycle arrest depended on p53 (Kim et al., 2006). Similarly, over-expression of IRF-3 in B16 melanoma cells resulted in growth suppression *in vivo* (Duguay et al., 2002). Recent evidence suggests that IRF-3 also induces apoptosis under certain circumstances such as in response to Sendai virus and NDV virus infection (Heylbroeck et al., 2000; Weaver et al., 2001). The molecular mechanisms of IRF-3-induced apoptosis are not well understood, but may in part rely on the ISRE promoter element present in TNF-related apoptosis-inducing ligand (TRAIL), an important member of the apoptotic machinery (Kirschner et al., 2005). In summary, it is possible that IRF-3 acts as a tumor suppressor gene that partially depends on p53 for its function.

3.2.3 IRF-5

IRF-5 is constitutively expressed in cytoplasm of a variety of cell types, particularly, in cells of lymphoid origins (Barnes et al., 2001; Yanai et al., 2007). IRF-5 is a direct target of p53 (Mori et al., 2002) and IRF-5 transcript levels further increase in response to DNA damage (Barnes et al., 2003; Hu et al., 2005). However, the induction of p53 target genes was not impaired in IRF5-deficient cells (Hu et al., 2005). Overexpression of IRF-5 rendered cells more susceptible to DNA damage-induced apoptosis even in p53-deficient cancer cell lines (Hu et al., 2005). In response to TLR agonists or DNA damage, IRF-5 is activated, possibly by phosphorylation, and translocates to the nucleus. Similar to other IRFs it promotes gene transcription by binding to target ISRE sequences in the regulatory region of target genes (Barnes et al., 2001), such as the interleukin-12b gene (Takaoka et al., 2005). In summary IRF-5 is a type I IFN-responsive p53 target gene that induces the expression of target genes distinct from those of p53.

3.2.4 Type I IFNs

Type I IFNs belong to a multigene family that includes IFN-α and IFN-β. Type I IFNs are expressed rapidly in response to many viral infections (Tanaka et al., 1998). They are best known to induce the expression of genes that increase the resistance of cells to virus infection (Taniguchi & Takaoka, 2002). In addition, type I IFNs were shown to modulate other cellular functions, such as proliferation and apoptosis (reviewed in Chawla et al., 2003). The increased sensitivity of cells to apoptosis in the presence of type I IFNs depends in part on their ability to increase p53 protein levels (Takaoka et al., 2003). Binding of type I IFNs to the IFN receptor activates the receptor-associated kinases Jak1 and Tyk2 leading to phosphorylation of the STAT1 and STAT2 proteins. The activated STAT proteins bind the IFN-regulatory factor 9 (IRF-9) to form the trimeric IFN-stimulated gene factor 3 (ISGF-3)

complex. The ISGF-3 complex translocates to the nucleus and binds to ISREs sites present in the mouse and human p53 genes thereby activating p53 transcription (Takaoka et al., 2003). However, type I IFN treatment is not sufficient to activate p53. It rather enhances the p53 response, thereby rendering cells more sensitive to the DDR (Takaoka et al., 2003; Yuan et al., 2007). In clinical trials type I IFNs have been successfully utilized for both first-line and salvage therapy for a variety of cancers such as human papilloma virus (HPV)-associated cervical cancer, hepatic cancer and leukemias (Parmar & Platanias, 2003; Wang et al., 2011).

