We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



29

Integration of the DNA Damage Response with Innate Immune Pathways

Gordon M. Xiong and Stephan Gasser
Department of Microbiology, National University of Singapore
Singapore

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

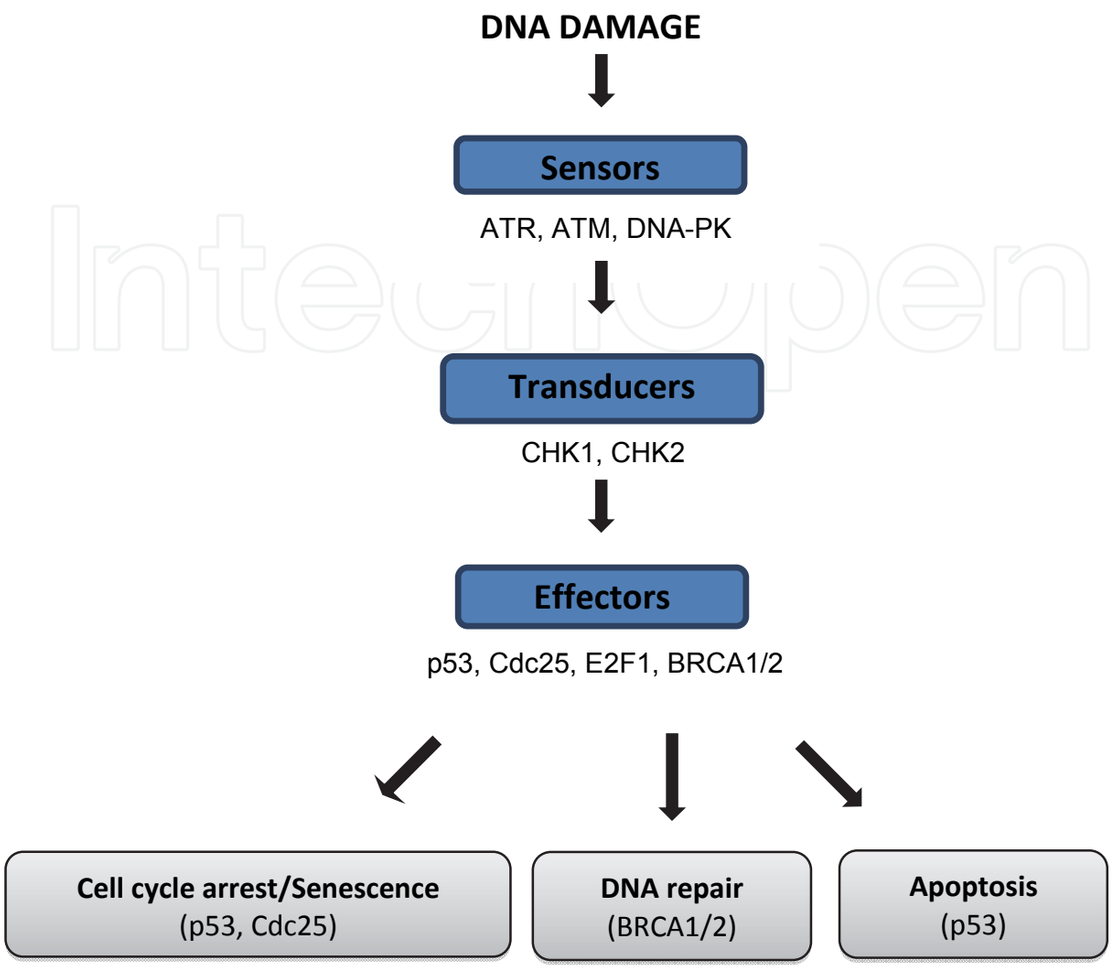


Fig. 1. Schematic diagram of the DNA damage response (DDR). The DDR is initiated by the sensors ATM and/or ATR depending of the nature of the DNA damage inducing cell cycle arrest and DNA repair or apoptosis if the damage is beyond repair.

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.

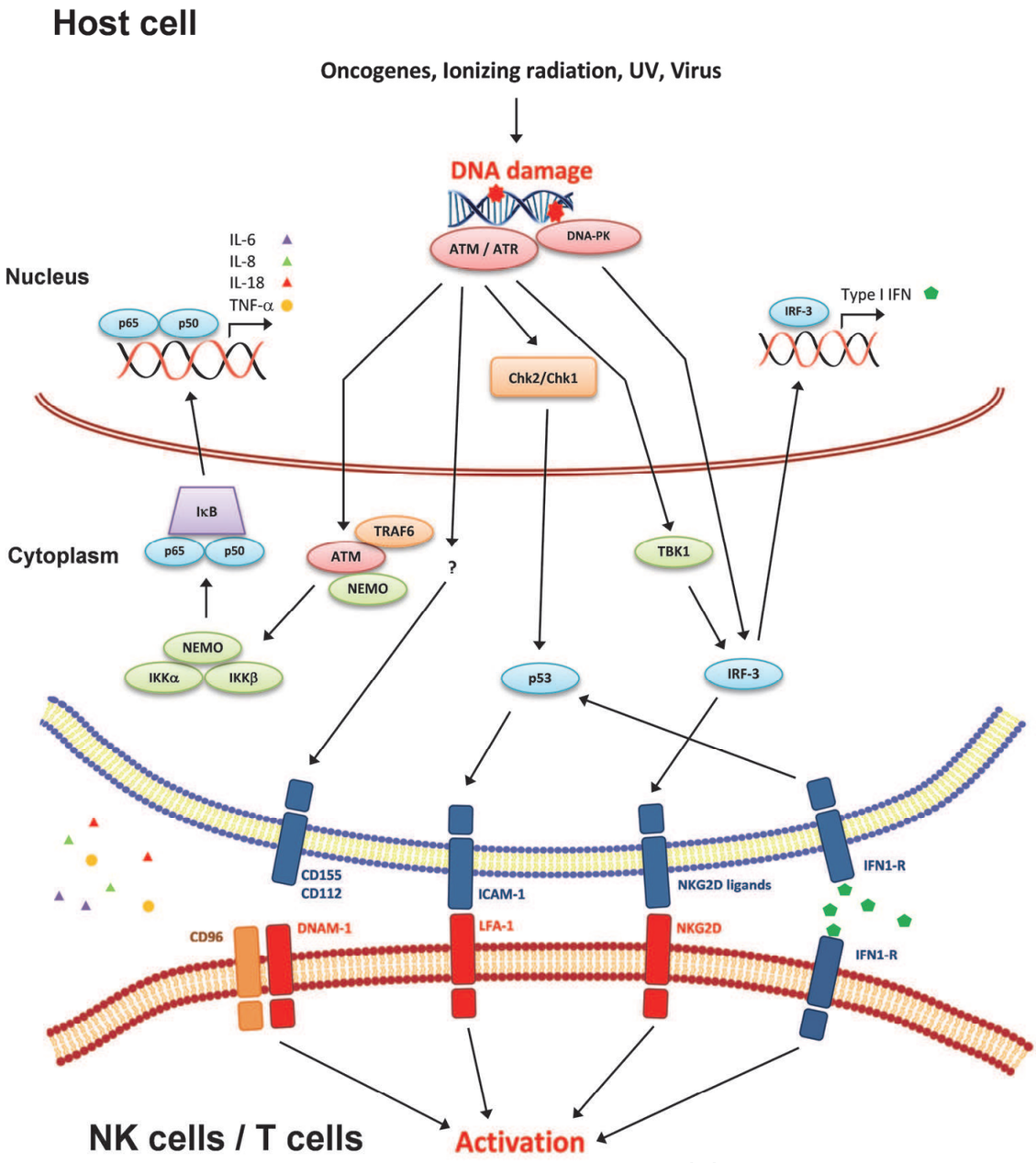


Fig. 2. Potential links between the DDR and the immune system. Activation of the DDR activates cytotoxic natural killer and T cells by inducing the expression of proinflammatory cytokines and ligands for activating immune receptors.

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).

6. References

Abraham RT (2001) Cell cycle checkpoint signaling through the ATM and ATR kinases. *Genes & Development* 15: 2177 -2196

Achanta G, Pelicano H, Feng L, Plunkett W & Huang P (2001) Interaction of p53 and DNA-PK in Response to Nucleoside Analogues. *Cancer Research* 61: 8723 -8729

Akira S, Uematsu S & Takeuchi O (2006) Pathogen Recognition and Innate Immunity. *Cell* 124: 783-801

Annunziata CM, Davis RE, Demchenko Y, Bellamy W, Gabrea A, Zhan F, Lenz G, Hanamura I, Wright G & Xiao W (2007) Frequent Engagement of the Classical and Alternative NF-κB Pathways by Diverse Genetic Abnormalities in Multiple Myeloma. *Cancer Cell* 12: 115-130

Baeuerle PA & Henkel T (1994) Function and activation of NF-kappa B in the immune system. *Annu. Rev. Immunol* 12: 141-179

Banin S, Moyal L, Shieh S, Taya Y, Anderson C, Chessa L, Smorodinsky N, Prives C, Reiss Y & Shiloh Y (1998) Enhanced phosphorylation of p53 by ATM in response to DNA damage. *Science* 281: 1674

Barber DF, Faure M & Long EO (2004) LFA-1 Contributes an Early Signal for NK Cell Cytotoxicity. *The Journal of Immunology* 173: 3653 -3659

Barnes BJ, Kellum MJ, Pinder KE, Frisancho JA & Pitha PM (2003) Interferon Regulatory Factor 5, a Novel Mediator of Cell Cycle Arrest and Cell Death. *Cancer Research* 63: 6424 -6431

Barnes BJ, Moore PA & Pitha PM (2001) Virus-specific Activation of a Novel Interferon Regulatory Factor, IRF-5, Results in the Induction of Distinct Interferon alpha Genes. *J. Biol. Chem.* 276: 23382-23390

Bartek J, Falck J & Lukas J (2001) Chk2 kinase - a busy messenger. *Nat Rev Mol Cell Biol* 2: 877-886

Bartkova J, Horejsi Z, Koed K, Kramer A, Tort F, Zieger K, Guldberg P, Sehested M, Nesland JM, Lukas C, Orntoft T, Lukas J & Bartek J (2005) DNA damage response as a candidate anti-cancer barrier in early human tumorigenesis. *Nature* 434: 864-870

Basu S, Rosenzweig KR, Youmell M & Price BD (1998) The DNA-Dependent Protein Kinase Participates in the Activation of NF[kappa]B Following DNA Damage. *Biochemical and Biophysical Research Communications* 247: 79-83

Beg AA & Baltimore D (1996) An Essential Role for NF-κB in Preventing TNF-α-Induced Cell Death. *Science* 274: 782 -784

Bennett M, Macdonald K, Chan S, Luzio J, Simari R & Weissberg P (1998) Cell surface trafficking of Fas: a rapid mechanism of p53-mediated apoptosis. *Science* 282: 290

Bierie B & Moses HL (2006) TGF-b and cancer. *Cytokine & Growth Factor Reviews* 17: 29-40

Billadeau DD, Upshaw JL, Schoon RA, Dick CJ & Leibson PJ (2003) NKG2D-DAP10 triggers human NK cell-mediated killing via a Syk-independent regulatory pathway. *Nat Immunol* 4: 557-564

Biron CA, Nguyen KB, Pien GC, Cousens LP & Salazar-Mather TP (1999) NATURAL KILLER CELLS IN ANTIVIRAL DEFENSE: Function and Regulation by Innate Cytokines. *Annu. Rev. Immunol.* 17: 189-220

Bottino C, Castriconi R, Pende D, Rivera P, Nanni M, Carnemolla B, Cantoni C, Grassi J, Marcenaro S, Reymond N, Vitale M, Moretta L, Lopez M & Moretta A (2003) Identification of PVR (CD155) and Nectin-2 (CD112) as Cell Surface Ligands for the Human DNAM-1 (CD226) Activating Molecule. *The Journal of Experimental Medicine* 198: 557 -567

Brach MA, Hass R, Sherman ML, Gunji H, Weichselbaum R & Kufe D (1991) Ionizing radiation induces expression and binding activity of the nuclear factor kappa B. *J Clin Invest* 88: 691-695

Bredemeyer AL, Helmink BA, Innes CL, Calderon B, McGinnis LM, Mahowald GK, Gapud EJ, Walker LM, Collins JB, Weaver BK, Mandik-Nayak L, Schreiber RD, Allen PM, May MJ, Paules RS, Bassing CH & Sleckman BP (2008) DNA double-strand breaks activate a multi-functional genetic program in developing lymphocytes. *Nature* 456: 819-823

Brown EJ & Baltimore D (2000) ATR disruption leads to chromosomal fragmentation and early embryonic lethality. *Genes Dev* 14: 397-402

Cai Z, Chehab NH & Pavletich NP (2009) Structure and Activation Mechanism of the CHK2 DNA Damage Checkpoint Kinase. *Molecular Cell* 35: 818-829

Carlsten M, Björkström NK, Norell H, Bryceson Y, van Hall T, Baumann BC, Hanson M, Schedvins K, Kiessling R, Ljunggren H-G & Malmberg K-J (2007) DNAX Accessory Molecule-1 Mediated Recognition of Freshly Isolated Ovarian Carcinoma by Resting Natural Killer Cells. *Cancer Research* 67: 1317 -1325

Carter T, Vancurová I, Sun I, Lou W & DeLeon S (1990) A DNA-activated protein kinase from HeLa cell nuclei. *Mol Cell Biol* 10: 6460-6471

Carvalho G, Fabre C, Braun T, Grosjean J, Ades L, Agou F, Tasdemir E, Boehrer S, Israel A, Veron M, Fenaux P & Kroemer G (2007) Inhibition of NEMO, the regulatory subunit of the IKK complex, induces apoptosis in high-risk myelodysplastic syndrome and acute myeloid leukemia. *Oncogene* 26: 2299-2307

Castriconi R, Dondero A, Corrias MV, Lanino E, Pende D, Moretta L, Bottino C & Moretta A (2004) Natural Killer Cell-Mediated Killing of Freshly Isolated Neuroblastoma Cells. *Cancer Research* 64: 9180 -9184

Cerboni C, Neri F, Casartelli N, Zingoni A, Cosman D, Rossi P, Santoni A & Doria M (2007) Human immunodeficiency virus 1 Nef protein downmodulates the ligands of the activating receptor NKG2D and inhibits natural killer cell-mediated cytotoxicity. *J Gen Virol* 88: 242-250

Cerwenka A (2000) Retinoic Acid Early Inducible Genes Define a Ligand Family for the Activating NKG2D Receptor in Mice. *Immunity* 12: 721-727

Chalupny NJ, Rein-Weston A, Dosch S & Cosman D (2006) Down-regulation of the NKG2D ligand MICA by the human cytomegalovirus glycoprotein UL142. *Biochemical and Biophysical Research Communications* 346: 175-181

Chawla-Sarkar M, Lindner DJ, Liu Y-F, Williams BR, Sen GC, Silverman RH & Borden EC (2003) Apoptosis and interferons: role of interferon-stimulated genes as mediators of apoptosis. *Apoptosis* 8: 237-249

Chen X, Bargonetti J & Prives C (1995) p53, through p21 (WAF1/CIP1), Induces Cyclin D1 Synthesis. *Cancer Research* 55: 4257 -4263

Chipuk JE, Maurer U, Green DR & Schuler M (2003) Pharmacologic activation of p53 elicits Bax-dependent apoptosis in the absence of transcription. *Cancer Cell* 4: 371-381

Chung HY, Cesari M, Anton S, Marzetti E, Giovannini S, Seo AY, Carter C, Yu BP & Leeuwenburgh C (2009) Molecular inflammation: Underpinnings of aging and age-related diseases. *Ageing Research Reviews* 8: 18-30