3.3 NKG2D ligands

One of the best-characterized NK cell-activating receptor in the context of cancer is the NKG2D receptor (reviewed in Raulet, 2003). All NK cells constitutively express the NKG2D receptor. In humans its cell surface expression requires association with the adaptor protein DAP10. Engagement of NKG2D leads to cytokine secretion and cytotoxicity (Billadeau et al., 2003; Upshaw et al., 2006). NKG2D recognizes MHC class I chain-related (MIC) A and B proteins and RAET1 (retinoic acid early transcript 1) gene family members in humans (Raulet, 2003, Cosman et al., 2001). No MIC homologs have been found in the mouse genome so far. The mouse Raet1 genes can be further divided into Rae1, H60 and Mult1 subfamilies that share little homology but are structurally similar. The Rae1 subfamily consists of highly related isoforms Rae1α - Rae1ε encoded by different genes (Diefenbach et al., 2000; Cerwenka et al., 2000; Raulet, 2003). NKG2D ligand expression has been observed on tumors of many origins, in particular in solid tumors, lymphomas and myeloid leukemia (Groh et al., 1999; Pende et al., 2002; Rohner et al., 2007). NKG2D was shown to be critical for the immunosurveillance of carcinoma, epithelial and lymphoid tumors in mouse models of de novo tumorigenesis. We and others have demonstrated that NKG2D ligand expression can be induced by DNA damage and oxidative stress (Gasser et al., 2005; Peraldi et al., 2009). The upregulation of NKG2D ligands in response to DNA damage critically depends on ATR or ATM, depending on the nature of the DNA damage (Gasser et al., 2005). On tumour cells that constitutively express NKG2D ligands, inhibition of the DDR decreased ligand cell surface expression (Gasser et al, 2005), suggesting that persistent DNA damage in the tumour cells at least partially maintains constitutive NKG2D ligand expression. An important question is if the p53- and the NKG2D-mediated tumor surveillance are linked or provide independent protection against the development of malignant cells. In favor of the latter idea, we found that NKG2D ligands could be induced in cells that lacked p53. While p53 is not required for the expression of NKG2D ligands in tumor cell lines or in cells with DNA damage, it is possible that other p53 family members, along with p53, function in a partially redundant fashion to induce NKG2D ligand expression. Intriguingly, the loss of p53 is implicated in the loss of genomic stability. It is therefore plausible that the resulting genomic lesions may further increase the DDR and upregulate the expression of NKG2D ligands on tumor cells.

3.4 DNAM-1 ligands

Although NKG2D is a major receptor implicated in recognition of cells with damaged DNA, NKG2D blocking experiments suggested that additional immunomodulatory molecules are required (Gasser et al., data not shown). A recent study showed that the DDR also upregulates the expression of DNAM-1 ligands (Soriani et al., 2009). DNAM-1 ligands include CD155 (also called poliovirus receptor, tumor associated antigen 4 and necl-5) and

CD112 (Nectin-2) (Bottino et al., 2003). CD112 and CD155 are ubiquitously expressed on most normal cells of neuronal, epithelial endothelial and fibroblast origin, however their expression levels are significantly enhanced in tumor cells including acute myeloid leukemias, neuroblastomas, melanomas and colorectal carcinomas (Castriconi et al., 2004; Carlsten et al., 2007; El-Sherbiny et al., 2007). DNAM-1 is a member of the immunoglobulin superfamily and is constitutively expressed on most immune cells including T cells, NK cells, a subset of B cells and monocytes/macrophages (Shibuya et al., 1996). DNAM-1 is physically and functionally associated with LFA-1, a receptor for ICAM-1 which is also upregulated in response to DNA damage (see below). The expression of CD112 or CD155 on tumor cells induces NK cell- and $CD8^+$ T cell-mediated cytotoxicity and cytokine secretion (Bottino et al., 2003). Strikingly, DNAM-1-deficient mice injected with carcinogen-induced tumor cells developed tumors faster and showed higher mortality (Iguchi-Manaka et al., 2008). CD155 is also recognized by CD96, a stimulatory receptor expressed by NK cells and other immune cells (Fuchs et al., 2004). The existence of a dual receptor system recognizing CD155 further suggests an important role of this ligand in NK cell-mediated recognition of tumor cells. In addition to its activating functions, CD155 has recently also been shown to suppress immune cell activation through a third receptor called TIGIT/ VSTM/WUCAM, primarily expressed on T cells and on NK cells (Stanietsky et al., 2009). Moreover, the binding of CD155 to TIGIT on DCs leads to the secretion of IL-10 and inhibition of pro-inflammatory cytokine secretion (Yu et al., 2009). CD155 has higher affinity for TIGIT than DNAM-1. In contrast CD112 preferentially binds to DNAM-1 (Bottino et al., 2003). Hence the over-all avidity of cells for DNAM-1 over TIGIT may ultimately determine if an immune response is initiated or inhibited by DNAM-1 ligands.