Cogswell J, Godlevski M, Wisely G, Clay W, Leesnitzer L, Ways J & Gray J (1994) NF-kappa B regulates IL-1 beta transcription through a consensus NF- kappa B binding site and a nonconsensus CRE-like site. *The Journal of Immunology* 153: 712 -723

Coppé J-P, Patil CK, Rodier F, Sun Y, Muñoz DP, Goldstein J, Nelson PS, Desprez P-Y & Campisi J (2008) Senescence-Associated Secretory Phenotypes Reveal Cell-Nonautonomous Functions of Oncogenic RAS and the p53 Tumor Suppressor. *PLoS Biol* 6: e301

Cortez D, Guntuku S, Qin J & Elledge SJ (2001) ATR and ATRIP: Partners in Checkpoint Signaling. *Science* 294: 1713 -1716

Cosman D, Müllberg J, Sutherland CL, Chin W, Armitage R, Fanslow W, Kubin M & Chalupny NJ (2001) ULBPs, novel MHC class I-related molecules, bind to CMV glycoprotein UL16 and stimulate NK cytotoxicity through the NKG2D receptor. *Immunity* 14: 123-133

Creagh EM & O'Neill LAJ (2006) TLRs, NLRs and RLRs: a trinity of pathogen sensors that co-operate in innate immunity. *Trends in Immunology* 27: 352-357

Cuconati A, Mukherjee C, Perez D & White E (2003) DNA damage response and MCL-1 destruction initiate apoptosis in adenovirus-infected cells. *Genes Dev.* 17: 2922-2932

Debbas M & White E (1993) Wild-type p53 mediates apoptosis by E1A, which is inhibited by E1B. *Genes & Development* 7: 546 -554

Dejana E, Bertocchi F, Bortolami MC, Regonesi A, Tonta A, Breviario F & Giavazzi R (1988) Interleukin 1 promotes tumor cell adhesion to cultured human endothelial cells. *J. Clin. Invest.* 82: 1466-1470

deRojas-Walker T, Tamir S, Ji H, Wishnok JS & Tannenbaum SR (1995) Nitric oxide induces oxidative damage in addition to deamination in macrophage DNA. *Chem. Res. Toxicol* 8: 473-477

Das S, Boswell SA, Aaronson SA & Lee SW (2008) p53 promoter selection: Choosing between life and death. *cc* 7: 154-157

Dharel N, Kato N, Muroyama R, Taniguchi H, Otsuka M, Wang Y, Jazag A, Shao R, Chang J, Adler MK, Kawabe T & Omata M (2008) Potential contribution of tumor suppressor p53 in the host defense against hepatitis C virus. *Hepatology* 47: 1136-1149

Diamond MS, Garcia-Aguilar J, Bickford JK, Corbi AL & Springer TA (1993) The I domain is a major recognition site on the leukocyte integrin Mac-1 (CD11b/CD18) for four distinct adhesion ligands. *The Journal of Cell Biology* 120: 1031 -1043

Diefenbach A, Jamieson AM, Liu SD, Shastri N & Raulet DH (2000) Ligands for the murine NKG2D receptor: expression by tumor cells and activation of NK cells and macrophages. *Nat Immunol* 1: 119-126

Duguay D, Mercier F, Stagg J, Martineau D, Bramson J, Servant M, Lin R, Galipeau J & Hiscott J (2002) In Vivo Interferon Regulatory Factor 3 Tumor Suppressor Activity in B16 Melanoma Tumors. *Cancer Research* 62: 5148 -5152

Dujka ME, Puebla-Osorio N, Tavana O, Sang M & Zhu C (2009) ATM and p53 are essential in the cell-cycle containment of DNA breaks during V(D)J recombination in vivo. *Oncogene* 29: 957-965

Dumaz N & Meek DW (1999) Serine 15 phosphorylation stimulates p53 transactivation but does not directly influence interaction with HDM2. *EMBO J* 18: 7002-7010

Dunn C, Chalupny NJ, Sutherland CL, Dosch S, Sivakumar PV, Johnson DC & Cosman D (2003) Human Cytomegalovirus Glycoprotein UL16 Causes Intracellular Sequestration of NKG2D Ligands, Protecting Against Natural Killer Cell Cytotoxicity. *The Journal of Experimental Medicine* 197: 1427 -1439

Dustin ML, Rothlein R, Bhan AK, Dinarello CA & Springer TA (1986) Induction by IL 1 and interferon-gamma: tissue distribution, biochemistry, and function of a natural adherence molecule (ICAM-1). *J. Immunol* 137: 245-254

Dvorak HF (1986) Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. *N. Engl. J. Med* 315: 1650-1659

El-Sherbiny YM, Meade JL, Holmes TD, McGonagle D, Mackie SL, Morgan AW, Cook G, Feyler S, Richards SJ, Davies FE, Morgan GJ & Cook GP (2007) The Requirement for DNAM-1, NKG2D, and NKp46 in the Natural Killer Cell-Mediated Killing of Myeloma Cells. *Cancer Research* 67: 8444 -8449

Falck J, Mailand N, Syljuasen RG, Bartek J & Lukas J (2001) The ATM-Chk2-Cdc25A checkpoint pathway guards against radioresistant DNA synthesis. *Nature* 410: 842-847

Fan Y, Ye J, Shen F, Zhu Y, Yeghiazarians Y, Zhu W, Chen Y, Lawton MT, Young WL & Yang G-Y (2008) Interleukin-6 stimulates circulating blood-derived endothelial progenitor cell angiogenesis in vitro. *J Cereb Blood Flow Metab* 28: 90-98

Fitzgerald KA, McWhirter SM, Faia KL, Rowe DC, Latz E, Golenbock DT, Coyle AJ, Liao S-M & Maniatis T (2003) IKKε and TBK1 are essential components of the IRF3 signaling pathway. *Nat Immunol* 4: 491-496

Fuchs A, Cella M, Giurisato E, Shaw AS & Colonna M (2004) Cutting Edge: CD96 (Tactile) Promotes NK Cell-Target Cell Adhesion by Interacting with the Poliovirus Receptor (CD155). *The Journal of Immunology* 172: 3994 -3998

Gao J, Senthil M, Ren B, Yan J, Xing Q, Yu J, Zhang L & Yim J (2010) IRF-1 transcriptionally up-regulates PUMA which mediates the mitochondrial apoptotic pathway in IRF-1 induced apoptosis in cancer cells. *Cell Death Differ* 17: 699-709

Gatei M, Sloper K, Sörensen C, Syljuäsen R, Falck J, Hobson K, Savage K, Lukas J, Zhou B-B, Bartek J & Khanna KK (2003) Ataxia-telangiectasia-mutated (ATM) and NBS1-dependent Phosphorylation of Chk1 on Ser-317 in Response to Ionizing Radiation. *Journal of Biological Chemistry* 278: 14806 -14811

Gaspar M & Shenk T (2006) Human cytomegalovirus inhibits a DNA damage response by mislocalizing checkpoint proteins. *Proceedings of the National Academy of Sciences of the United States of America* 103: 2821 -2826

Gasser S (2007) DNA - damage response and development of targeted cancer treatments. *Annals of Medicine* 39: 457

Gasser S & Raulet DH (2006) Activation and self-tolerance of natural killer cells. *Immunological Reviews* 214: 130-142

Gasser S, Orsulic S, Brown EJ & Raulet DH (2005) The DNA damage pathway regulates innate immune system ligands of the NKG2D receptor. *Nature* 436: 1186-1190

Gaugler, C. Squiban, A. Van Der Mee M-H (1997) Late and persistent up-regulation of intercellular adhesion molecule-1 (ICAM-1) expression by ionizing radiation in human endothelial cells in vitro. *Int J Radiat Biol* 72: 201-209

Ghosh S & Karin M (2002) Missing Pieces in the NF-κB Puzzle. *Cell* 109: S81-S96

Ghosh S, May MJ & Kopp EB (1998) NF-κB AND REL PROTEINS: Evolutionarily Conserved Mediators of Immune Responses. *Annu. Rev. Immunol.* 16: 225-260

Goh WC, Rogel ME, Kinsey CM, Michael SF, Fultz PN, Nowak MA, Hahn BH & Emerman M (1998) HIV-1 Vpr increases viral expression by manipulation of the cell cycle: A mechanism for selection of Vpr in vivo. *Nat Med* 4: 65-71

Gorgoulis VG, Pratsinis H, Zacharatos P, Demoliou C, Sigala F, Asimacopoulos PJ, Papavassiliou AG & Kletsas D (2005) p53-Dependent ICAM-1 overexpression in senescent human cells identified in atherosclerotic lesions. *Lab Invest* 85: 502-511

Groh V, Rhinehart R, Secrist H, Bauer S, Grabstein KH & Spies T (1999) Broad tumor-associated expression and recognition by tumor-derived γδ T cells of MICA and MICB. *Proceedings of the National Academy of Sciences* 96: 6879 -6884

Grosjean-Raillard J, Tailler M, Ades L, Perfettini J-L, Fabre C, Braun T, De Botton S, Fenaux P & Kroemer G (2008) ATM mediates constitutive NF-[kappa]B activation in high-risk myelodysplastic syndrome and acute myeloid leukemia. *Oncogene* 28: 1099-1109

Halazonetis T, Gorgoulis V & Bartek J (2008) An oncogene-induced DNA damage model for cancer development. *Science* 319: 1352

Hallahan DE & Virudachalam S (1997) Ionizing Radiation Mediates Expression of Cell Adhesion Molecules in Distinct Histological Patterns within the Lung. *Cancer Research* 57: 2096 -2099

Hallahan D, Kuchibhotla J & Wyble C (1996) Cell Adhesion Molecules Mediate Radiation-induced Leukocyte Adhesion to the Vascular Endothelium. *Cancer Research* 56: 5150 -5155

Hanahan D & Weinberg RA (2000) The Hallmarks of Cancer. *Cell* 100: 57-70

Hayden MS & Ghosh S (2008) Shared Principles in NF-κB Signaling. *Cell* 132: 344-362

Herbig U, Ferreira M, Condel L, Carey D & Sedivy JM (2006) Cellular Senescence in Aging Primates. *Science* 311: 1257

Heylbroeck C, Balachandran S, Servant MJ, DeLuca C, Barber GN, Lin R & Hiscott J (2000) The IRF-3 transcription factor mediates Sendai virus-induced apoptosis. *J. Virol* 74: 3781-3792

Hinz M, Stilmann M, Arslan SÇ, Khanna KK, Dittmar G & Scheidereit C (2010) A Cytoplasmic ATM-TRAF6-cIAP1 Module Links Nuclear DNA Damage Signaling to Ubiquitin-Mediated NF-κB Activation. *Molecular Cell* 40: 63-74

Hirao A, Kong Y-Y, Matsuoka S, Wakeham A, Ruland J, Yoshida H, Liu D, Elledge SJ & Mak TW (2000) DNA Damage-Induced Activation of p53 by the Checkpoint Kinase Chk2. *Science* 287: 1824-1827

Honda K & Taniguchi T (2006) IRFs: master regulators of signalling by Toll-like receptors and cytosolic pattern-recognition receptors. *Nat Rev Immunol* 6: 644-658

Hu G, Mancl ME & Barnes BJ (2005) Signaling through IFN Regulatory Factor-5 Sensitizes p53-Deficient Tumors to DNA Damage-Induced Apoptosis and Cell Death. *Cancer Res* 65: 7403-7412

Huang TT, Feinberg SL, Suryanarayanan S & Miyamoto S (2002) The Zinc Finger Domain of NEMO Is Selectively Required for NF-κB Activation by UV Radiation and Topoisomerase Inhibitors. *Mol. Cell. Biol.* 22: 5813-5825

Huang TT, Wuerzberger-Davis SM, Seufzer BJ, Shumway SD, Kurama T, Boothman DA & Miyamoto S (2000) NF-κB Activation by Camptothecin. *Journal of Biological Chemistry* 275: 9501 -9509

Huang TT, Wuerzberger-Davis SM, Wu Z-H & Miyamoto S (2003) Sequential Modification of NEMO/IKKγ by SUMO-1 and Ubiquitin Mediates NF-κB Activation by Genotoxic Stress. *Cell* 115: 565-576

Iguchi-Manaka A, Kai H, Yamashita Y, Shibata K, Tahara-Hanaoka S, Honda S-ichiro, Yasui T, Kikutani H, Shibuya K & Shibuya A (2008) Accelerated tumor growth in mice deficient in DNAM-1 receptor. *The Journal of Experimental Medicine* 205: 2959 -2964

Jackson SP & Bartek J (2009) The DNA-damage response in human biology and disease. *Nature* 461: 1071-1078

Janssens S, Tinel A, Lippens S & Tschopp J (2005) PIDD Mediates NF-[kappa]B Activation in Response to DNA Damage. *Cell* 123: 1079-1092

Jeyapalan JC, Ferreira M, Sedivy JM & Herbig U (2007) Accumulation of senescent cells in mitotic tissue of aging primates. *Mechanisms of Ageing and Development* 128: 36-44

Kaneko YS, Watanabe N, Morisaki H, Akita H, Fujimoto A, Tominaga K, Terasawa M, Tachibana A, Ikeda K, Nakanishi M & Kaneko Y (1999) Cell-cycle-dependent and ATM-independent expression of human Chk1 kinase. *Oncogene* 18: 3673-3681

Kanneganti T-D, Lamkanfi M & Núñez G (2007) Intracellular NOD-like Receptors in Host Defense and Disease. *Immunity* 27: 549-559

Karen KA & Hearing P (2011) Adenovirus Core Protein VII Protects the Viral Genome from a DNA Damage Response at Early Times after Infection. *J. Virol.*: JVI.02540-10

Karpova AY, Trost M, Murray JM, Cantley LC & Howley PM (2002) Interferon regulatory factor-3 is an in vivo target of DNA-PK. *Proc Natl Acad Sci U S A.* 99: 2818–2823

Kastan M, Onyekwere O, Sidransky D, Vogelstein B & Craig R (1991) Participation of p53 protein in the cellular-response to DNA damage. *Cancer Research* 51: 6304-6311

Kawanishi S, Hiraku Y, Pinlaor S & Ma N (2006) Oxidative and nitrative DNA damage in animals and patients with inflammatory diseases in relation to inflammation-related carcinogenesis. *Biological Chemistry* 387: 365-372

Khanna. KK, Keating KE, Kozlov S, Scott S, Gatei M, Hobson K, Taya Y, Gabrielli B, Chan D, Lees-Miller SP & Lavin MF (1998) ATM associates with and phosphorylates p53: mapping the region of interaction. *Nat Genet* 20: 398-400

Kim TY, Lee K-H, Chang S, Chung C, Lee H-W, Yim J & Kim TK (2003) Oncogenic Potential of a Dominant Negative Mutant of Interferon Regulatory Factor 3. *Journal of Biological Chemistry* 278: 15272 -15278

Kim T, Kim TY, Song Y-H, Min IM, Yim J & Kim TK (1999) Activation of Interferon Regulatory Factor 3 in Response to DNA-damaging Agents. *J. Biol. Chem.* 274: 30686-30689

Kim T-K, Lee J-S, Jung J-E, Oh S-Y, Kwak S, Jin X, Lee S-Y, Lee J-B, Chung YG, Choi YK, You S & Kim H (2006) Interferon regulatory factor 3 activates p53-dependent cell growth inhibition. *Cancer Letters* 242: 215-221

Kirshner JR, Karpova AY, Kops M & Howley PM (2005) Identification of TRAIL as an Interferon Regulatory Factor 3 Transcriptional Target. *J. Virol.* 79: 9320-9324

Kessis TD, Slebos RJ, Nelson WG, Kastan MB, Plunkett BS, Han SM, Lorincz AT, Hedrick L & Cho KR (1993) Human papillomavirus 16 E6 expression disrupts the p53-mediated cellular response to DNA damage. *Proceedings of the National Academy of Sciences of the United States of America* 90: 3988 -3992