3.5 ICAM-1

Intercellular adhesion molecule-1 (ICAM-1, also called CD54) is a cell adhesion molecule, which is expressed by fibroblasts, epithelial, endothelial and immune cells such as lymphocytes and macrophages (Dustin et al., 1986; Rothlein et al., 1986). Binding of ICAM-1 to its receptors LFA-1 and macrophage-1 antigen (Mac-1) expressed on leukocytes is often required to initiate inflammatory and immune responses (Simmons et al., 1988; Diamond et al., 1993; Sligh et al., 1993). The expression of ICAM-1 is induced by several pro-inflammatory cytokines (Dustin et al., 1986; Pober et al., 1986). However, ICAM-1 expression has also been shown to be upregulated by ionizing radiation in a p53-dependent manner (Hallahan et al., 1996; Gaugler et al., 1997; Hallahan & Virudachalam, 1997). Recently it was discovered that ICAM-1 expression correlates with senescence (see 4.1 and Gourgoulis et al., 2005).

4. The role of DDR in diseases

4.1 Senescence-associated secretory phenotype (SASP)

If low levels of DNA damage persist in cells, the DDR induces an irreversible cell cycle arrest called senescence. Recent data have shown *in vivo* accumulation of senescent cells with age (Herbig et al., 2006; Jeyapalan et al., 2007). Senescent cells secrete a broad spectrum of factors, including the cytokines IL-6, IL-8, transforming growth factor-b (TGF-β), plasminogen activator inhibitor 1 (PAI-1), and others, collectively often referred to as the senescence-associated secretory phenotype (SASP) (Kortlever & Bernards, 2006; Coppé et al., 2009; Rodier et al., 2009). There is good evidence that some of these factors contribute to

senescence entry and maintenance. For instance, the autocrine secretion of IL-6 is required for the establishment of oncogene-induced senescence (Kuilman et al. 2008). Some IRFs, including IRF-1, IRF-5 and IRF-7, have been functionally linked to senescence (Li et al., 2008; Upreti et al., 2010). Some members of the SASP do not function exclusively in a cell-autonomous manner, but they also affect neighboring cells. Paradoxically, their paracrine effects sometimes promote tumorigenesis. IL-6 contributes to tumorigenesis by promoting angiogenesis (Wei et al., 2003; Fan et al., 2008). In addition, IL-6 secretion by HRasV12-transformed cancer cells has been reported to mediate tumour growth (Leslie 2010). Tumor-promoting effects have also been described for other SASP members, such as TGF-β (reviewed in Bierie & Moses, 2006), IL-1 (Dejana et al., 1988; Voronov et al., 2003) and IL-8 (Norgauer et al., 1996). These opposite effects may be explained by differences in cells type, stage of transformation or the mode of signaling (autocrine versus paracrine). It is possible that healthy, normal cells enter senescence in response to oncogene-induced DNA damage, and possibly due to the subsequent SASP, whereas the SASP can promote tumorigenesis in neighboring precancerous lesions harboring specific mutations. DNA damage-induced senescence may therefore have dual roles in preventing and promoting tumorigenesis, depending on the cellular context. Some characteristics of senescent cells, such as the ability of SASP members to modify the extracellular environment, may play a role in aging and age-related pathology (Chung et al., 2009). Of note many of DDR-induced ligands for activating immune receptors, such as NKG2D, DNAM-1 and LFA-1 are upregulated in senescent cells. It remains currently unclear if the underlying DDR in senescent cells is regulating the expression of these ligands or if the expression depends on senescence-specific pathways.