Kos FJ (1998) Regulation of adaptive immunity by natural killer cells. *Immunol Res* 17: 303-312

Kortlever RM & Bernards R (2006) Senescence, Wound Healing, and Cancer: the PAI-1 Connection. *cc* 5: 2697-2703

Krmpotic A, Hasan M, Loewendorf A, Saulig T, Halenius A, Lenac T, Polic B, Bubic I, Kriegeskorte A, Pernjak-Pugel E, Messerle M, Hengel H, Busch DH, Koszinowski UH & Jonjic S (2005) NK cell activation through the NKG2D ligand MULT-1 is selectively prevented by the glycoprotein encoded by mouse cytomegalovirus gene m145. *The Journal of Experimental Medicine* 201: 211 -220

Kuilman T, Michaloglou C, Vredeveld LCW, Douma S, Doorn R van, Desmet CJ, Aarden LA, Mooi WJ & Peeper DS (2008) Oncogene-Induced Senescence Relayed by an Interleukin-Dependent Inflammatory Network. *Cell* Vol 133: 1019-1031

Kumar KP, McBride KM, Weaver BK, Dingwall C & Reich NC (2000) Regulated Nuclear-Cytoplasmic Localization of Interferon Regulatory Factor 3, a Subunit of Double-Stranded RNA-Activated Factor 1. *Mol Cell Biol* 20: 4159-4168

Kunkel TA (2004) DNA Replication Fidelity. *Journal of Biological Chemistry* 279: 16895 -16898

Kunsch C, Lang R, Rosen C & Shannon M (1994) Synergistic transcriptional activation of the IL-8 gene by NF-kappa B p65 (RelA) and NF-IL-6. *The Journal of Immunology* 153: 153 -164

Kurimasa A, Kumano S, Boubnov NV, Story MD, Tung C-S, Peterson SR & Chen DJ (1999) Requirement for the Kinase Activity of Human DNA-Dependent Protein Kinase Catalytic Subunit in DNA Strand Break Rejoining. *Mol Cell Biol* 19: 3877-3884

Lakshmikanth T, Burke S, Ali TH, Kimpfler S, Ursini F, Ruggeri L, Capanni M, Umansky V, Paschen A, Sucker A, Pende D, Groh V, Biassoni R, Höglund P, Kato M, Shibuya K, Schadendorf D, Anichini A, Ferrone S, Velardi A, et al (2009) NCRs and DNAM-1 mediate NK cell recognition and lysis of human and mouse melanoma cell lines in vitro and in vivo. *J Clin Invest* 119: 1251-1263

Lau A, Swinbank KM, Ahmed PS, Taylor DL, Jackson SP, Smith GCM & O'Connor MJ (2005) Suppression of HIV-1 infection by a small molecule inhibitor of the ATM kinase. *Nat Cell Biol* 7: 493-500

Lemon SM, Hutt LM, Shaw JE, Li J-LH & Pagano JS (1977) Replication of EBV in epithelial cells during infectious mononucleosis. *Nature* 268: 268-270

Lenac T, Budt M, Arapovic J, Hasan M, Zimmermann A, Simic H, Krmpotic A, Messerle M, Ruzsics Z, Koszinowski UH, Hengel H & Jonjic S (2006) The herpesviral Fc receptor fcr-1 down-regulates the NKG2D ligands MULT-1 and H60. *The Journal of Experimental Medicine* 203: 1843 -1850

Leslie K, Gao S, Berishaj M, Podsypanina K, Ho H, Ivashkiv L & Bromberg J (2010) Differential interleukin-6/Stat3 signaling as a function of cellular context mediates Ras-induced transformation. *Breast Cancer Research* 12: R80

Li N, Banin S, Ouyang H, Li GC, Courtois G, Shiloh Y, Karin M & Rotman G (2001) ATM Is Required for IκB Kinase (IKK) Activation in Response to DNA Double Strand Breaks. *Journal of Biological Chemistry* 276: 8898-8903

Li Q, Tang L, Roberts PC, Kraniak JM, Fridman AL, Kulaeva OI, Tehrani OS & Tainsky MA (2008) Interferon Regulatory Factors IRF5 and IRF7 Inhibit Growth and Induce Senescence in Immortal Li-Fraumeni Fibroblasts. *Molecular Cancer Research* 6: 770 -784

Libermann TA & Baltimore D (1990) Activation of interleukin-6 gene expression through the NF-kappa B transcription factor. *Mol. Cell. Biol.* 10: 2327-2334

Lilley CE, Schwartz RA & Weitzman MD (2007) Using or abusing: viruses and the cellular DNA damage response. *Trends in Microbiology* 15: 119-126

Lindahl T (1993) Instability and decay of the primary structure of DNA. *Nature* 362: 709-715

Liu Q, Guntuku S, Cui X-S, Matsuoka S, Cortez D, Tamai K, Luo G, Carattini-Rivera S, DeMayo F, Bradley A, Donehower LA & Elledge SJ (2000) Chk1 is an essential kinase that is regulated by Atr and required for the G2/M DNA damage checkpoint. *Genes & Development* 14: 1448 -1459

Lodoen M, Ogasawara K, Hamerman JA, Arase H, Houchins JP, Mocarski ES & Lanier LL (2003) NKG2D-mediated Natural Killer Cell Protection Against Cytomegalovirus Is Impaired by Viral gp40 Modulation of Retinoic Acid Early Inducible 1 Gene Molecules. *The Journal of Experimental Medicine* 197: 1245 -1253

Lodoen MB, Abenes G, Umamoto S, Houchins JP, Liu F & Lanier LL (2004) The Cytomegalovirus m155 Gene Product Subverts Natural Killer Cell Antiviral Protection by Disruption of H60–NKG2D Interactions. *The Journal of Experimental Medicine* 200: 1075 -1081

Lowe SW & Ruley HE (1993a) Stabilization of the p53 tumor suppressor is induced by adenovirus 5 E1A and accompanies apoptosis. *Genes & Development* 7: 535 -545

Lowe SW, Schmitt EM, Smith SW, Osborne BA & Jacks T (1993b) p53 is required for radiation-induced apoptosis in mouse thymocytes. *Nature* 362: 847-849

Lukas C, Bartkova J, Latella L, Falck J, Mailand N, Schroeder T, Sehested M, Lukas J & Bartek J (2001) DNA Damage-activated Kinase Chk2 Is Independent of Proliferation or Differentiation Yet Correlates with Tissue Biology. *Cancer Research* 61: 4990 -4993

Matsuoka S, Huang M & Elledge SJ (1998) Linkage of ATM to Cell Cycle Regulation by the Chk2 Protein Kinase. *Science* 282: 1893 -1897

Matsuoka S, Ballif BA, Smogorzewska A, McDonald ER, Hurov KE, Luo J, Bakalarski CE, Zhao Z, Solimini N, Lerenthal Y, Shiloh Y, Gygi SP & Elledge SJ (2007) ATM and

ATR Substrate Analysis Reveals Extensive Protein Networks Responsive to DNA Damage. *Science* 316: 1160-1166

McGowan CH (2002) Checking in on Cds1 (Chk2): A checkpoint kinase and tumor suppressor. *BioEssays* 24: 502-511

McMichael A (1998) T Cell Responses and Viral Escape. *Cell* 93: 673-676

Meylan E, Dooley AL, Feldser DM, Shen L, Turk E, Ouyang C & Jacks T (2009) Requirement for NF-κB signaling in a mouse model of lung adenocarcinoma. *Nature* 462: 104-107

Mihara M, Erster S, Zaika A, Petrenko O, Chittenden T, Pancoska P & Moll UM (2003) p53 has a direct apoptogenic role at the mitochondria. *Molecular Cell* 11: 577-590