4.2 Cancer

As mentioned earlier, the DDR may represent a major barrier to tumorigenesis (Bartkova et al., 2005; Gorgoulis et al., 2005). Replication stress in response to oncogene activation results in the collapse of DNA replication forks. The resulting DNA breaks activate the DDR, leading to either senescence or cellular apoptosis. In addition to these largely cell-intrinsic barrier effects of the DDR, recent evidence suggests that cell-extrinsic barriers could exist, some of which may depend on the immune system. A link between the DDR and immune system was suggested by the upregulation of ligands for the activating immune receptors NKG2D, DNAM-1 and LFA-1 in tumor cells or in cells undergoing genotoxic stress. In addition the DDR also regulates the expression of the apoptosis-inducing death receptor 5 (DR5), a ligand for TRAIL (Wu et al., 1997). NKG2D, DNAM-1 and LFA-1 participate in 'induced self-recognition' of target cells by cytotoxic NK cells (Lakshmikanth et al., 2009). "Induced self-ligands" are absent or only poorly expressed by normal cells, but upregulated on diseased cells (Castriconi et al., 2004; Gasser et al., 2005; Gorgoulis et al., 2005). The activating receptors NKG2D, DNAM-1 and LFA-1 are mainly expressed by natural killer (NK) cells and T cells, which play an important role in the immunity against cancer (Shibuya et al., 1996; Barber et al., 2004; El-Sherbiny et al., 2007). The recognition of tumor cells by NK cells is governed by activating and inhibitory receptor-mediated signals (Gasser & Raulet, 2006). Many of the inhibitory receptors expressed by NK cells are specific for major histocompatibility complex (MHC) class I molecules. MHC class I molecules are expressed by normal cells but are often downregulated from tumour cells. Increased expression of activating ligands by tumor cells can override inhibitory receptor signaling, resulting in NK cell activation and NK cell-mediated lysis of tumor cells. NK cells also

produce pro-inflammatory cytokines such as IFN-γ, which help to initiate an adaptive immune response (reviewed in Kos, 1998). In addition to their role in NK cells, NKG2D, DNAM-1 and LFA-1 provide signals that enhance the activation of specific T cell subsets, such as the cytotoxic $CD8^+$ T cells (Shibuya et al., 1996; Barber et al., 2004; Gasser & Raulet, 2006). The qualitative and quantitative effector responses of NK and T cells are regulated by cytokines such as interleukin-2 (IL-2), IL-12, IL-15, IL-18, IL-21, TGF-β and the type I IFNs (Biron et al., 1999). Hence, in addition to the effects described above, the DDR-induced expression of type I interferons may also help in stimulating an immune response through the activation of NK and T cells.

4.3 Viral infections

The DDR is also triggered when cells are infected with certain viruses, including retroviruses such as the human immunodefiency virus 1 (HIV-1), adenoviruses, herpes simplex viruses 1 and 2 (HSV-1 and 2), cytomegalovirus (CMV), hepatitis B virus, Epstein-Barr virus (EBV) and the human papilloma virus type 16 and 18 (HPV-16 and 18) (Lilley et al., 2007). In many cases, the DDR is triggered in response to viral nucleic acid intermediates produced during the viral "life cycle" (Lilley et al., 2007). The importance of the DDR in preventing virus-induced tumorigenesis is evidenced by the fact that oncogenic viruses infect many cells but rarely lead to tumorigenesis. For example, infectious mononucleosis can be caused by the infection of EBV, but rarely leads to Burkitt's and Hodgkin's lymphoma (Lemon et al., 1977). The ATM-CHK2 pathway is triggered in B cells during a latent EBV infection, which is thought to supress EBV-induced transformation by inducing cell cycle arrest and apoptosis (Nikitin et al., 2010). Adenovirus infection results in the phosphorylation of ATM and H2AX, the stabilization of p53 and the downregulation of the anti-apoptotic protein myeloid cell leukemia 1 (MCL-1), thereby promoting the induction of apoptosis in virus-infected cells (Debbas & White, 1993; Lowe & Ruley, 1993a; Cuconati et al., 2003). In summary, the DDR is not restricted to controling tumorigenesis induced by the activation of host oncogenes, but also functions to control the activity of viral genes and may therefore participate in defending organisms from viral infections. In support of this idea, p53-deficient mice show higher viral titer and mortality after vesicular stomatitis virus infection (Takaoka et al., 2003). In another study, the knockdown of p53 in a liver cell line resulted in higher levels of hepatitis C virus replication (Dharel et al., 2008). In addition, p53 was shown to be activated in cells infected with the Newcastle disease virus, herpes simplex virus and influenza virus (Takaoka et al., 2003; Turpin et al., 2005).

Many viruses have developed means to interfere with the DDR, further supporting the idea that the DDR may restrict viral infection and proliferation of infected cells. The adenovirus core protein VII protects the viral genome from the DDR (Karen & Hearing, 2011). Tax, a protein encoded by HTLV-1 attenuates the ATM-mediated DDR by interacting with CHK1 and CHK2 (Park et al., 2004; Park et al., 2005). The activation of the DDR is disrupted by the human CMV through altering the localization of CHK2 by viral structural proteins (Gaspar & Shenk, 2005). During the EBV infection of B cells, the latent EBNA3C protein attenuates the DDR by modulating CHK2 and p53 activity (Nikita et al., 2010). Other proteins (E6 protein of the HPV-16, HPV-18, S40 large T antigen of simian virus etc.) of oncogenic viruses interfere with p53 functions in infected cells (Werness et al., 1990; Kessis et al., 1993).

Despite the potential antiviral properties of the DDR, many viruses have also evolved ways to activate at least part of the DDR for their own replication. In retroviral integration, for instance, the viral integrase cleaves the host DNA to facilitate the integration of the viral

double-stranded cDNA, and as a consequence, leaves a dsDNA break that requires NHEJ repair (Skalka & Katz, 2005). Viral replication of HIV-1 was suppressed when cells were treated with an ATM-specific inhibitor (Lau et al., 2005). Furthermore, HIV-1 encodes a protein, Vpr, which activates the ATR-CHK1 pathway to arrest infected cells in the G2 phase of the cell cycle and to repair dsDNA breaks by homologous recombination (Goh et al., 1998; Roshal et al., 2003; Nakai-Murakami et al., 2006).

The activation of the DDR in response to viral infection renders cell sensitive to immune cell-mediated lysis by upregulating ligands for NKG2D, DNAM-1 and LFA-1. Two recent reports show that HIV-1 ATR-CHK1 activation by the HIV-1 Vpr upregulates the expression of ligands for the activating NKG2D receptor and promotes NK cell-mediated killing (Richard et al., 2009; Ward et al., 2009). EBV-transformed B-cell lines are relatively resistant to NK cell-mediated lysis possibly as a result of their attenuated DDR in addition to high expression of MHC class I molecules, which inhibit NK cells (Pappworth et al., 2007). However, the reactivation of EBV in transformed B cells renders them susceptible to NK-cell-mediated lysis, which was partially depends on NKG2D and DNAM-1 (Pappworth et al., 2007). NKG2D ligand expression is upregulated upon infection by a number of viruses, such as CMV, HBV, poxvirus and hepatitis C virus, although the role of the DDR in the regulation has yet to be explored in detail.