Mori T, Anazawa Y, Iiizumi M, Fukuda S, Nakamura Y & Arakawa H (2002) Identification of the interferon regulatory factor 5 gene (IRF-5) as a direct target for p53. *Oncogene* 21: 2914-8

Nakai-Murakami C, Shimura M, Kinomoto M, Takizawa Y, Tokunaga K, Taguchi T, Hoshino S, Miyagawa K, Sata T, Kurumizaka H, Yuo A & Ishizaka Y (online) HIV-1 Vpr induces ATM-dependent cellular signal with enhanced homologous recombination. *Oncogene* 26: 477-486

Nikitin PA, Yan CM, Forte E, Bocedi A, Tourigny JP, White RE, Allday MJ, Patel A, Dave SS, Kim W, Hu K, Guo J, Tainter D, Rusyn E & Luftig MA (2010) An ATM/Chk2-Mediated DNA Damage-Responsive Signaling Pathway Suppresses Epstein-Barr Virus Transformation of Primary Human B Cells. *Cell Host & Microbe* 8: 510-522

Norgauer J, Metzner B & Schraufstatter I (1996) Expression and growth-promoting function of the IL-8 receptor beta in human melanoma cells. *The Journal of Immunology* 156: 1132 -1137

Nyberg KA, Michelson RJ, Putnam CW & Weinert TA (2002) Toward Maintaining the Genome: DNA Damage and Replication Checkpoints. *Annu. Rev. Genet.* 36: 617-656

Ou Y-H, Chung P-H, Sun T-P & Shieh S-Y (2005) p53 C-Terminal Phosphorylation by CHK1 and CHK2 Participates in the Regulation of DNA-Damage-induced C-Terminal Acetylation. *Mol Biol Cell* 16: 1684-1695

Pahl HL (1999) Activators and target genes of Rel/NF-kappaB transcription factors. *Oncogene* 18: 6853-6866

Pamment J, Ramsay E, Kelleher M, Dornan D & Ball KL (2002) Regulation of the IRF-1 tumour modifier during the response to genotoxic stress involves an ATM-dependent signalling pathway. *Oncogene* 21: 7776-85

Pappworth IY, Wang EC & Rowe M (2007) The Switch from Latent to Productive Infection in Epstein-Barr Virus-Infected B Cells Is Associated with Sensitization to NK Cell Killing. *J. Virol.* 81: 474-482

Park HU, Jeong S-J, Jeong J-H, Chung JH & Brady JN (2005) Human T-cell leukemia virus type 1 Tax attenuates γ-irradiation-induced apoptosis through physical interaction with Chk2. *Oncogene* 25: 438-447

Park HU, Jeong J-H, Chung JH & Brady JN (2004) Human T-cell leukemia virus type 1 Tax interacts with Chk1 and attenuates DNA-damage induced G2 arrest mediated by Chk1. *Oncogene* 23: 4966-4974

Parmar S & Platanias LC (2003) Interferons: mechanisms of action and clinical applications. *Curr Opin Oncol* 15: 431-439

Pende D, Rivera P, Marcenaro S, Chang C-C, Biassoni R, Conte R, Kubin M, Cosman D, Ferrone S, Moretta L & Moretta A (2002) Major Histocompatibility Complex Class I-related Chain A and UL16-Binding Protein Expression on Tumor Cell Lines of Different Histotypes. *Cancer Research* 62: 6178 -6186

Peraldi M-N, Berrou J, Dulphy N, Seidowsky A, Haas P, Boissel N, Metivier F, Randoux C, Kossari N, Guérin A, Geffroy S, Delavaud G, Marin-Esteban V, Glotz D, Charron D & Toubert A (2009) Oxidative Stress Mediates a Reduced Expression of the Activating Receptor NKG2D in NK Cells from End-Stage Renal Disease Patients. *The Journal of Immunology* 182: 1696 -1705

Perkins EJ, Nair A, Cowley DO, Van Dyke T, Chang Y & Ramsden DA (2002) Sensing of intermediates in V(D)J recombination by ATM. *Genes & Development* 16: 159 - 164

Pober JS, Gimbrone MA Jr, Lapierre LA, Mendrick DL, Fiers W, Rothlein R & Springer TA (1986) Overlapping patterns of activation of human endothelial cells by interleukin 1, tumor necrosis factor, and immune interferon. *J. Immunol* 137: 1893-1896

Raulet DH (2003) Roles of the NKG2D immunoreceptor and its ligands. *Nat Rev Immunol* 3: 781-790

Richard J, Sindhu S, Pham TNQ, Belzile J-P & Cohen ÉA (2010) HIV-1 Vpr up-regulates expression of ligands for the activating NKG2D receptor and promotes NK cell–mediated killing. *Blood* 115: 1354 -1363

Rodier F, Coppe J-P, Patil CK, Hoeijmakers WAM, Munoz DP, Raza SR, Freund A, Campeau E, Davalos AR & Campisi J (2009) Persistent DNA damage signalling triggers senescence-associated inflammatory cytokine secretion. *Nat Cell Biol* 11: 973-979

Rohner A, Langenkamp U, Siegler U, Kalberer CP & Wodnar-Filipowicz A (2007) Differentiation-promoting drugs up-regulate NKG2D ligand expression and enhance the susceptibility of acute myeloid leukemia cells to natural killer cell-mediated lysis. *Leukemia Research* 31: 1393-1402

Rölle A, Mousavi-Jazi M, Eriksson M, Odeberg J, Söderberg-Nauclér C, Cosman D, Kärre K & Cerboni C (2003) Effects of Human Cytomegalovirus Infection on Ligands for the Activating NKG2D Receptor of NK Cells: Up-Regulation of UL16-Binding Protein (ULBP)1 and ULBP2 Is Counteracted by the Viral UL16 Protein. *The Journal of Immunology* 171: 902 -908

Roshal M, Kim B, Zhu Y, Nghiem P & Planelles V (2003) Activation of the ATR-mediated DNA Damage Response by the HIV-1 Viral Protein R. *Journal of Biological Chemistry* 278: 25879 -25886

Rothlein R, Dustin M, Marlin S & Springer T (1986) A human intercellular adhesion molecule (ICAM-1) distinct from LFA-1. *The Journal of Immunology* 137: 1270 - 1274

Scheidereit C (2006) IκB kinase complexes: gateways to NF-κB activation and transcription. *Oncogene* 25: 6685-6705

Sen R & Baltimore D (1986) Inducibility of kappa immunoglobulin enhancer-binding protein Nf-kappa B by a posttranslational mechanism. *Cell* 47: 921-928

Shibuya A, Campbell D, Hannum C, Yssel H, Franz-Bacon K, McClanahan T, Kitamura T, Nicholl J, Sutherland GR, Lanier LL & Phillips JH (1996) DNAM-1, A Novel

Adhesion Molecule Involved in the Cytolytic Function of T Lymphocytes. *Immunity* 4: 573-581

Shieh S-Y, Ikeda M, Taya Y & Prives C (1997) DNA Damage-Induced Phosphorylation of p53 Alleviates Inhibition by MDM2. *Cell* 91: 325-334

Shieh S-Y, Ahn J, Tamai K, Taya Y & Prives C (2000) The human homologs of checkpoint kinases Chk1 and Cds1 (Chk2) phosphorylate p53 at multiple DNA damage-inducible sites. *Genes & Development* 14: 289 -300

Shiloh Y (2003) ATM and related protein kinases: safeguarding genome integrity. *Nat Rev Cancer* 3: 155-168

Simmons D, Makgoba MW & Seed B (1988) ICAM, an adhesion ligand of LFA-1, is homologous to the neural cell adhesion molecule NCAM. *Nature* 331: 624-627

Simon MM, Aragane Y, Schwarz A, Luger TA & Schwarz T (1994) UVB Light Induces Nuclear Factor κB (NFκB) Activity Independently from Chromosomal DNA Damage in Cell-Free Cytosolic Extracts. *J Investig Dermatol* 102: 422-427

Skalka AM & Katz RA (2005) Retroviral DNA integration and the DNA damage response. *Cell Death Differ* 12: 971-978

Sligh JE, Ballantyne CM, Rich SS, Hawkins HK, Smith CW, Bradley A & Beaudet AL (1993) Inflammatory and immune responses are impaired in mice deficient in intercellular adhesion molecule 1. *Proceedings of the National Academy of Sciences* 90: 8529 -8533

Sørensen CS, Syljuåsen RG, Falck J, Schroeder T, Rönnstrand L, Khanna KK, Zhou B-B, Bartek J & Lukas J (2003) Chk1 regulates the S phase checkpoint by coupling the physiological turnover and ionizing radiation-induced accelerated proteolysis of Cdc25A. *Cancer Cell* 3: 247-258

Soriani A, Zingoni A, Cerboni C, Iannitto ML, Ricciardi MR, Di Gialleonardo V, Cippitelli M, Fionda C, Petrucci MT, Guarini A, Foa R & Santoni A (2009) ATM-ATR-dependent up-regulation of DNAM-1 and NKG2D ligands on multiple myeloma cells by therapeutic agents results in enhanced NK-cell susceptibility and is associated with a senescent phenotype. *Blood* 113: 3503-3511

Stanietsky N, Simic H, Arapovic J, Toporik A, Levy O, Novik A, Levine Z, Beiman M, Dassa L, Achdout H, Stern-Ginossar N, Tsukerman P, Jonjic S & Mandelboim O (2009) The interaction of TIGIT with PVR and PVRL2 inhibits human NK cell cytotoxicity. *Proceedings of the National Academy of Sciences* 106: 17858 -17863

Stang MT, Armstrong MJ, Watson GA, Sung KY, Liu Y, Ren B & Yim JH (2007) Interferon regulatory factor-1-induced apoptosis mediated by a ligand-independent fas-associated death domain pathway in breast cancer cells. *Oncogene* 26: 6420-6430

Stern-Ginossar N, Elefant N, Zimmermann A, Wolf DG, Saleh N, Biton M, Horwitz E, Prokocimer Z, Prichard M, Hahn G, Goldman-Wohl D, Greenfield C, Yagel S, Hengel H, Altuvia Y, Margalit H & Mandelboim O (2007) Host Immune System Gene Targeting by a Viral miRNA. *Science* 317: 376 -381

Stiff T, O'Driscoll M, Rief N, Iwabuchi K, Löbrich M & Jeggo PA (2004) ATM and DNA-PK Function Redundantly to Phosphorylate H2AX after Exposure to Ionizing Radiation. *Cancer Research* 64: 2390 -2396

Swift LP, Rephaeli A, Nudelman A, Phillips DR & Cutts SM (2006) Doxorubicin-DNA Adducts Induce a Non-Topoisomerase II–Mediated Form of Cell Death. *Cancer Research* 66: 4863 -4871

Smyth MJ, Swann J, Cretney E, Zerafa N, Yokoyama WM & Hayakawa Y (2005) NKG2D function protects the host from tumor initiation. *J. Exp. Med* 202: 583-588

Takai H, Tominaga K, Motoyama N, Minamishima YA, Nagahama H, Tsukiyama T, Ikeda K, Nakayama K, Nakanishi M & Nakayama K-ichi (2000) Aberrant cell cycle checkpoint function and early embryonic death in Chk1 −/− mice. *Genes & Development* 14: 1439 -1447

Takai H, Naka K, Okada Y, Watanabe M, Harada N, Saito S, Anderson CW, Appella E, Nakanishi M, Suzuki H, Nagashima K, Sawa H, Ikeda K & Motoyama N (2002) Chk2-deficient mice exhibit radioresistance and defective p53-mediated transcription. *EMBO J* 21: 5195-5205

Takaoka A, Hayakawa S, Yanai H, Stoiber D, Negishi H, Kikuchi H, Sasaki S, Imai K, Shibue T, Honda K & Taniguchi T (2003) Integration of interferon-[alpha]/[beta] signalling to p53 responses in tumour suppression and antiviral defence. *Nature* 424: 516-523

Takaoka A, Yanai H, Kondo S, Duncan G, Negishi H, Mizutani T, Kano S-ichi, Honda K, Ohba Y, Mak TW & Taniguchi T (2005) Integral role of IRF-5 in the gene induction programme activated by Toll-like receptors. *Nature* 434: 243-249

Tamura T, Ishihara M, Lamphier MS, Tanaka N, Oishi I, Aizawa S, Matsuyama T, Mak TW, Taki S & Taniguchi T (1995) An IRF-1-dependent pathway of DNA damage-induced apoptosis in mitogen-activated T lymphocytes. *Nature* 376: 596-599

Tanaka N, Ishihara M, Kitagawa M, Harada H, Kimura T, Matsuyama T, Lamphier MS, Aizawa S, Mak TW & Taniguchi T (1994) Cellular commitment to oncogene-induced transformation or apoptosis is dependent on the transcription factor IRF-1. *Cell* 77: 829-839

Tanaka N, Sato M, Lamphier MS, Nozawa H, Oda E, Noguchi S, Schreiber RD, Tsujimoto Y & Taniguchi T (1998) Type I interferons are essential mediators of apoptotic death in virally infected cells. *Genes Cells* 3: 29-37

Tanaka N, Kawakami T & Taniguchi T (1993) Recognition DNA sequences of interferon regulatory factor 1 (IRF-1) and IRF-2, regulators of cell growth and the interferon system. *Mol Cell Biol.* 13: 4531–4538

Tanaka N, Ishihara M, Lamphier MS, Nozawa H, Matsuyama T, Mak TW, Aizawa S, Tokino T, Oren M & Taniguchi T (1996) Cooperation of the tumour suppressors IRF-1 and p53 in response to DNA damage. *Nature* 382: 816-818

Taniguchi T & Takaoka A (2002) The interferon-α/β system in antiviral responses: a multimodal machinery of gene regulation by the IRF family of transcription factors. *Current Opinion in Immunology* 14: 111-116

Taniguchi T, Ogasawara K, Takaoka A & Tanaka N (2001) IRF family of transcription factors as regulators of host defense. *Annu. Rev. Immunol.* 19: 623-655

Tibbetts RS, Brumbaugh KM, Williams JM, Sarkaria JN, Cliby WA, Shieh S-Y, Taya Y, Prives C & Abraham RT (1999) A role for ATR in the DNA damage-induced phosphorylation of p53. *Genes Dev* 13: 152-157

Tomasec P, Wang ECY, Davison AJ, Vojtesek B, Armstrong M, Griffin C, McSharry BP, Morris RJ, Llewellyn-Lacey S, Rickards C, Nomoto A, Sinzger C & Wilkinson GWG

(2005) Downregulation of natural killer cell-activating ligand CD155 by human cytomegalovirus UL141. *Nat Immunol* 6: 181-188

Turpin E, Luke K, Jones J, Tumpey T, Konan K & Schultz-Cherry S (2005) Influenza Virus Infection Increases p53 Activity: Role of p53 in Cell Death and Viral Replication. *J. Virol.* 79: 8802-8811

Upreti M, Koonce NA, Hennings L, Chambers TC & Griffin RJ (2010) Pegylated IFN-α sensitizes melanoma cells to chemotherapy and causes premature senescence in endothelial cells by IRF-1-mediated signaling. *Cell Death Dis* 1: e67

Upshaw JL, Arneson LN, Schoon RA, Dick CJ, Billadeau DD & Leibson PJ (2006) NKG2D-mediated signaling requires a DAP10-bound Grb2-Vav1 intermediate and phosphatidylinositol-3-kinase in human natural killer cells. *Nat Immunol* 7: 524-532

Unger T, Juven-Gershon T, Moallem E, Berger M, Vogt Sionov R, Lozano G, Oren M & Haupt Y (1999) Critical role for Ser20 of human p53 in the negative regulation of p53 by Mdm2. *EMBO J* 18: 1805-1814

Voronov E, Shouval DS, Krelin Y, Cagnano E, Benharroch D, Iwakura Y, Dinarello CA & Apte RN (2003) IL-1 is required for tumor invasiveness and angiogenesis. *Proceedings of the National Academy of Sciences of the United States of America* 100: 2645 -2650

Vousden KH & Lu X (2002) Live or let die: the cell's response to p53. *Nat Rev Cancer* 2: 594-604

Wade Harper J, Adami GR, Wei N, Keyomarsi K & Elledge SJ (1993) The p21 Cdk-interacting protein Cip1 is a potent inhibitor of G1 cyclin-dependent kinases. *Cell* 75: 805-816

Walker JR, Corpina RA & Goldberg J (2001) Structure of the Ku heterodimer bound to DNA and its implications for double-strand break repair. *Nature* 412: 607-614

Wang BX, Rahbar R & Fish EN (2011) Interferon: Current Status and Future Prospects in Cancer Therapy. *J Interferon Cytokine Res* ahead of print. doi:10.1089/jir.2010.0158.