A number of viruses have developed means to interfere with the expression of ligands for activating receptors. This phenomenon is best characterized for the ligands of NKG2D. Nef (Negative factor) protein encoded by HIV-1 downregulates the expression of NKG2D ligands, HLA-A and HLA-B, to potentially evade recognition by NK cells and HLA-A-/HLA-B- restricted HIV-1-specific cytotoxic T cells (McMichael 1998; Cerboni et al., 2007). Hepatitis C virus impairs the NKG2D-dependent NK cell responses by downregulating NKG2D ligand and receptor expression (Wen et al., 2008). Both murine and human CMV have developed strategies to evade the NKG2D-dependent recognition. The murine CMV encodes the viral glycoproteins m138, m145 and m152 for evasion strategies. The m152 targets Rae1 for degradation (Lodoen et al., 2003), m145 and m138 prevent MULT1 expression (Krmpotic et al., 2005), while m138 cooperates with m155 to impair H60 expression (Lodoen et al., 2004; Lenac et al., 2006). The human CMV (HCMV)-encoded UL16 protein inhibits the expression of MICB, ULBP1, ULBP2 and RAET1G (Dunn et al., 2003; Rölle et al., 2003). The HCMV protein UL142 prevents the expression of some, but not all, alleles of MICA (Chalupny et al., 2006). Some alleles of MICA, such as the prevalent allele of MICA, MICA*008, are resistant to downregulation by HCMV because of a truncation of the cytoplasmic domain (Chalupny et al., 2006). These polymorphisms may reflect a counter-offensive of the host to evade viral protein-mediated inhibition of NKG2D ligand expression. Furthermore, it was recently discovered that a microRNA encoded by HCMV downregulates MICB expression by targeting a specific site in the *MICB* 3' untranslated region (Stern-Ginossar et al., 2007). Finally, the HCMV protein UL141 protein impedes the expression of DNAM-1 ligand CD155 (Tomasec et al., 2005). Interestingly, CD155 functions as a poliovirus receptor, but the role of NK cells or the DDR in poliovirus infection has not been studied in detail. Taken together, the DDR presents a challenge to many viruses as their replication critically depends on certain aspects of the DDR. At the same time, the DDR can induce apoptosis of infected cells or render infected cells sensitive to immune cell-mediated lysis (Figure 2). In response, viruses most likely target the specific effector molecules of the DDR that prevent their subsequent infection of new target cells, while leaving the part of the pathway required for their replication intact.

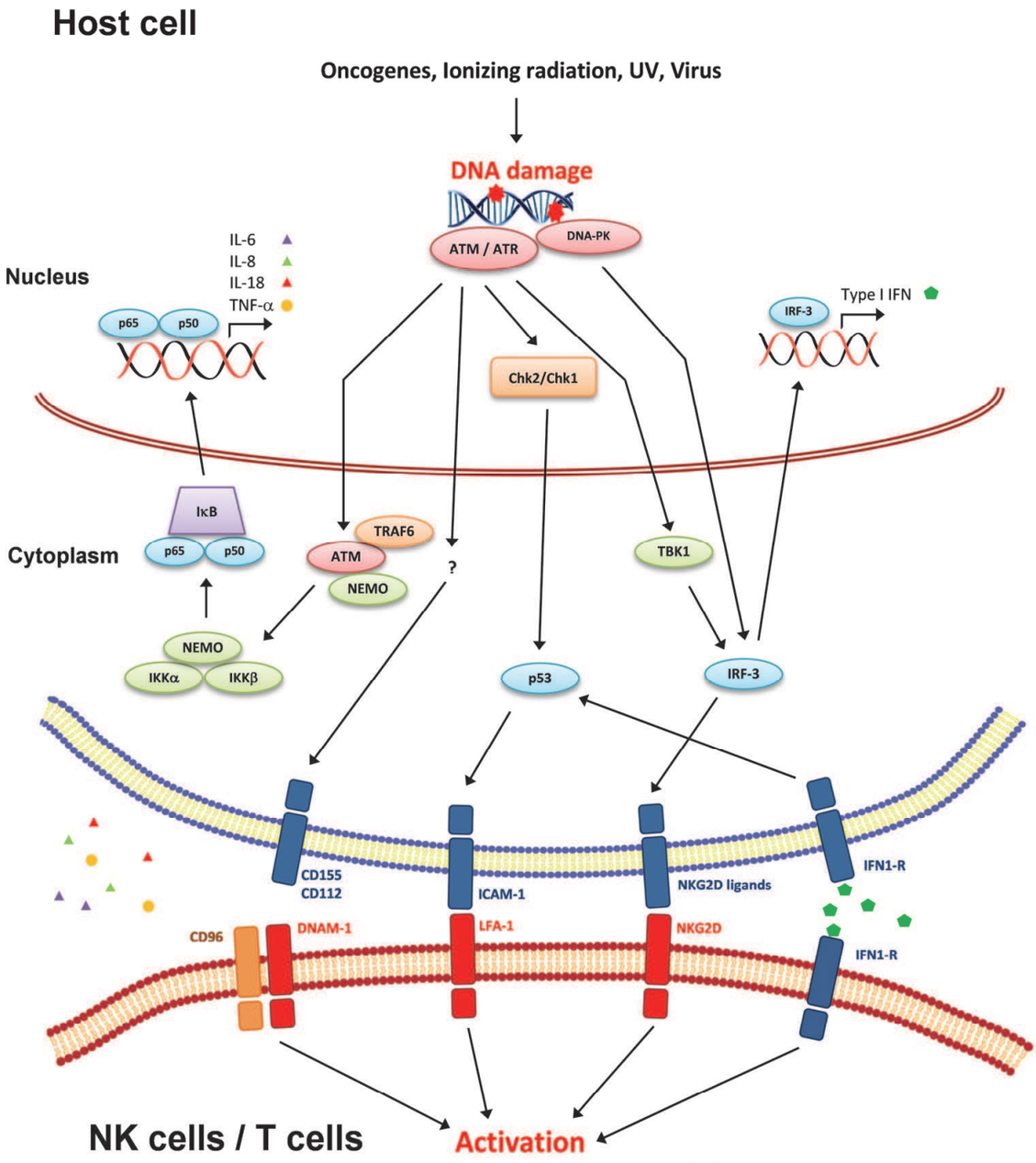

Fig. 2. Potential links between the DDR and the immune system. Activation of the DDR activates cytotoxic natural killer and T cells by inducing the expression of proinflammatory cytokines and ligands for activating immune receptors.

5. Conclusion

The DDR is activated in response to genotoxic stress caused by oncogene activation, viral infection or other environmental insults to the cell. The DDR initiates cell autonomous programmes to try to repair the damaged DNA, or to induce apoptosis if the damage is not repairable, in order to preserve the genome integrity and the survival of the organism.

Recent evidence links the DDR to innate and possibly, adaptive immunity. The activation of an immune response may contribute to the removal of these potentially harmful cells (Figure 2).

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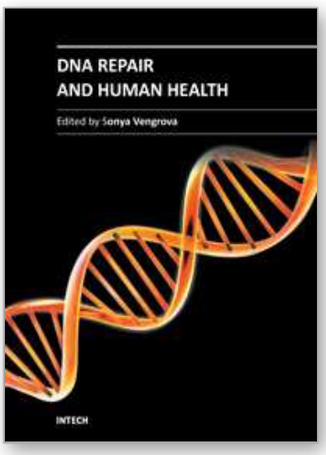

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Over the past decades, great advances have been made in understanding the cellular DNA repair pathways. At the same time, a wealth of descriptive knowledge of human diseases has been accumulated. Now, the basic research of the mechanisms of DNA repair is merging with clinical research, placing the action of the DNA repair pathways in the context of the whole organism. Such integrative approach enables understanding of the disease mechanisms and is invaluable in improving diagnostics and prevention, as well as designing better therapies. This book highlights the central role of DNA repair in human health and well-being. The reviews presented here, contain detailed descriptions of DNA repair pathways, as well as analysis of a large body of evidence addressing links between DNA damage repair and human health. They will be of interest to a broad audience, from molecular biologists working on DNA repair in any model system, to medical researchers.

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