Wang C-Y, Mayo MW & Baldwin AS (1996) TNF- and Cancer Therapy-Induced Apoptosis: Potentiation by Inhibition of NF-κB. *Science* 274: 784 -787

Wang C-Y, Mayo MW, Korneluk RG, Goeddel DV & Baldwin AS (1998) NF-kB Antiapoptosis: Induction of TRAF1 and TRAF2 and c-IAP1 and c-IAP2 to Suppress Caspase-8 Activation. *Science* 281: 1680-1683

Wang C-Y, Guttridge DC, Mayo MW & Baldwin AS (1999) NF-kappa B Induces Expression of the Bcl-2 Homologue A1/Bfl-1 To Preferentially Suppress Chemotherapy-Induced Apoptosis. *Mol. Cell. Biol.* 19: 5923-5929

Ward J, Davis Z, DeHart J, Zimmerman E, Bosque A, Brunetta E, Mavilio D, Planelles V & Barker E (2009) HIV-1 Vpr Triggers Natural Killer Cell–Mediated Lysis of Infected Cells through Activation of the ATR-Mediated DNA Damage Response. *PLoS Pathog* 5: e1000613

Weaver BK, Ando O, Kumar KP & Reich NC (2001) Apoptosis is promoted by the dsRNA-activated factor (DRAF1) during viral infection independent of the action of interferon or p53. *FASEB J* 15: 501-515

Weaver BK, Kumar KP & Reich NC (1998) Interferon Regulatory Factor 3 and CREB-Binding Protein/p300 Are Subunits of Double-Stranded RNA-Activated Transcription Factor DRAF1. *Mol. Cell. Biol.* 18: 1359-1368

Wei L-H, Kuo M-L, Chen C-A, Chou C-H, Lai K-B, Lee C-N & Hsieh C-Y (2003) Interleukin-6 promotes cervical tumor growth by VEGF-dependent angiogenesis via a STAT3 pathway. *Oncogene* 22: 1517-1527

Wen C, He X, Ma H, Hou N, Wei C, Song T, Zhang Y, Sun L, Ma Q & Zhong H (2008) Hepatitis C Virus Infection Downregulates the Ligands of the Activating Receptor NKG2D. *Cell Mol Immunol* 5: 475-478

Werness B, Levine A & Howley P (1990) Association of human papillomavirus types 16 and 18 E6 proteins with p53. *Science* 248: 76 -79

Wold MS (1997) Replication protein A: a heterotrimeric, single-stranded DNA-binding protein required for eukaryotic DNA metabolism. *Annu. Rev. Biochem* 66: 61-92

Wu GS, Burns TF, McDonald ER, Jiang W, Meng R, Krantz ID, Kao G, Gan D-D, Zhou J-Y, Muschel R, Hamilton SR, Spinner NB, Markowitz S, Wu G & El-Deiry WS (1997) KILLER/DR5 is a DNA damage-inducible p53-regulated death receptor gene. *Nat Genet* 17: 141-143

Wu Z-H, Shi Y, Tibbetts RS & Miyamoto S (2006) Molecular Linkage Between the Kinase ATM and NF-{kappa}B Signaling in Response to Genotoxic Stimuli. *Science* 311: 1141-1146

Wu Z-H, Wong ET, Shi Y, Niu J, Chen Z, Miyamoto S & Tergaonkar V (2010) ATM- and NEMO-Dependent ELKS Ubiquitination Coordinates TAK1-Mediated IKK Activation in Response to Genotoxic Stress. *Molecular Cell* 40: 75-86

Yajima H, Lee K-J & Chen BPC (2006) ATR-Dependent Phosphorylation of DNA-Dependent Protein Kinase Catalytic Subunit in Response to UV-Induced Replication Stress. *Mol Cell Biol* 26: 7520-7528

Yang J, Yu Y, Hamrick HE & Duerksen-Hughes PJ (2003) ATM, ATR and DNA-PK: initiators of the cellular genotoxic stress responses. *Carcinogenesis* 24: 1571 -1580

Yanai H, Chen H-min, Inuzuka T, Kondo S, Mak TW, Takaoka A, Honda K & Taniguchi T (2007) Role of IFN regulatory factor 5 transcription factor in antiviral immunity and tumor suppression. *Proc Natl Acad Sci U S A*. 104: 3402–3407

Yoneyama M & Fujita T (2007) Function of RIG-I-like Receptors in Antiviral Innate Immunity. *J. Biol. Chem.* 282: 15315-15318

Yu X, Harden K, C Gonzalez L, Francesco M, Chiang E, Irving B, Tom I, Ivelja S, Refino CJ, Clark H, Eaton D & Grogan JL (2009) The surface protein TIGIT suppresses T cell activation by promoting the generation of mature immunoregulatory dendritic cells. *Nat Immunol* 10: 48-57

Yuan X-wei, Zhu X-feng, Huang X-fang, Sheng P-yi, He A-shan, Yang Z-bo, Deng R, Feng G-kan & Liao W-ming (2007) Interferon-[alpha] enhances sensitivity of human osteosarcoma U2OS cells to doxorubicin by p53-dependent apoptosis. *Acta Pharmacol Sin* 28: 1835-1841

Zhao H & Piwnica-Worms H (2001) ATR-Mediated Checkpoint Pathways Regulate Phosphorylation and Activation of Human Chk1. *Mol. Cell. Biol.* 21: 4129-4139

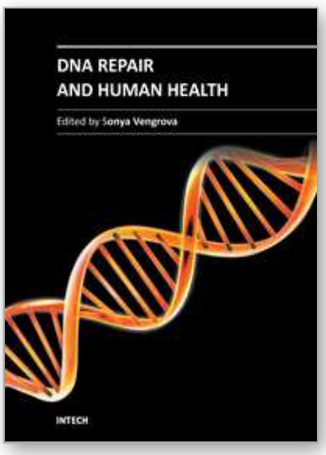
Zhao H, Watkins JL & Piwnica-Worms H (2002) Disruption of the checkpoint kinase 1/cell division cycle 25A pathway abrogates ionizing radiation-induced S and G2 checkpoints. *Proceedings of the National Academy of Sciences* 99: 14795 -14800

Zhou B-BS & Elledge SJ (2000) The DNA damage response: putting checkpoints in perspective. *Nature* 408: 433-439

Zou L & Elledge SJ (2003) Sensing DNA damage through ATRIP recognition of RPA-ssDNA complexes. *Science* 300: 1542-1548

IntechOpen

IntechOpen



DNA Repair and Human Health

Edited by Dr. Sonya Vengrova

ISBN 978-953-307-612-6
Hard cover, 792 pages
Publisher InTech
Published online 26, October, 2011
Published in print edition October, 2011

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.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Gordon M. Xiong and Stephan Gasser (2011). Integration of the DNA Damage Response with Innate Immune Pathways, DNA Repair and Human Health, Dr. Sonya Vengrova (Ed.), ISBN: 978-953-307-612-6, InTech, Available from: http://www.intechopen.com/books/dna-repair-and-human-health/integration-of-the-dna-damage-response-with-innate-immune-pathways

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the Creative Commons Attribution 3.0 License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen