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# The DNA damage response and immune signaling alliance: Is it good or bad? Nature decides when and where

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*Abbreviations:* 53BP1 (TP53BP1), P53-binding protein 1; 9–1–1, Rad9–Rad1–Hus1 complex; Ab(s), antibodie(s); AGS, Aicardi–Goutières syndrome; AJCC, American Joint Committee on Cancer; alt-EJ, alternative end joining; AMPK, AMP-activated protein kinase; APC, Antigen-presenting cell; APE1, Apyrimidinic/apurinic endonuclease 1; APLF, Aprataxin and PNK-like factor; ARF, Alternative reading frame; ASC, Apoptosis-associated speck-like protein containing a CARD; ATM, Ataxia telangiectasia mutated; ATR, Ataxia telangiectasia and Rad3 related; BCR, B cell receptor; BER, Base excision repair; BRCA(1), Breast cancer susceptibility gene (1); BRCA(2), Breast cancer susceptibility gene (2); CARD, Caspase activation and recruitment domain; CD, Cluster of differentiation; CDC25A, Cell division cycle 25A; CDC25B, Cell division cycle 25B; CDC25C, Cell division cycle 25C; CDC45, Cell division cycle 45; CDK1, Cyclin-dependent kinase 1; CDK2, Cyclin-dependent kinase 2; CFS, Common fragile sites; cGAS/MB21D1, cyclic GMP–AMP synthase/Mab-21 domain containing 1; Chk1, Checkpoint kinase 1; Chk2, Checkpoint kinase 2; CKD, Catalytic kinase domain; COX, Cyclooxygenase; CSA, Cockayne syndrome group A; CSB, Cockayne syndrome group B; CtIP, C-terminal interacting protein; CTLA4, Cytotoxic T-lymphocyte-associated antigen 4; DAI/ZBP1/DLM-1, DNA-dependent activator of interferon (IFN) regulatory factor/Z-DNA-binding protein 1; DAMPs, Damage-associated molecular patterns; DCs, Dendritic cells; DDR/R, DNA damage response/repair; DExD/H-box helicases, Defined by the Asp–Glu–Ala–Asp (DEAD) pattern and variations thereof (DExD/H); DNAM-1, DNAX accessory molecule-1; DNA-PKcs, DNA protein kinase catalytic subunit; D/PAMPs, Damage/pathogen-associated molecular patterns; DSB(s), Double-strand break(s); dsRBM1/2, dsRNA-binding motifs 1 and 2; DSS, Dextran sulfate sodium; e, Endosome; EBNA3C, Epstein–Barr virus nuclear antigen 3C; EME1, Essential meiotic endonuclease 1; EMT, Epithelial and mesenchymal transition; euh, Euchromatin; FA, Fanconi anemia; FAAP24, Fanconi anemia-associated protein of 24 kDa; FANCC, Fanconi anemia complementation group C; FANCD2, Fanconi anemia complementation group D2; FANCI, Fanconi anemia complementation group I; FANCM, Fanconi anemia complementation group M; FEN1, Flap endonuclease-1; FRET assay, Fluorescence resonance energy transfer assay; FUO, Fever of unknown origin; G(M)-CSF, Granulocyte (monocyte) colony-stimulating factor; GG-NER, Global genome NER; GOF, Gain of function; H, Histidine; het, Heterochromatin; HIV, Human immunodeficiency virus; HMGB1,2,3, High-mobility group box 1,2,3; HR, Homologous recombination; HUVEC, Human umbilical endothelial cells; IB, Immunoblotting; ICAM1, Intracellular adhesion molecule 1; ICE, IL-1b-converting enzyme ICE; ICL, Interstrand cross-links; ICOS, Inducible costimulator; ICOS-L, Inducible costimulator ligand; IFN-γ, Interferon-γ; IKK complex, IκB kinase complex; IL(s), Interleukin(s); ImmR, Immune response; ImmR1, Immune response type 1; ImmR2, Immune response type 2; IR, Ionizing radiation; IRF3,7, INF regulatory factor 3,7; ISG, Interferon stimulatory gene; JAK, Janus kinase; LFA1, Lymphocyte-function-associated antigen 1; LRRFIP1, Leucine-rich repeat (In FLII) interacting protein 1; LT, Lymphotoxin; m, Mitochondrion; M1/M2, Macrophages 1/2; MAPK, Mitogen-activating protein kinase; Mavs, Mitochondrial antiviral signaling protein; MCDS, Monte Carlo damage simulation; MDC1, Mediator of DNA damage checkpoint 1; MDM2, Murine double minute 2; MDSCs, Myeloid-derived suppressor cells; MEFs, Mouse embryo fibroblasts; MHCII, Major histocompatibility complex type II; MICA/B, MHC Class I polypeptide-related sequence A/B; MITA, Mediator of IRF3 activation (also known as STING); MMP, Matrix metalloproteinase; MMR, Mismatch repair; MRN, Mre11–Rad50–Nbs1; mTOR, Mammalian target of rapamycin; MUS81, Methyl methanesulfonate and UV-sensitive clone 81; MyD88, Myeloid differentiation primary response gene 88; N, Nucleus; n, Nucleolus; NAC, N-Acetyl-cysteine; NBS1, Nijmegen breakage syndrome 1 (Nibrin); NEMO, NF-kappa-B essential modulator (also known as IKKγ (Inhibitor of nuclear factor kappa-B kinase subunit gamma)); NER, Nucleotide excision repair; NF-κB, Nuclear factor kappa light-chain enhancer of activated B cells; NHEJ, Nonhomologous end joining; NK, Natural killer cells; NKG2D, Natural killer group 2, member D; NKG2DL, NKG2D ligand; NLR, Nucleotide-binding oligomerization domain receptors; NLRP3, NOD-like receptor family, pyrin domain containing 3; NSAIDs, Nonsteroidal anti-inflammatory drug(s); OIS, Oncogene-induced senescence; PAMPs, Pathogen-associated molecular patterns; PARP-1, Poly [ADP-ribose] polymerase 1; PCNA, Proliferating cell nuclear antigen; PD, Programmed death; PDL1(CD274/B7-H1), Programmed death ligand 1; PKR, Protein kinase, interferon-inducible double-stranded RNA-dependent activator; PML, Promyelocytic leukemia protein; PNK, Polynucleotide kinase; pRb, Retinoblastoma protein; PRKDC (DNA-PKcs), Protein kinase, DNA-activated, catalytic polypeptide; PRR, Pattern recognition receptor; PS, Paraneoplastic syndromes; PVR (CD155), Poliovirus receptor; PYHIN, Pyrin/PYD and HIN domain-containing protein family; R, Arginine; RAE1, Retinoic acid early transcript 1; RER, Rough endoplasmic reticulum; RIPK1,2, Receptor-interacting protein kinase 1,2; RNA polIII, RNA polymerase III; RO(N)S, Reactive oxygen (and nitrogen) species; RPA, Replication protein A; SAR, Systemic acquired resistance; SASP, Senescence-associated secretory phenotype; SCC, Squamous cell carcinoma; Ser, Serine; SIR, Senescence inflammatory response; SLE, Systemic lupus erythematosus; SLX4, Synthetic lethal X (of unknown function) 4; SSA, Single-strand annealing; SSB, Single-strand break; ssDNA, Single-stranded DNA; STAT, Signal transducer activator of transcription; STING, Stimulator of IFN genes (also known as MITA); TAMs, Tissue-associated macrophages; TBK1, TANK-binding kinase 1; TBK1/IRF, TANK-binding kinase 1/Interferon regulatory factor; TC-NER, Transcription-coupled NER; TCR, T cell receptor; TGFβ1, Transforming growth factor β1; $T_h$1,2, T helper1,2; Thr, Threonine; TILs, Tumor-infiltrating lymphocytes; TLR, Toll-like receptors; TLS, Translesion synthesis; TNFα, Tumor necrosis factor alpha; TNM, Tumor, node, metastasis; TopBP1, DNA topoisomerase 2-binding protein 1; $T_{regs}$, Regulatory T cells; TS, Template switching; UICC, Union for International Cancer Control; ULBP1–6, UL-binding protein 1–6; UTR, Untranslated region; UV, Ultraviolet; VEGF, Vascular endothelial growth factor; Vpr, Viral protein R; *WRN*, Werner syndrome helicase; XRCC1, X-ray repair complementing defective repair in Chinese hamster cells 1; XRCC5/Ku80, X-ray repair complementing defective repair in Chinese hamster cells 5; XRCC6/Ku70, X-ray repair complementing defective repair in Chinese hamster cells 6.

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ABSTRACT

The characteristic feature of healthy living organisms is the preservation of homeostasis. Compelling evidence highlight that the DNA damage response and repair (DDR/R) and immune response (ImmR) signaling networks work together favoring the harmonized function of (multi)cellular organisms. DNA and RNA viruses activate the DDR/R machinery in the host cells both directly and indirectly. Activation of DDR/R in turn favors the immunogenicity of the incipient cell. Hence, stimulation of DDR/R by exogenous or endogenous insults triggers innate and adaptive ImmR. The immunogenic properties of ionizing radiation, a prototypic DDR/R inducer, serve as suitable examples of how DDR/R stimulation alerts host immunity. Thus, critical cellular danger signals stimulate defense at the systemic level and vice versa. Disruption of DDR/R–ImmR cross talk compromises (multi)cellular integrity, leading to cell-cycle-related and immune defects. The emerging DDR/R–ImmR concept opens up a new avenue of therapeutic options, recalling the Hippocrates quote "everything in excess is opposed by nature."



**Contents**





## 1. The DNA damage response/repair and immune signaling networks: Is their intertwining a teleological demand?

To perform its physiological function, the cell requires, above all, the integrity of all of the encoded information it harbors. Experiencing numerous genotoxic insults on a daily basis, it has developed a highly conserved and sophisticated DNA damage recognition and repair network to cope with the variety of DNA lesions that occur. The DNA damage response (Jackson & Bartek, 2009) is a hierarchically structured signaling pathway consisting of DNA damage sensors, mediators, transducers, and effectors (Fig. 1A). Depending on the specific types of alterations and the cell cycle phase they occur in, the DNA damage response/repair (DDR/R) signaling cascade demonstrates variations in order to coordinate effectively recognition of the defect and "assign" the proper repair process (Fig. 1A) (Thompson, 2012). In the event of unrepaired lesions and depending on the extent and type of damage, the cell either passes the mutated genome to its offspring or is neutralized by programmed cell death (apoptosis) or senescence (Ciccia & Elledge, 2010).

When apoptosis ensues at the multicellular level (metazoa), a clearance process removes the apoptotic bodies, thus preserving tissue homeostasis. Senescent cells must be removed as well, because they can systemically affect neighboring cells by triggering various pathologies, including cancer, due to their so-called senescence-associated secretory phenotype (SASP), despite being a beneficial response, particularly in oncogenic events (Coppe et al., 2008). In both cases, the cells are cleared by the mononuclear phagocyte system, the main cellular compartment of the innate immune system that recognizes exposed ligands on apoptotic and senescent cells (Munoz-Espin & Serrano, 2014). Within this system, p53, one of the main downstream effectors of the DDR/R pathway, has been shown to drive an inflammatory response contributing to tumor clearance by eliminating tumor cells undergoing senescence (Xue et al., 2007). Given that the triggering signal is extensive DNA damage in the majority of these cases, this type of cellular recognition is considered as a damage-associated molecular pattern (DAMP), thus represents a link between DDR/R and immune response (ImmR) (Chatzinikolaou et al., 2014; Ermolaeva & Schumacher, 2014).

As with the DDR/R cascade, the ImmR system is also organized in a hierarchical manner. It relies on both innate and adaptive immune subsystems (Fig. 1Bi). The innate subsystem is considered a generic first-line defense against pathogens, and it does not confer long-lasting immunity to the host, unlike the adaptive immune subsystem. Conversely, the adaptive immune subsystem is highly specialized, composed of cells that are capable of discriminating "non-self" from "self," through the process of antigen presentation. These cells develop responses that are tailored to eliminate specific antigens effectively, and most importantly they are capable of "remembering" (immunological memory) the "pathogen" and thus being prepared if it reappears (Fig. 1Bi).

The innate immune subsystem employs individual germ-line-encoded pattern recognition receptors (PRRs), which recognize non-self products from infectious agents, including foreign nucleic acids, termed pathogen-associated molecular patterns (PAMPs), as well as host molecules called DAMPs, as previously mentioned. Toll-like receptors (TLRs) are among the best-characterized PRRs. In particular, the TLR9 recognizes the highly immunogenic CpG motifs frequently found in bacteria. As discussed later, this activates the transcription factors nuclear factor kappa B (NF-κB) and interferon-regulatory factor 7 (IRF7), which in turn induce a number of pro-inflammatory cytokines promoting an inflammatory response (Bauer et al., 2001). This is an example demonstrating that immunosurveillance is capable of discriminating foreign from host DNA in a sequence-independent manner, as suggested, by recognizing physicochemical structural differences (Kawasaki et al., 2011). However, DNA replication by-products that are not rapidly turned over and released from the "immune-privileged" nucleus into the cytoplasm can also act as potent immunostimulators engaging DNA sensors, eventually setting the pathophysiological basis for autoimmune reactions. At another level, innate immune system adaptors have been shown to interact with DNA damage sensors in the cytosol. A similar interaction is observed between caspase activation and recruitment domain 9 (CARD9) and the DNA damage sensor Rad50, a key component of the Mre11–Rad50–Nbs1 (MRN) DNA double-strand break (DSB) recognition complex, thus forming a module required for NF-κB activation and pro-interleukin (IL)-1β induction (Roth et al., 2014). One of the most characteristic links between innate immunity and DDR/R is the activation of natural killer group 2, member D (NKG2D) ligands in DNA-damaged cells by ataxia telangiectasia

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mutated (ATM), which alerts and recruits mainly natural killer (NK) cells at the injured site (Gasser et al., 2005). The macrophage is common to both the innate and acquired immune subsystems: On the one hand, it is a key player in innate immunity and, on the other, it is capable of antigen presentation, placing it in the front line of the cells that initiate acquired immunity. A number of cell surface molecules involved in antigen presentation and expressed by macrophages, such as intercellular adhesion molecule 1 (ICAM-1), CD59, lymphocyte-function-associated antigen-3 (LFA-3), and CD58, are activated by p53 (Gazouli et al., 2002; Gorgoulis et al., 2003). Moreover, DDR/R activation can trigger antigen-presenting-like functions in fibroblasts and in turn activate naive cytotoxic T cells in a DNA-dependent manner, which demonstrates the ability of the DDR/R to modulate both the innate and adaptive ImmR (Tang et al., 2014).

From these introductory paradigms, an interplay between DDR/R and ImmR is evident, clearly emerging as a necessity in metazoans, during their long evolutionary transition from their unicellular ancestors, to supervise and intervene at both the systematic and cellular levels. As presented in the following sections, several bidirectional DDR/R–ImmR links are evident, which we believe will steadily increase in the future providing us with a novel insight into how these fundamental biochemical and cellular networks orchestrate their function during pathological conditions.

## 2. Evidence supporting a bidirectional connection between DDR/R and ImmR

Over the past years, our perception into the immunological properties of DNA and RNA has changed significantly, with studies demonstrating that nucleic acids trigger a robust ImmR under certain circumstances. The vigorous cellular reactions occurring after foreign genetic material is detected within the cytoplasm or the nucleus of eukaryotic cells as well as the systemic immune reactions occurring after DNA damage herald a new era in the conceptualization of the defense mechanisms of (multi)cellular organisms. In the following section, we provide strong evidence supporting the bidirectional relationship between DNA damage and ImmRs (Fig. 2). We begin our study of the DDR/R–ImmR cross talk by first investigating the activation of the DDR/R machinery via infection of eukaryotic cells by foreign genetic material.

### *2.1. Lessons from viruses, part 1: the first evidence supporting the DDR/R–ImmR cross talk*

In 1963, Isaacs et al. (1963) demonstrated that infection of mouse cells with chick nucleic acid triggered the production of interferons (IFNs), which supports the notion of IFN stimulation as a cell response

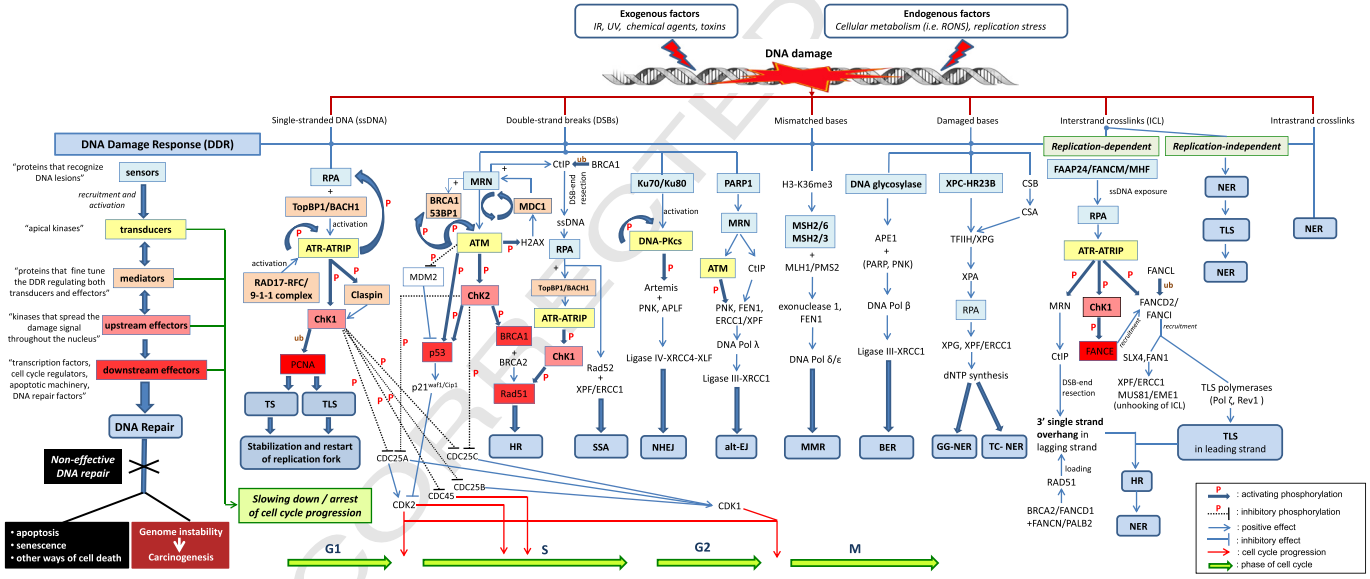


**Fig. 1.** A. Schematic presentation of the DNA damage response and repair (DDR/R) pathways activated by various exogenous and endogenous insults. The DNA damage is recognized by sensor proteins (in light blue boxes) that recruit and activate the transducer kinases (in yellow boxes). The latter convey the "threatening" signal to the upstream effector kinases (in pink boxes), which phosphorylate their substrates – the downstream effectors (in red boxes) – in turn recruiting the appropriate DNA repair module (in blue boxes) depending on the type of DNA lesion. The fine-tuning of DDR/R is performed by the mediators (in light pink boxes), which are substrates and regulators of both the transducers and effector kinases. Each DNA repair route may work either independently or in coordination with other repair mechanisms depending on the complexity of the DNA lesion. The time for repair is provided by the DNA damage signaling checkpoints, which inhibit the cyclin–CDK complexes that slow down or arrest cell cycle progression. If the DNA damage is extensive or not effectively repaired, the cell is driven to apoptosis, senescence, or acquiring chromosomal aberrations, which may lead to genomic instability and carcinogenesis. Detailed description of each DDR/R pathway is provided in the corresponding Supplemental Data. B: (i) The early first-line defense against pathogens that invade the body is provided by innate immunity, which is characterized by rapid but not specific responses. Adaptive immunity is activated subsequently, providing a specific and efficient response against pathogens, as well as immunological memory protecting the body from a second encounter of the same invader. (ii) CD4+ T helper ($T_h$) cells are critical for proper immune cell homeostasis and host defense. Among the effector Th subsets ($T_{h1}$, $T_{h2}$, $T_{h17}$, $T_{h22}$, $T_{h9}$, and $T_{reg}$) characterized by specific cytokine profiles (Raphael et al., 2014), $T_{h1}$ and $T_{h2}$ are major contributors to the achievement of balance in the immune defense, developing the immune response type 1 (ImmR1) and immune response type 2 (ImmR2), respectively. In ImmR1, $T_{h1}$ cells orchestrate the activation of M1 (classically activated) macrophages, B and NK cells, as well as neutrophils (Abbas et al., 2010; Biswas & Mantovani, 2010). In ImmR2, $T_{h2}$ cells direct the activation of M2 (alternatively activated) macrophages, B cells, basophils, and eosinophils. The prototype cytokines of ImmR1 are IFN-γ and IL12, whereas those of ImmR2 are IL4, IL5, and IL13, and to a lesser extent IL10. Note that IFN-γ has a potent microbicidal role, promoting phagocytosis first by acting on M1 macrophages and second by promoting IgG antibody production by B cells that in turn opsonize microbes. TGF-β is produced, among others, by M2 macrophages and it has an anti-inflammatory function. Imbalance in the type 1/type 2 cytokine ratio is implicated in the pathogenesis of several conditions throughout life (Zhang et al., 2014). A fine example arises from studying the immunology during pregnancy and in neonatal pathology. A Th2-predominant state is favored during pregnancy, supporting the tolerance of fetal and placental antigens and hence promoting pregnancy maintenance (Sykes et al., 2012). A shift towards a Th1 immune profile is implicated in recurrent pregnancy loss (Nakashima et al., 2012). Moreover, premature infants with respiratory distress syndrome exhibit Th1 polarization (Varvarigou et al., 2012). Within this frame, there is a modest remission in Th1-based autoimmune diseases during pregnancy (i.e., rheumatoid arthritis and multiple sclerosis) (Sykes et al., 2012). (iii) Schematic presentation of costimulatory and inhibitory receptors involved in antigen-presenting cells (APCs) and T cell interplay (Abbas et al., 2010). The costimulatory receptors of T cell are depicted in shades of green, whereas the inhibitory receptors of T cell are depicted in shades of red.

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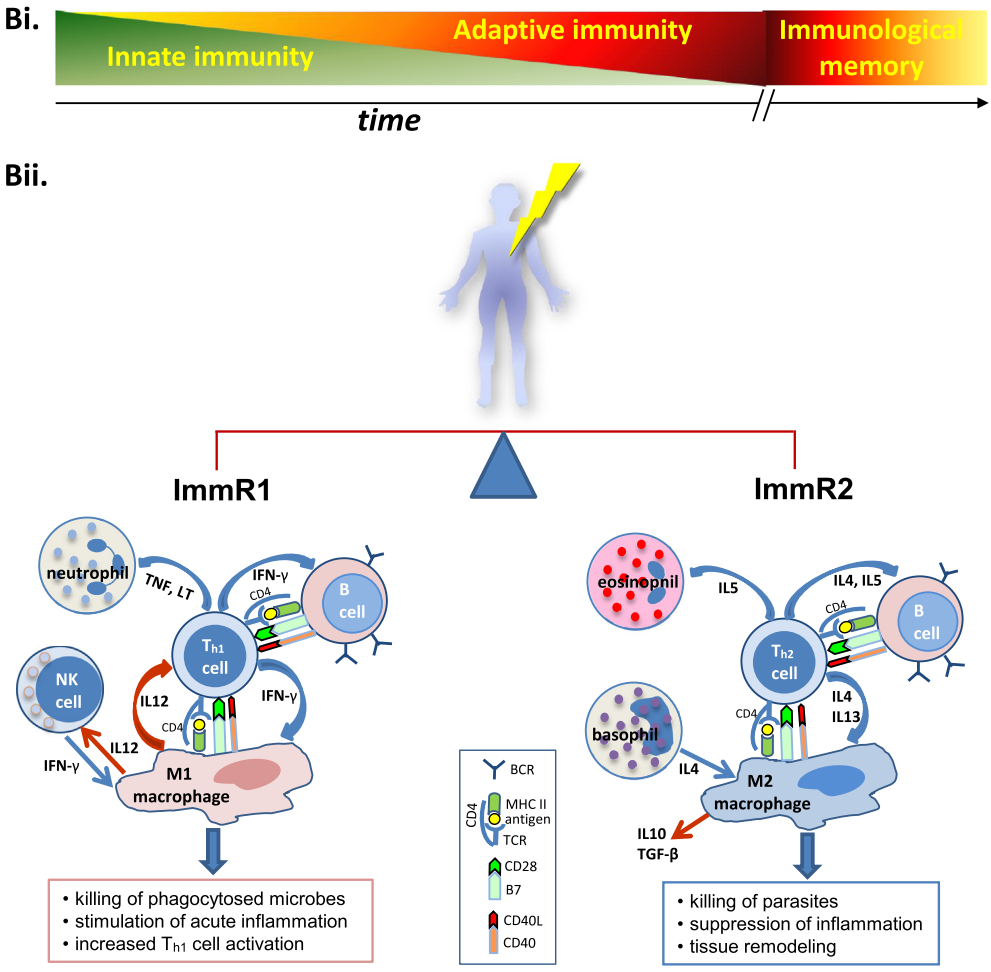


**Fig. 1** (*continued*).

to the introduction of foreign nucleic acids. The term "interferon" was introduced because these cytokines were capable of interfering with viral replication (Isaacs & Lindenmann, 1957). Currently, it is well established that viral genetic material triggers animal immunity by directly inducing Type I IFN in most cases, mainly IFN-α along with its numerous isoforms as well as IFN-β, and Type III IFN comprising IFN-λ1, IFN-λ2, and IFN-λ3 to a lesser extent (McKenna et al., 2005; Fensterl & Sen, 2009). IFN-γ, also called Type II IFN, is produced as an indirect response to viral PAMPs, with a less potent antiviral effect than Type I and III IFNs. The action of IFNs action lies at the intersection of innate and adaptive immunity, promoting an "antiviral state" in an autocrine, paracrine, and systemic manner. Hence, it is not surprising that knockout mice lacking Type I IFN receptors are highly susceptible to viral infections. In a similar manner to animals, introduction of viral nucleic acids in plants elicits a systemic defense mechanism that travels ahead of the virus, named as systemic acquired resistance (SAR) (Kachroo & Robin, 2013). Interestingly, it has been demonstrated that viral infection in plants leads to systemic DNA genetic and epigenetic changes including an increased frequency of homologous recombination along with altered methylation patterns. In turn, these alterations possibly favor the creation of resistance (R) genes with varying specificities, thus promoting the antiviral defense of the host plant (Lucht et al., 2002; Kovalchuk et al., 2003; Boyko & Kovalchuk, 2011). Of note, induction of SAR not only protects the individual plant but also passes on the immune memory to the next generations (Luna et al., 2012; Slaughter et al., 2012).

### 2.2. PRRs: behind the curtains

In both animals and plants, PRR-induced defense is the core of the ImmR to infection by foreign genetic material. So far, six categories of

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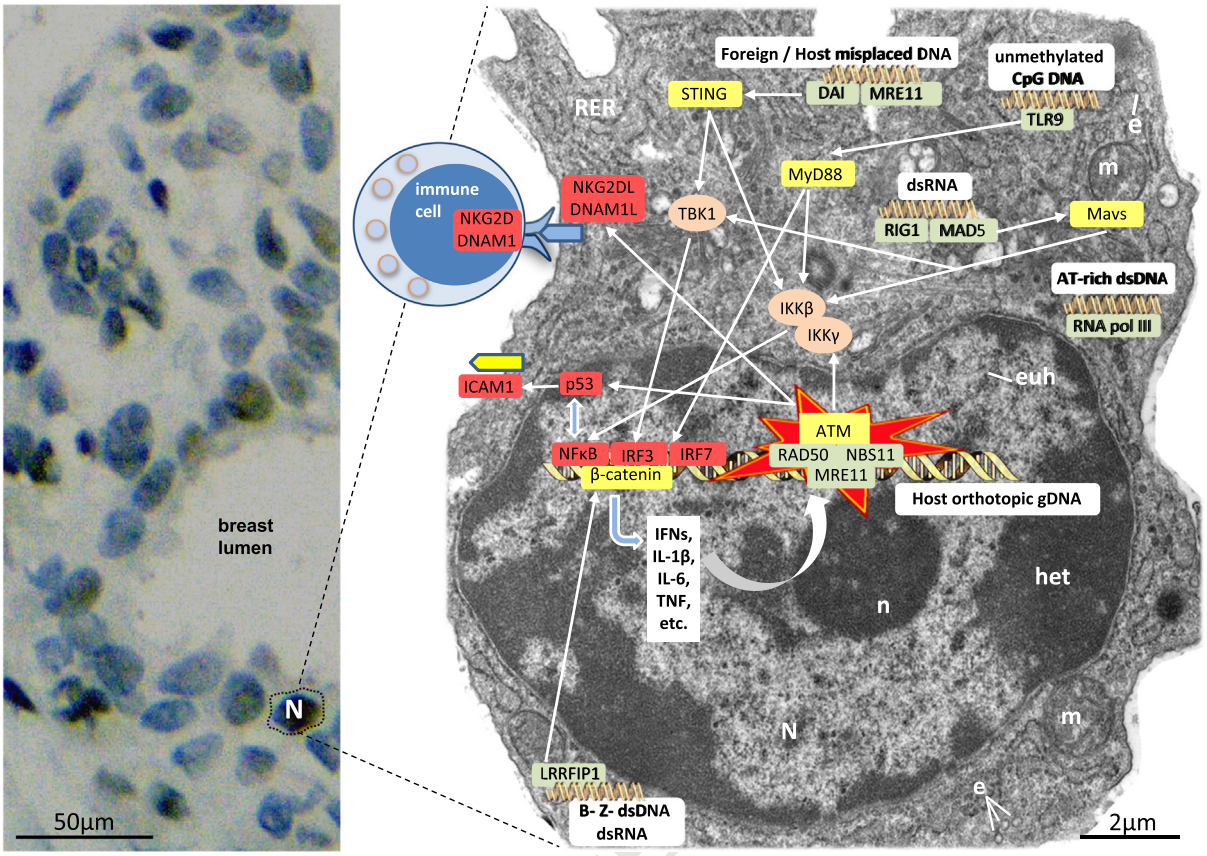


**Fig. 2.** Interplay between DNA damage response and repair (DDR/R) and immune response (ImmR) (DDR/R⇄ImmR). Electron micrograph of a representative breast luminal epithelial cell found within normal-appearing tubuloalveolar secretory unit (demonstrated in the left-side image with γH2AX immunohistochemistry), adjacent to invasive ductal breast carcinoma (not shown). DNA damage including the formation of double-strand breaks (DSBs) in the host orthotopic gDNA triggers the DDR/R machinery by recruiting the MRE11–RAD50–NBS11 (MRN) complex along with the apical kinase ATM. ATM may in turn: a) upregulate NKG2DL and DNAM1L favoring the sequestration of immune cells such as NK, NKT, γδT, and CD8+ T cytotoxic cells; b) induce ICAM1 expression; and c) activate nuclear factor κB (NF-κB) in an IKKγ (NEMO)-dependent manner. Several PRRs including TLR9, RIG1, MAD5, MRE11, DAI, RNA polIII, and LRRFIP1 sense foreign genetic material as well as host misplaced DNA, and they promote the production of proinflammatory mediators including INFs, interleukins, and TNF production. IFN signaling potentially triggers the DDR/R pathway, denoting the strong relationship between ImmR and DDR/R. Note that MRE11 has a dual role serving as a component of the DDR/R machinery and as a PRR sensing cytoplasmic DNA. The functional cross talk between the two nodal transcription factors p53 and NF-κB is complex, and this should be studied in a context-dependent manner (Cooks & Oren, 2010). All DNA/RNA sensors are depicted in green; adaptors in yellow, mediators in pink, and downstream effectors in red. *e:* endosome; *euh:* euchromatin; *het:* heterochromatin; *IRF3,7:* INF regulatory factor 3,7; *m:* mitochondrion; *Mavs:* mitochondrial antiviral signaling protein; *MyD88:* myeloid differentiation primary response gene 88; *N:* nucleus; *n:* nucleolus; *RER:* rough endoplasmic reticulum; *STING:* stimulator of IFN genes (also known as MITA, mediator of IRF3 activation); *TBK1:* TANK-binding kinase 1; *arrow:* positive effect; *double ended arrow:* bidirectional effect; *curved arrow:* potential activation of DDR/R pathways.

PRRs sensing nucleic acids have been recognized, including TLR, NOD-like receptor (NLR), PYHIN, DExD/H-box helicases, DDR/R families, as well a few additional unclassified receptors presented as "other" in Table 1; this list will continue to grow. Because several of these PRRs were discovered only recently, at present, we cannot verify that all sensors included therein are indeed *bona fide* sensors (Unterholzner, 2013). Nevertheless, the multiplicity of DNA/RNA sensors underlines their significance in host immunity. This supports the original view of Charles A. Janeway, who introduced the term PRR in 1989 in the pioneering article titled "Approaching the asymptote? Evolution and Revolution in Immunology." He stated that PRRs are part of a primitive immune system before the onset of clonal selection (Janeway, 1989). Beyond their diversity, PRRs share a common structural pattern, evolutionarily conserved especially among vertebrates (Tam & Jacques, 2014), consisting of a high-affinity domain for nucleic acids (Table 1, depicted in red) attached to a domain mediating protein–protein interaction (Table 1, colored in blue). The latter is involved in the recruitment of the appropriate adaptor protein for linking the specific PAMP–PRR pair with the stimulation of identical but shared signaling pathways (Fig. 2).

### 2.2.1. Effects following PAMP–PRR axis activation

So far, the most well described adaptors include STING, MyD88, Mavs, and β-catenin (interacting with leucine-rich repeat (in FLII) interacting protein 1 (LRRFIP1)) (Ishikawa & Barber, 2011; Keating et al., 2011; Cavlar et al., 2012; Paludan & Bowie, 2013; Maringer & Fernandez-Sesma, 2014; Ran et al., 2014). Mostly IFNβ are directly produced by nonimmune cells including epithelial cells and fibroblasts, as well as IFNα by plasmacytoid dendritic cells (DCs), when the STING–TANK-binding kinase 1 (TBK1)–IRF3, MyD88–IRF7–NF-κB, Mavs–TBK1–IRF3, and β-catenin–IRF3 signaling pathways are activated (Fig. 2). Interaction between IFNs and the corresponding receptors (with the generic term IFNR) in the target cells activates the Janus kinase (JAK)–signal transducer activator of transcription (STAT) pathway that a) leads to the transcription of interferon-stimulated genes (ISGs) and b) favors adaptive immunity, altogether inducing cellular defense (driving an antimicrobial and antitumoral state) (further discussed, Schoggins et al., 2011). Of note, negative feedback mechanisms are activated in parallel in order to balance and inhibit the pro-inflammatory signaling pathways (Ivashkiv & Donlin, 2014). In addition, several Q6 other inflammatory mediators are released, including IL-6, IL-8, IL-12, and tumor necrosis factor (TNF), in a NF-κB- or p38-dependent manner, therefore enhancing host immunity (Langefeld et al., 2009). In immune cells including macrophages and DCs as well as in epithelial cells, members of the NLR family and the PYHIN protein AIM2 associate in a stimulus-specific manner with apoptosis-associated speck-like protein containing a CARD (ASC) by homotypic interactions via the CARD and

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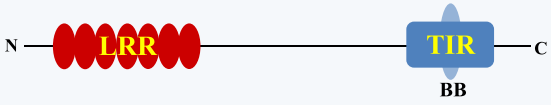
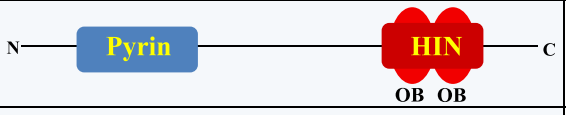
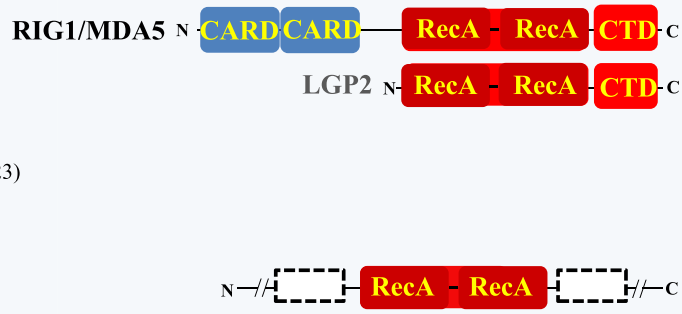
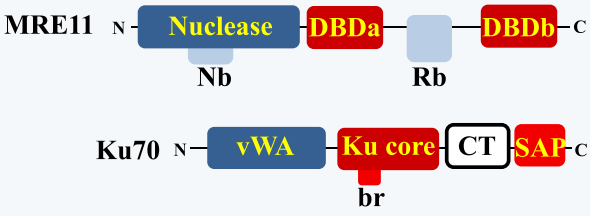
t1.1 **Table 1**

t1.2 Well-characterized types of PRRs along with the corresponding members functioning as intracellular DNA/RNA sensors. A few still-unclassified PRRs are

t1.3 presented as "other." The size of the protein domains is not depicted to scale; blue-colored domains are implicated in protein–protein interactions,

t1.4 whereas red-colored domains interact with nucleic acids. Detailed description of each PRR member is provided in the corresponding Supplemental Data.

| Type | Members | Protein domains |
|---|---|---|
| TLR | TLR3 (4q35)<br>TLR7 (Xp22.3)<br>TLR8 (Xp22.2)<br>TLR9 (3p21.3) |   |
| NLR | NOD2/CARD15 (16q21) |   |
| PYHIN | AIM2 (1q21-23)<br>IFI16 (1q21-23) |   |
| DExD/H-box helicases | RLR helicases<br>RIGI/DDX58 (9p12)<br>MDA5/IFIH1 (2q24.2)<br>LGP2/DHX58 (17q21.2)<br>Other helicases<br>DDX1 (2p24)<br>DDX3/DDX3X (Xp11.3-p11.23)<br>DDX21 (10q21)<br>DHX36/DDX36 (3q25.2)<br>DDX41 (5q35.3)<br>DDX60 (4q32.3)<br>DHX9/DDX9/RHA/NDHII (1q25)<br>DHX15/DDX15 (4p15.3)<br>DHX33/DDX33 (17p13)<br>DHX36/DDX36 (3q25.2) |   |
| DDR/R | MRE11 (11q21)<br>Ku70 (22q13.2) |   |
| Other | PKR (2q31.2)<br>DAI/ZBP1/DLM-1 (20q13.31)<br>RNA pol III<br>HMGB1(13q12),2(4q31),3(Xq28)<br>LSm14A (19q13.2)<br>LRRFIP1 (2q37.3)<br>cGAS/MB21D1 (6q13) |   |

t1.6

237 Pyrin/PYD domains. This in turn favors the recruitment of the 45-kDa
238 procaspase-1 (also described as zymogen), forming a multimeric cyto-
239 solic complex termed as an inflammasome (Mariathasan & Monack,
240 2007). Inflammasome assembly triggers the autoactivation of caspase-
241 1 (previously known as ICE), leading to the production of the potent py-
242 rogen IL-1β responsible for fever reactions IL-18 coupling innate to
Q7 adaptive immunity (Kim et al., 2010; Rathinam et al., 2010a, 2010b;
Kersse et al., 2011; Lamkanfi, 2011). Besides this, stimulation of the 244
caspase-1 inflammasome complex may also promote pyroptosis, a pro- 245
grammed form of cell death, wherein cells lose their membrane integri- 246
ty. Therefore, in contrast to apoptosis, it is a highly inflammatory type of 247
cell death (Aachoui et al., 2013). Interestingly, induction of AIM or 248
NLRP3 inflammasomes in macrophages can be accompanied by autoph- 249
agy in a p62-dependent manner, which limits inflammasome activity, 250

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suggesting a negative feedback loop by autophagy that restricts excessive inflammation (Shi et al., 2012). However, a large volume data also support the pro-inflammatory role of autophagy, including the induction of NF-κB activity and the stimulation of the Type I INF axis, suggesting that the interplay between autophagy and innate immunity remains a key challenge (Faure & Lafont, 2013). In addition, activation of PRRs triggers immunological "silent" apoptosis as well as necrosis, including a form of necrotic cell death termed as necroptosis, which is dependent on TNF and mediated by RPK1 and RPK3 (Vanlangenakker et al., 2012; Aachoui et al., 2013).

The regulation of the cell's fate by PRR activity is followed by metabolic and cell cycle modulations. Stimulation of TLR signaling shifts the metabolism of immune cells towards aerobic glycolysis, a phenomenon originally described in cancer metabolism known as the "Warburg effect" (Cheng et al., 2014). Furthermore, there is strong evidence of PRRs interfering with critical modulators of the cell cycle (Ludlow et al., 2005). Overexpression of IFI16 and the murine p202 and p204 HIN-200/PYHIN proteins induces cell cycle arrest through their interaction with the pRb–E2F1 and p53–p21 molecules (Choubey et al., 1996; Sangfelt et al., 1999; Hertel et al., 2000; Johnstone et al., 2000). Noticeably, IFI16 and p53 form a positive feedback loop (H. Song et al., 2008; L.L. Song et al., 2008). On the one hand, IFI16 directly binds to the C-terminal region of p53 and promotes p53-mediated transcriptional activity, and on the other p53 directly upregulates IFI16, through a functional p53 DNA-binding site in the 5′ regulatory region of IFI16. Hence, it is not surprising that IFI16 expression favors cellular senescence both in human normal and cancerous prostatic epithelial cells and in human fibroblasts (Xin et al., 2003; Xin et al., 2004; Song et al., 2010; Duan et al., 2011). In addition, there is evidence supporting the cross talk of the cytosolic and nucleic double-stranded DNA (dsDNA) sensors of the PYHIN/HIN-200 family with DDR/R components (Ouchi & Ouchi, 2008). BRCA1 interacts with the Pyrin domain of IFI16 favoring DNA-damage-induced apoptosis (Aglipay et al., 2003). Likewise, p202 interacts via the conserved MFHATVAT region within the HIN domain of murine homolog of human 53 binding protein 1 (53BP1) both *in vitro* and *in vivo* (Datta et al., 1996). Interestingly, the authors demonstrated that p202 inhibits the transcriptional activity of p53; the underlying mechanism warrants further investigation. Despite the lack of a human homolog for p202, a potential interaction between 53BP1 and human HIN-200 members may also be valid because the conservative MFHATVAT sequence is involved (Cridland et al., 2012). Based on these findings, we conducted a bioinformatics analysis and found that several PRRs interact with components of the DRR/R machinery (Fig. 3).

### 2.3. From ImmR to DDR/R activation: let the main story begin

Within this frame, there is a growing body of evidence on the activation of the DDR/R pathway by microbial infection in humans. Takaoka et al. (2003) clearly proved that IFNα/β signaling promotes p53 in turn evoking apoptosis that is critical for antiviral immunity, thus showing a novel link between IFNs and p53 in antiviral immunity and tumor suppression. The authors showed that infection of mouse embryo fibroblasts (MEFs) and the human hepatic cancer cell line HepG2 with different viruses including vesicular stomatitis virus (VSV), Newcastle disease virus (NDV), and herpes simplex virus (HSV) induces ATM-mediated phosphorylation of p53 at Ser-18 (mouse equivalent of human p53

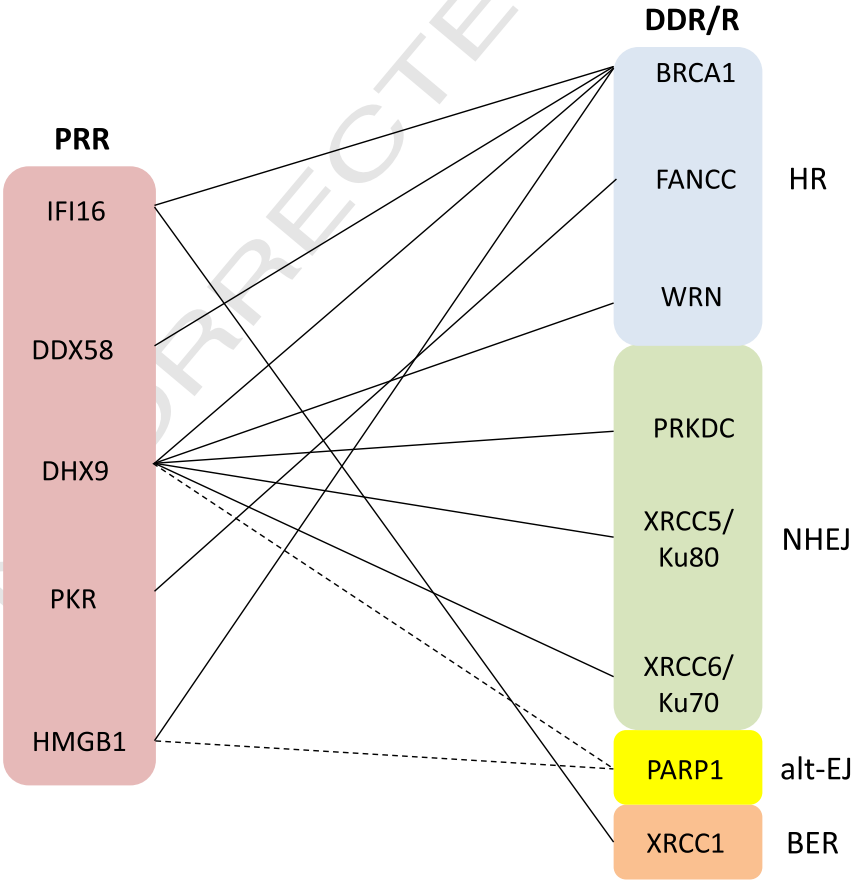


**Fig. 3.** Putative interactions between different pattern recognition receptors (PRRs) with components of the DNA damage response and repair machinery (DDR/R). The Ingenuity Pathway Analysis Software (Qiagen) along with the underlying Ingenuity Knowledge Base, which comprises ~5.1 million relationships, was used for the network analysis. Initially, all proteins of the DDR/R where recalled from the Knowledge Base. The interactions of DDR/R proteins with the groups of proteins defined in Table 1 were retrieved and visualized as networks. Only experimentally verified interactions were selected from the Knowledge Base in order for highly valid networks to be constructed. Solid lines in the networks indicate direct relationships whereas dashed lines indicate indirect ones.



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Ser-15) and Ser-15, respectively. Of note, within this setting, p53 induction was accompanied only by *Mdm2* and *Puma* but not by *p21* and *Noxa* transcription, implying a differential activation of p53-inducible genes after viral infection, thus warranting further studies. In line with the above mentioned data, prolonged expression of IFNβ in normal human diploid fibroblasts and of IFNγ in human umbilical endothelial cells (HUVEC) induces the DDR-p53 axis in a $p16^{INK4A}$-independent manner, in addition to the accumulation of γ-H2AX foci along with the phosphorylated forms of ATM–Ser1981, checkpoint kinase 2 (Chk2)–Thr68, and p53-Ser15 with ensuing senescence (Kim et al., 1999; Moiseeva et al., 2006). Interestingly, both studies demonstrated that the DNA damage signaling pathway was stimulated by an increase in reactive oxygen species (ROS), because treatment with the antioxidant N-acetyl-cysteine (NAC) inhibited DDR/R activation. Notably, despite activating the ATM–Chk2–p53 pathway, Guo et al. (2010) did not observe phosphorylation of H2A at Ser139 in response to $H_2O_2$ treatment in human primary fibroblasts, thus implying that oxidative stress triggers a DDR that is below the threshold needed to activate the "canonical" DDR/R route. Instead, treatment with bleomycin, a genuine radiomimetic drug that induces complex DSBs, results in H2A phosphorylation (Regulus et al., 2007). Hence, oxidative stress potentially induces both "canonical" and "non-canonical" DDR/R signaling (Ogrunc et al., 2014). Canonical signaling is favored when triggered by IFNs, although discrepancies between the various settings may exist. Furthermore, stimulation of the downstream effector of IFN–IFNR axis, STAT1, induces the ATM–Chk2–CDC25A and ATM–Nijmegen breakage syndrome 1 (NBS1) pathways by modulating the expression of MDC1 and 53BP1, triggering the S phase and the G2–M checkpoint (Townsend et al., 2005). Moreover, the DNA repair protein FANCC facilitates the trafficking of STAT1 to the IFNγR1 docking site (Pang et al., 2000).

### 2.3.1. How do viruses trigger DDR/R in the host?

Several DNA and RNA viruses trigger DDR/R in the host (Table 2) (reviewed by Georgakilas et al., 2010; Lilley et al., 2013; McFadden & Luftig, 2013; Xiaofei & Kowalik, 2014). Although the underlying mechanisms are still obscure, viral infection may stimulate DDR both directly and indirectly by the following mechanisms: a) the recognition of viral DNA as damaged DNA, such as the exposed (unintegrated) viral DNA ends that could resemble DSBs; b) the presence of DNA breaks within the viral genome; c) the induction of host DNA damage during viral infection (e.g., retroviral DNA integration); d) the identification of aberrant viral DNA structures; e) the expression of viral oncoproteins leading to a hyperproliferative phase, which may in turn cause DNA replication stress, favoring the generation of single-strand breaks (SSBs) and DSBs; and f) PRR–IFN-dependent axis as previously described (Wilkinson & Weller, 2003; Sinclair et al., 2006; McFadden & Luftig, 2013; Xiaofei & Kowalik, 2014). With respect to aberrant viral DNA structures in particular, the rolling-circle structure as well as the newly produced linear products and the presence of replication intermediates often with a nonlinear, branched structure synthesized during lytic replication may be recognized as SSBs or DSBs. In addition to these features, increased expression of the newly described PRR adaptor β-catenin in thymocytes induces DDR/R, favoring senescence independently of p53 and apoptosis dependent on p53 (Xu et al., 2008). In addition, the cross talk between DDR/R machinery and ImmR is further strengthened by the dual role of MRE11 and Ku70 both as PRRs sensing cytoplasmic DNA and as DDR/R components (Fig. 2).

**Table 2**
Viruses triggering the DNA damage response and repair machinery (DRR/R). All viruses presented therein potentially activate ATM (Lilley et al., 2013). There is evidence supporting the fact that HIV-1 stimulates both ATM and ATR. Besides induction of ATM, B19V as well as HTLV1 may also activate DNA-PKcs (Xiaofei & Kowalik, 2014). It is well documented that EBV, KSHV, HPV, HCV, HTLV1, HIV-1, and SV40 promote human carcinogenesis (Georgakilas et al., 2010).

| |
|---|
| Epstein Barr Virus (EBV) |
| Herpes Simplex Virus 1, 2 (HSV-1, HSV-2) |
| Kaposi's Sarcoma-associated Herpes Virus (KSHV) |
| Murine gamma Herpes Virus 68 (γHV68), |
| Human Papilloma Virus 8, 16 (HPV8, 16) |
| Adeno-Associated Virus (AAV) |
| Polyomavirus |
| Human Cytomegalovirus (HCMV) |
| Hepatitis C Virus (HCV) |
| Human parvovirus B19 (B19V) |
| Rift Valley Fever Virus (RVFV) |
| Human T-cell lymphotrophic Virus type 1 (HTLV1) |
| Human Immunodeficiency Virus 1 (HIV-1) |
| Simian Virus 40 (SV40) |

### 2.4. Lessons from viruses, part 2: interplay with DDR/R machinery

Perhaps, one of the strongest proofs of the tight association between ImmR and DDR machinery stems from the various strategies employed by viruses to take control of DDR (Lilley et al., 2007; McFadden & Luftig, 2013). Viruses abrogate the activity of critical components of DDR/R, including the MRE11 complex, usually by mislocalizing them and/or targeting them for proteasome-mediated degradation, implying a potential "bright" side of DDR/R stimulation. Indeed, DDR/R can be envisaged as part of the innate immunity of the host against several viruses. The Epstein–Barr virus (EBV) is a good example of this connection. Infection of B lymphocytes with EBV leads to a transient hyperproliferative phase that coincides with c-Myc up-regulation and robust DDR activation, followed by slower cell divisions (Nikitin et al., 2010). Inhibition of ATM or Chk2 during this initial period increases B cell proliferation and enhances their transformation, whereas ATM or Chk2 suppression had minimal effect after this initial phase, denoting the antitumor activity of DDR/R activation during this acute oncogenic stress period. In light of our recent work demonstrating a functional cross talk between DDR/R and p14 alternate reading frame (p14ARF) antitumor barriers (Velimezi et al., 2013), the status of p14ARF after ATM silencing in the initial phase is of interest. Subsequent upregulation of the Epstein–Barr virus nuclear antigen 3C (EBNA3C) results in reduced c-Myc expression, attenuated DDR/R activity, and repressed $p16^{INK4A}$ and $p14^{ARF}$ expression, favoring the establishment of latency (Jiang et al., 2014). It is highly interesting that this ubiquitous herpes virus infecting >90% of adults causes malignancy only in a limited number of human hosts. The increased incidence of EBV-related malignancies in immunocompromised patients suggests that the interplay between EBV and the host cellular and systemic responses possibly determines the final outcome of this symbiosis. To this end, studies have maintained that disruption of T cell activity leads EBV-transformed cells to escape (Hislop et al., 2007).

DDR/R activity may also possess a "dark" side, facilitating viral infection. HIV-1 infection triggers ATM-dependent DDR/R, favoring the efficient repair of the integrase-induced DNA damage, ultimately leading to the survival of host cells (Lau et al., 2005). Inhibition of ATM activity suppresses HIV-1 replication because the integrase-related DNA damage cannot be efficiently restored (Lau et al., 2005; Nunnari et al., 2005).

Noticeably, a key step in the activation of the two major RNA sensors RIG1 and MDA5 is the dephosphorylation of their CARD domain by protein phosphatase 1α (PP1α) and PP1γ (Wies et al., 2013). Of note, activation of ATM in response to DNA damage leads to stimulation of PP1 (Tang et al., 2008). Therefore, DDR/R may activate PP1 directly (including the integrase-induced DNA damage) or indirectly manner (like the RLR-IFNα/β axis) when cells are infected with RNA viruses, which augments RLR activity forming a positive feedback loop that promotes the ImmR. Two recent works depict two identical mechanisms wherein the antiviral response is suppressed by the V protein of measles virus via downregulation of the PP1-mediated dephosphorylation of RLRs in human DCs (Davis et al., 2014; Mesman et al., 2014). In addition, during



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lytic replication, several viruses including EBV hijack the DDR/R machinery to promote their own replication, suggesting a yin–yang virus–host relationship according to the different stages of the viral life cycle (Li & Hayward, 2011; Grywalska et al., 2013). In the lytic stage, DDR/R may be activated in two ways: a) during the generation of a prolonged pseudo-S-phase environment where the downstream activity of DDR/R is mitigated and b) during replication of the viral DNA itself. In both cases, DDR/R activity may foster viral replication contributing to faithful DNA replication and packaging. Recently, Laguette et al. (2014) demonstrated that HIV-1 viral protein R (Vpr) induces the Holliday junction resolution pathway relying on Synthetic lethal X (of unknown function) 4 (SLX4)–MUS81–essential meiotic endonuclease 1 (EME1), leading to FANCD2 foci accumulation and G2/M arrest. Activation of the SLX4 complex suppresses the spontaneous production of Type I IFN. The latter finding reveals a novel interaction between the DDR machinery and innate immunity suggesting that HIV-1 DNA can escape immunosurveillance mechanisms when processed through Vpr–SLX4–MUS81–EME-1. Interestingly, apart from viruses, two well-known bacterial pathogens known to cause common human infections, namely *Escherichia coli* and *Helicobacter pylori*, trigger DDR/R in host cells (Nougayréde et al., 2006; Toller et al., 2011).

### 2.5. Ionizing radiation: from DDR/R to ImmR

So far, we examined how immune insults trigger DDR/R. In the following, we focus on the reciprocal relationship of how DDR/R activates host immunity. First, we discuss the immunogenic function of ionizing radiation (IR).

IR induces complex DNA damage comprising a variety of closely spaced DNA lesions such as DSBs, SSBs, oxidized bases, and abasic (AP) sites (Georgakilas et al., 2013). This type of damage is expected to induce DDR and a variety of DNA repair pathways (Fig. 1A). This multi-pathway induction of DNA damage may first involve a danger signal for labeling this damage as a type of "special stress" above the regular DDR thresholds (Nikitaki et al., 2015), thereafter triggering the systemic effects and participating in secondary signaling based on inflammatory (cytokines and chemokines) or oxidative molecules (ROS/reactive nitrogen species (RNS), oxidized proteins, lipids, etc.) (Georgakilas et al., in press).

Radio-immunotherapeutic approaches are promising new curative anticancer treatments (de la Cruz-Merino et al., 2014; Vatner et al., 2014; Golden et al., 2015; Pilones et al., 2015). In addition to being directly cytotoxic, IR has also been traditionally considered as immunosuppressive. However, several findings over the past years suggest that it may promote host immune effector mechanisms, favoring antitumor immunity (Haikerwal et al., 2015). Almost two decades ago, Hallahan et al. (1989) demonstrated that exposure to X-rays increases the levels of the pro-inflammatory cytokine TNFα in human sarcoma cells, thus enhancing the lethality of radiation. Since then, a number of studies have corroborated the immunostimulatory (immunogenic) role of IR therapy. Interestingly, low doses of IR (0.5 Gy) can exert an immunosuppressive effect in some cases, revealing the crucial role of the level and type of DNA damage as a control switch for the type of effect of IR on the immune system (Scheithauer et al., 2014). For an in-depth analysis of this topic, the reader is advised to refer to the aforementioned recent reviews. Within this context, ablative local radiotherapy induces Type I INF signaling when IFNβ is upregulated by the tumor microenvironment (Burnette et al., 2011). The latter enhances the cross-priming ability of tumor-infiltrating DCs, thus triggering antitumor immunity and in turn tumor regression. On investigating this issue further, Deng *et al.* (2014) showed that IR activates the cGAS–STING–IRF3–IFNβ axis in DCs favoring cross-priming to CD8+ T cells. This suggests that DCs sense the DNA produced by irradiated tumor cells. Indeed, the authors demonstrated that DNA from irradiated tumor cells activates cGAS in DCs during a cell–cell contact-mediated process. Noticeably, IR triggers the expression of major histocompatibility complex (MHC) class I, which boosts T cytotoxic lymphocytic adoptive transfer, restricting tumor growth *in vivo* in mouse colon adenocarcinoma (Reits et al., 2006). Treatment with rapamycin blocked the cell surface expression of MHC-I as a response to IR treatment in the later phase, suggesting the involvement of mammalian target of rapamycin (mTOR). Indeed, two other studies have shown that IR promotes mTOR activity, which is greatly enhanced in MEFs and in the human colon carcinoma cell line HCT116 in the absence of adenosine monophosphate-activated protein kinase (AMPK), an upstream negative regulator of mTOR (Braunstein et al., 2009; Zannella et al., 2011). It is worth noting that IR activates AMPK in an ATM-dependent manner, inhibiting excessive mTOR expression in both normal and cancerous environments, leading to cell cycle arrest and favoring cell survival (Sanli et al., 2010; Zannella et al., 2011; Sanli et al., 2014). In addition to the lately established immunomodulatory role of mTOR these findings (Cobbold, 2013) highlight the importance of the AMPK–mTOR signaling pathway in radiation biology with potential therapeutic applications.

### 2.6. Bystander or non-targeted effects enter the game

The effect of IR is not limited to the cells, tissues, and organs subject to irradiation; it also acts "out of field" within the same organism. The radiation-induced bystander or non-targeted effects are well accepted, although the underlying mechanisms are still obscure especially *in vivo* (Hatzi et al., 2015; Georgakilas et al., in press). Irradiated cells send signals to non-exposed neighboring cells such as damage-mediated or protective responses that include DNA damage formation, apoptosis, senescence, terminal differentiation, as well as radioadaptive responses (Prise & O'Sullivan, 2009; Martin et al., 2011). Bonner's group examined the dynamics of DSBs in irradiated and bystander cells in three-dimensional (3-D) human tissue models (Sedelnikova et al., 2007). Maximal γ-H2AX foci formation was observed 30 min after irradiation in the former, whereas the incidence of γ-H2AX foci reached a maximum by 12–24 h after irradiation in the latter, followed by increased apoptosis, micronucleus formation, senescence, and loss of nuclear DNA methylation. The bystander effect is mediated through two key routes: a) by direct cell–cell contact via gap junctions allowing molecules weighing up to 1.0–1.5 kDa to pass through and b) by release of soluble factors including RONS and cytokines such as TNFα, transforming growth factor-beta 1 (TGFβ1), IL-1β, IL-6, IL-8, and IL-33 (Najafi et al., 2014; Havaki et al., 2015). In addition, activated macrophages are recruited to the irradiated sites, thus promoting cytokine production and in turn oxidative stress further. Interestingly, experimental evidence points to the saturation of bystander responses, which indicates that no additional effect occurs above a certain dose, instead reaching a plateau (Nagasawa et al., 2002). The latter contrasts with the direct effect of IR, where the response increases with elevated radiation dose. However, even in this case, the relative biological effect (RBE) increases up to 100–200 keV/μm and starts decreasing, possibly because the additional energy deposited does not cause further damage *per se* (Prise & O'Sullivan, 2009). Monte Carlo damage simulation (MCDS), which relies on repeated random sampling, is frequently used to reproduce clustered DNA damage (closely spaced DNA lesions), including DSBs and SSBs, in irradiated tissues (Carlson et al., 2008). For a population of cells uniformly inflicted by irradiation, the induction and repair of DSBs can be measured by determining the rate of change of the average number of potentially rejoinable DSBs per cell at time t with the following equation (Carlson et al., 2008):

$$\frac{dL(t)}{dt} = f_R \sum \dot{D}(t) - \left(\lambda + \eta f_R \overline{Z_F} \sum\right) L(t) - \eta L(t) L(t).$$

| | |
|---|---|
| L | average number of DSBs in a cell |
| $\dot{D}(t)$ | absorbed doserate |
| $f_R \sum \dot{D}(t)dt$ | potentiallt rejoinable DSBs occuring in a cell during dt |



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λ L(t) the first-order DBS repair process, where the rate constant λ is the sum of $\lambda_R$ (rate of DBS repair) and $\lambda_F$ (rate of damage fixation)

$\eta f_R \overline{Z_F} \sum L(t)$

intratrack (along on track) misrepair

$\eta L^2(t)$ intertrack (along different tracks) misrepair

Although difficult, a mathematical formula can be developed to determine the rate of DSBs in bystander cells in the near future. Considering that the irradiated and bystander cells have similar effects of irradiation, but different time and extent, the equation should include the following parameters: a) the rate of DSBs in the irradiated cells and b) the underlying mechanisms mediating the bystander effect. The former has already been addressed, whereas the latter warrants further investigation as it is challenging.

### 2.7. How does DDR/R induce ImmR?

In the following section, we discuss the underlying mechanisms linking DDR activity with ImmR.

#### 2.7.1. NF-κB: linking DDR/R activity with ImmR

Brzostek-Racine et al. (2011) demonstrated a clear connection between DDR/R activation and IFN production, despite IR being a prototypic DDR/R inducer (Han & Yu, 2011) (Fig. 2). The authors showed that treatment of human cell lines with various DNA-damaging agents induce IRF7 and IRF1, leading to elevated levels of IFN-α and IFN-λ1 in an NF-κB-dependent manner. MEFs that lack nuclear factor kappa B essential modulator (NEMO), one of the regulatory subunits of the IKK complex, could not upregulate IFN-α and IFN-λ1 after etoposide treatment. Activation of NEMO allows NF-κB dimers to translocate to the nucleus favoring gene transcription (Pasparakis, 2009). An interesting role of NEMO is that it serves as the molecular linkage between ATM and NF-κB signaling after genotoxic stress, revealing a novel function of ATM in the cytoplasm, mediating NF-κB activation in response to DSBs (Fig. 2) (Li et al., 2001; Wu et al., 2006, reviewed in Miyamoto, 2011). Thus, NEMO (phosphorylated at Ser85) triggers an inside-out signaling pathway when shuttling between the nucleus and the cytoplasm, leading to an ImmR because of DDR activity (Fig. 2B). The ATM–NF-κB cross talk is further analyzed in Section 3. Moreover, UV-mediated activation of NF-κB is compromised in primary skin fibroblasts isolated from patients with xeroderma pigmentosum (Muotri et al, 2006), thus reiterating the strong interaction between the DDR/R machinery and NF-κB, the master regulator of inflammation. Within this frame, the critical role of p38 mitogen-activated protein kinase (MAPK) signaling pathway should be recognized. p38MAPK responds to a variety of external and internal stimuli including DDR/R activity, which in turn modulates several genes involved in the inflammatory response (Cuadrado & Nebreda, 2010). The latter is frequently mediated by the positive regulation of NF-κB activity.

#### 2.7.2. Activation of DDR triggers NKG2DL and DNAML expression

In 2005, Gasser et al. (Nature 2005) demonstrated that constitutive activation of DDR/R in human dermal foreskin fibroblasts upregulates NKG2D ligands (NKG2DL). Pharmacological inhibition of ATM, ataxia telangiectasia and Rad3 related (ATR), and checkpoint kinase 1 (Chk1) prevented their overexpression in nontumor cell lines. Moreover, NKG2DL expression was reduced when ATM was silenced in a murine ovarian cancer cell line, whereas no difference was observed with ATR short interfering RNA (siRNA) in this particular setting. Likewise, treatment of multiple myeloma (MM) cell lines with low doses of chemotherapeutic agents elevates the status of NKG2D and DNAX accessory molecule-1 (DNAM-1)/CD226 ligands in an ATM/ATR-dependent manner (Soriani et al., 2009). Of note, NKG2D and DNAM-1 ligands were upregulated in MM cells expressing a senescence phenotype. NKG2D is an activating and costimulatory receptor that belongs to a family of lectin-like Type II transmembrane proteins expressed in humans as a homodimer on NK cells, γδ T cells, and a subset of CD8+ and CD4+ T cells (Burgess et al., 2008). DNAM-1 is another activating immune receptor that belongs to the Ig superfamily, expressed in humans at the cell surface of NK and NKT cells; CD8+, CD4+, and γδ T lymphocytes; and macrophages (de Andrade et al., 2014). MICA, MICB, UL binding protein 1–6 (ULBP1–6), and RAE1 as well as CD112/nectin-2 and CD155/PVR (poliovirus receptor) are the human ligands for NKG2D and DNAM-1, respectively. NKG2D and DNAM-1 ligands are usually expressed poorly by healthy cells, but they are up-regulated on the surface of infected, transformed, or otherwise "stressed" cells of various cell types (Zingoni et al., 2013; Cerboni et al., 2014) (Fig. 2). Ligation with the NKG2D and DNAM-1 receptors triggers innate and adaptive immunity, leading to enhanced cytokine production and cytotoxicity, favoring cell lysis of the incipient cells. Several viruses have evolved the ability to downregulate NKG2D and DNAM-1 ligands (Cerboni et al., 2014). Moreover, certain tumors reduce the levels of NKG2DL or DNAM-1L at the cell surface and release soluble NKG2DL via proteolytic shedding or phospholipace C cleavage, exosome secretion, and alternative splicing to promote immune escape (Chitadze et al., 2013; de Andrade Immunol, 2014). Therefore, it is not surprising that NKG2D- and DNAM-1-deficient mice are susceptible to tumorigenesis (reviewed in Raulet & Guerra, 2009). Of note, the acquisition of an EMT phenotype in the Snail-HT29 M6 colon carcinoma cell line is associated with an upregulation of NKG2DL, followed by enhanced lysis of cancer cells by NK cells (Lopez-Soto et al., 2013). In a conceptual twist, human cancer cells in several common carcinomas express the NKG2D immunoreceptor themselves, which confers a growth advantage by triggering the PI3K–AKT–mTOR axis (Benitez et al., 2011). The latter reveals a complex role for NKG2D/NKG2DL during tumorigenesis, which should be taken into account in future therapeutic applications.

#### 2.7.3. Persistent DDR activation promotes the accumulation of cytoplasmic DNA

Hence, in addition to the evidence of DDR/R machinery stimulation soon after viral infection, the activation of DDR/R from the earliest stages of carcinogenesis (Bartkova et al., 2005; Gorgoulis et al., 2005a, 2005b) suggests a critical role of the DDR–NKG2D/DNAM-1 axis as a prompt immunosurveillance mechanism (Fig. 2). The recent finding that activation of the DDR cascade induces the expression of NKG2DL and RAE1, in a STING–TBK1–IRF3-dependent manner in lymphoma cell lines, further elucidates the underlying pathways linking DDR/R with ImmR (A.R. Lam et al., 2014; E. Lam et al., 2014). Of note, the same group very recently depicted that induction of DDR in normal and various cancerous settings favors the presence of cytosolic single-stranded DNA (ssDNA) and dsDNA (Shen et al., 2015). Accumulation of cytosolic DNA promotes the expression of Type I IFNs, contributing to the immunogenicity of tumor cells. Overexpression of RNASE H1, which hydrolyzes RNA from RNA:DNA hybrids, as well as Trex1, a major mammalian 3′ DNA exonuclease, reduces the levels of cytoplasmic DNA, thus inhibiting Type I IFN-mediated rejection. By contrast, Trex1-deficient cells exhibit ATM-dependent checkpoint activation (Yang et al., 2007). According to Yang et al. (2007), Trex1 degrades ssDNA generated from the aberrant processing of replication intermediates, thereby suppressing abnormal DDR/R activity. Mutations in *TREX1*, resulting in a dysfunctional nuclease enzyme, have been identified in Aicardi–Goutières Syndrome (AGS) (Aicardi & Goutieres, 2000). AGS shares common features with the autoimmune syndrome systemic lupus erythematosus (SLE). Trex1 deficiency possibly promotes a pathological ImmR via aberrant DDR/R activation. However, some questions remain unanswered: How does the loss of Trex1 trigger autoimmunity? This may be partly explained by the accumulation of ectopic nucleic acids in the cytoplasm, which ultimately leads to the upregulation of NKG2D and DNAM-1 ligands. Further, NKG2DL may be activated by histone deacetylase inhibitors, demethylating agents, all-*trans*-retinoic acid, HER2/HER3 signaling, and IL-18 (which can be induced after inflammasome activation as mentioned earlier) (reviewed by Chitadze et al., 2013).



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#### 2.7.4. Activation of p53 favors immunosurveillance

Conflicting data on the role of p53 in the immunosurveillance mechanism exist. Although previous studies described that p53 was not required for NKGDL upregulation (Gasser et al., 2005), two other studies demonstrated the presence of functional p53-responsive elements in ULBP1-2 (Li et al., 2011; Textor et al., 2011). Conversely, the expression of miR-34 represses ULBP2 in a p53-dependent manner (Heinemann et al., 2012). Further, restoration of p53 in mouse liver carcinomas promotes tumor regression because senescence activity and a robust ImmR interact cooperatively (Xue et al., 2007). Reactivation of p53 increased the expression of several inflammatory modulators by tumor cells including ICAM-1 (CD54), LFA-1 as well as MICA, ULBP2, and CD155, accompanied by the recruitment of neutrophils, macrophages, and NK cells, thus promoting tumor elimination (Xue et al., 2007; Krizhanovsky et al., 2008). The presence of a functional p53-responsive element in *ICAM-1* conferring inducibility to p53, as observed in our laboratory, further supports a direct immunosurveillance role of wild-type p53 (Fig. 2) (Gorgoulis et al., 2003; Gorgoulis et al., 2005a, 2005b). Of course, we should bear in mind that p53 reactivation triggers senescence, which in turn produces an inflammatory response called SASP (Rodier & Campisi, 2011). Overall, p53 is found to favor immunosurveillance in different settings both directly and indirectly (Collado & Serrano, 2010; Gorgoulis & Halazonetis, 2010; Salama et al., 2014). However, the extent of their action in parallel or separately in eradicating tumors needs to be addressed.

### 2.8. Senescence-associated secretory phenotype: another paradigm of DDR/R–ImmR cross talk

The persistent activation of the DDR/R machinery favors the secretion of inflammatory cytokines, including IL-6 and IL-8 (Rodier et al., 2009). Activation of ATM, NBS1, and Chk2 is essential for cytokine production, whereas p53 activity is dispensable. The term Senescence-associated secretory phenotype (SASP) encompasses several of these inflammatory elements, as they are also associated with the senescence phenotype. Hence, DDR activity triggers inflammation, again demonstrating that DDR/R and ImmR form a functional network with highly connected associations. The state of chronic inflammation observed in several pathological settings, including neoplasias and autoimmune diseases, may be partially attributed to persistent DDR activation. The senescence inflammatory response (SIR) is a unique type of senescence-related inflammation that overlaps with the SASP signature (Lasry & Ben-Neriah, in press), thereby conforming to the term "parainflammation" introduced by Medzhitov (2008). SIR/parainflammation represents a state of low-grade inflammation, an intermediate between homeostasis and overt inflammation. However, the control of SIR by persistent DDR and the sequence of events in relation with SASP remain elusive. SASP components in the cell act both autonomously and non-autonomously, favoring communication between damaged cells and their neighboring cells. The net effect of the non-cell-autonomous activity depends on the cell and tissue context. SASP favors senescence in normal or low-grade premalignant cells but it boosts tumorigenesis in high-grade premalignant or malignant cells (Gorgoulis & Halazonetis, 2010). SIR exerts a "yin–yang" effect, with a pro- or antitumorigenic activity based on the cell context (Pribluda et al., 2013).

### 2.9. A common denominator behind different diseases

Overall, the DDR/R and ImmR are clearly part of a tightly regulated mechanism protecting (multi)cellular integrity from both exogenous and endogenous threats. Thus, a unifying model emerges with DDR/R, PRR, and inflammatory/immune mediators (including INFs and ILs) being activated in concert as a response to D/PAMPs within a particular time frame (Fig. 5). Aberrant activation disrupts cellular and systemic homeostasis, often leading to chronic and potentially fatal diseases. Hence, this model underlines the common routes activated during malignancies, connective tissue diseases, and infectious diseases. Stimulation of the INF signaling pathway in a TLR-dependent and TLR-independent manner contributes to autoimmunity (Moutsopoulos & Hooks, 1983; Meyer, 2009; Conigliaro et al., 2010; Delgado-Vega et al., 2010; Crow, 2014; Kato & Fujita, 2014; Lemos et al., 2014; Smith & Jefferies, 2014; Land, 2015). Similarly, the TLR pathway plays a significant role in inflammation-associated carcinogenesis (Mairov et al., 2013). Recently, Funabiki et al. (2014) demonstrated that lupus-like features developed spontaneously with a mutant MDA5 gain of function (GOF) that activated the corresponding signaling in the absence of the appropriate ligand. In the past, we demonstrated a marked association of particular NOD2/CARD15 variants with sarcoidosis as well as with ulcerative colitis and Crohn's disease, two chronic inflammatory conditions that pose an elevated risk of colorectal carcinoma (Gazouli et al., 2004; Gazouli et al., 2005; Gazouli et al., 2006). In addition, DDR has been proven to be involved in the pathogenesis of autoimmune diseases (Schild-Poulter et al., 2008; Davies et al., 2012; Solier & Pommier, 2014; Gunther et al., 2015). Examples from bedside experience support the common molecular background behind the different pathologies mentioned previously. Fever is one of the most common manifestations of several diseases. It is a prominent sign that reflects the activation of a common route leading to the release of pyrogens irrespective of the initial trigger. Based on our previous analysis, activation of both sensors, PRR and DDR/R, may lead to the production of pyrogenic substances including IL-1β, TNF-α, IL-6, and INF-α (Dinarello, 1999). This explains why fever of unknown origin (FUO) is a major challenge for physicians, as the underlying cause may fall under one of the following three entities capable of activating the PRR–DDR/R–inflammatory mediator circuit: neoplasms, collagen vascular diseases, or infections (Becker & Wu, 2010). In addition, one of the characteristics of DNA repair-deficient syndromes is elevated expression of immune and inflammatory genes (Ermolaeva & Schumacher, 2014). Werner syndrome (WS), a progeroid disorder caused by a deficiency in a RecQ-type DNA helicase (encoded by *WRN*), exhibits an increased inflammatory status (Turaga et al., 2009). Moreover, prolonged DDR/R activation has been linked with diabetes mellitus (Shimizu et al., 2014). DNA damage promotes increased inflammation, which in turn interferes with insulin signaling as well as reduced regenerative ability, impaired metabolism, and suppressed endocrine function provoking insulin resistance. Paraneoplastic syndromes (PSs) can represent another example, from daily practice, supporting the DDR/R–ImmR cross talk. PSs are disorders attributed to benign or malignant neoplasms remote from the direct local or metastatic effects and are considered to be immune mediated (Darnell & Posner, 2003). The oncogene-induced DNA replication stress pathway, which leads to deregulated DDR/R activation and in turn favors genomic instability (Halazonetis et al., 2008), may increase the levels of certain cytokines including IL-6, IL-5, granulocyte colony-stimulating factor (G-CSF), and granulocyte/macrophage colony-stimulating factor (GM-CSF), as well as the production of paraneoplastic autoantibodies observed in PSs. This hypothesis remains to be confirmed in the future. In the following section, we present an interesting connection between ATM and NF-κB, further supporting the DDR/R–ImmR interplay.

## 3. The ATM apical DDR/R kinase as a hub of the DDR/R–ImmR network

It is well known that the main function of ATM is to coordinate the DDR/R network (Jackson & Bartek, 2009). However, ATM also responds to a wider variety of stressogenic stimuli, bringing about cellular reactions that aim to preserve cellular homeostasis (Shiloh & Ziv, 2013). Within this context, ATM seems to modulate NF-κB activity in a multifaceted manner.

One of the best characterized ATM–NF-κB interactions occurs in the cytoplasm where ATM assembles with IKKγ (NEMO) dimers, activating IκB kinases (IKKα and IKKβ) and in turn triggering NF-κB-dependent gene expression (Miyamoto, 2011). This type of ATM signaling



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constitutes a nuclear to cytoplasmic ("inside-out") innate pathway, as mentioned previously (Fig. 2), and it is part of the endogenous DAMP mechanism that is triggered independently of membrane and cytosolic receptors (Fang et al., 2014). Nevertheless, ATM has also been shown to coordinate NF-κB-mediated signaling initiated by membrane and cytosolic receptors ("outside-in"), predominantly by modulating NF-κB-dependent activation of early pro-inflammatory cytokines upon TNF stimulation (Fang et al., 2014).

The cross talk between ATM and NF-κB has been demonstrated in both normal and malignant cells. For example, in the differentiation of pre-B cells, ATM–NEMO mediates the stimulation of NF-κB during DSB-induced V(D)J recombination of the immunoglobulin loci (Bredemeyer et al., 2008), whereas the same axis is constitutively activated in patients suffering from primary myelodysplastic syndrome (MDS) and acute myeloid leukemia (Miyamoto, 2011). Persistent activation of NF-κB is observed in many types of cancer, but the underlying mechanism remains obscure (Chatuverdi et al., 2011). Given that genomic instability is an "enabling" hallmark of cancer, it is possible that the DDR/R network could fill this mechanistic gap in certain cases (Negrini et al., 2010). In line with this notion, evidence from human cancer cell lines has shown the significance of NF-κB in processes such as homologous recombination (HR)-mediated repair as well as nonhomologous end joining (NHEJ) repair of DSBs, thereby potentially explaining NF-κB-based chemotherapy and radiotherapy resistance in certain malignancies (Lim et al., 2002; Volcic et al., 2012).

An intriguing link between ATM and NF-κB was revealed based on an earlier study showing that mouse skin cells bypassed senescence and became more invasive upon ATM inhibition (Bartkova et al., 2006). Prompted by this finding, we set out to investigate the mechanistic basis of this outcome. As invasiveness is associated with increased metalloproteinase activity in most instances (Hadler-Olsen et al., 2013), we measured, for example, the generic matrix metalloproteinase (MMP) activity in ATM-depleted cells and found it increased (Fig. 4A). From the various MMPs assessed, we discovered that the enhanced generic MMP activity was driven by increased transcriptionally-based MMP-3 (stromelysin-1) expression (Fig. 4B, C). On conducting a bioinformatic analysis of the mouse MMP-3 promoter, we noticed, among various regulatory elements, an NF-κB-binding site (Fig. 4D), which is reported to be responsive and evolutionarily conserved in mammals (Gilmore, 2006). To test whether ATM could control MMP-3, via NF-κB, we examined the subcellular localization and phosphorylation status of the latter. Notably, ATM silencing was followed by a shift of the

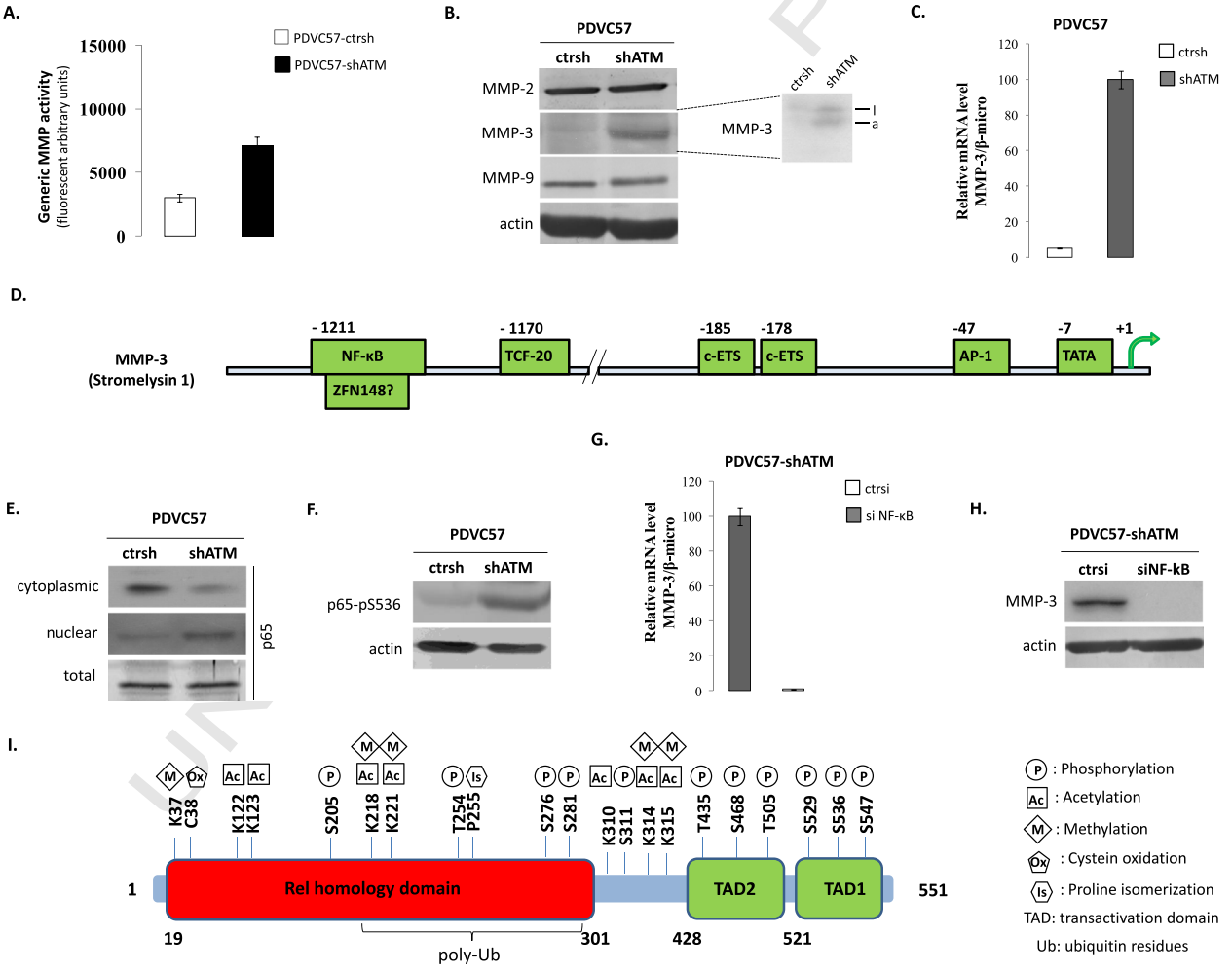


**Fig. 4.** Silencing of ATM expression in mouse skin PDVC57 cells leads to an increased, NF-κB-mediated, MMP3 status. (A) Genetic silencing of ATM in the PDVC57 mouse skin cell line results in increased MMP activity. Histogram depicting total MMP activity exhibited by PDVC57 and PDVC57–shATM cells as assessed by FRET assay. (B) Immunoblot depicting the increased levels of MMP-3 (stromelysin 1) produced by PDVC57–shATM cells. Inset showing that PDVC57–shATM cells secrete higher levels of MMP-3 in the culture supernatant. l: latent form of MMP-3; a: active form of MMP-3. (C) Histogram showing that PDVC57-shATM cells express increased transcription levels of MMP-3. (D) Structural organization of the MMP-3 promoter. Note the presence of a NF-κB-responsive element. (E and F) Silencing of ATM in the PDVC57 cells increases NF-κB activity as assessed by nuclear translocation (E) and S536 phosphorylation (F) of the p65 subunit. (G and H) siRNA silencing of the p65 subunit decreases MMP-3 expression in the ATM-deficient PDVC57 cells, at the mRNA (G) and protein (H) levels. (I) Structural presentation of the RelA/p65 protein subunit along with characterized positions of posttranslational modifications. Material and methods are provided in Supplemental Data.

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RelA/p65 subunit from the cytoplasm to the nucleus (Fig. 4E), with a concomitant increase in NF-κB phosphorylation levels at Ser 536 (Fig. 4F), whereas silencing of NF-κB evoked a remarkable reduction in MMP-3 levels (Fig. 4G, H). Although most studies have shown ATM to activate NF-κB, it must be noted that cellular context, in the form of either a cell type or a species, could dictate the outcome of the protein network interplay. NF-κB is posttranslationally modified to a great extent, and these modifications control its transcriptional activities or stability in the cytoplasm and the nucleus (Fig. 4I) (Perkins, 2006; Huang et al., 2010). In this context, phosphorylation at Ser 536 is a well-established activating modification that enhances its global transcriptional capabilities in response to a variety of stimuli. However, other phosphorylations have a more limited or temporal effect on its transcriptional repertoire. Characteristically, ATM has been reported to directly bind and phosphorylate NF-κB, upon genotoxic stress, at Ser 547 leading to transactivation of a small number of genes (Sabatel et al., 2012). This ATM-dependent NF-κB-stimulating route is unrelated to the NEMO-mediated mechanism (Wu et al., 2006). In our cellular setting, silencing, and not activation, of ATM triggered NF-κB activity, suggesting that ATM either does not stimulate NF-κB or exerts a constrained effect, similar to that reported from the phosphorylation of NF-κB at Ser 547 (Sabatel et al., 2012).

Altogether, these studies and results clearly demonstrate that ATM and NF-κB cross talk as two of the most important players in DDR/R and ImmR, respectively, and ATM appears to act to be a vital center that harmonizes cell autonomous defense(s) within a wider systematic response.

## 4. Questions and perspectives from the DDR/R–ImmR link in human diseases

Until now, with the exception of immune disorders linked to NHEJ defects, the DDR/R pathways were mainly examined with respect to cell-cycle-related defects, such as cancers, whereas the deregulated ImmR network was mainly studied related to infectious diseases and autoimmune disorders. From the concepts provided in this study, a common role of these interlinked networks in disease pathogenesis and development can be envisioned. For example, the recently proposed oncogene-induced model for cancer development can be embedded in a broader model (Fig. 5) that includes the ImmR and other noncancer-related disorders. In line with this, the recently revised "Hallmarks of Cancer" include genomic instability and tumor-promoting inflammation as enabling hallmarks and immune evasion as an emerging hallmark (Hanahan & Weinberg, 2011). From this aspect, patients suffering from cell-cycle-deregulated defects concurrently with autoimmune disorders, with different pathologies and separate treatment, may ultimately have a common denominator. This unifying view raises certain issues so that effective therapeutic tools can be developed.

A "yin–yang" relationship exists between the immune system and the most common human diseases. The immunosurveillance theory proposed by Burnet (1957), and by Thomas (1959) about the same time, supported the tumor-protecting role of the immune system. In 2002, Dunn et al. (2002) proposed the three Es of cancer immunoediting, namely elimination, equilibrium, and escape. The first E corresponds to immunosurveillance; the second, which lasts longer than the others, to a period of Darwinian selection favoring the less immunogenic tumor cells; and the third to the last phase where the immunologically sculpted transformed cells breach the host immunity. The DDR/R pathway seems to follow a similar route. Replication-stress-mediated DDR/R activates the antitumor barriers of apoptosis and senescence to protect the host at the precancerous stage, whereas key tumor suppressors such as p53 are eliminated during the "battle," favoring genomic instability and malignant clonal expansion. Thus, the DDR/R network loses its "bright" side, transforming into a "dark servant" that supports cancer survival (Bartkova et al., 2005; Gorgoulis et al., 2005a, 2005b; Halazonetis et al., 2008). Of course, the level and type of DNA damage may act as a regulating switch in this case. Considering the cross talk between the DDR/R and the ImmR networks, the following question arises: does the DDR/R machinery interfere with each "E"? If so, then what is its effect at the turning point when the immune system is overcome by malignant transformation? Within this frame and considering that genomic instability triggers PRR activity (Nagi et al., 2014), what is the role of PRRs in the initial phases of cancer development? The expression of PRRs in both immune and nonimmune cells highlights the significance of examining these relationships in different cellular compartments such as the stroma. Recently, ARF was shown to act as a complementary and delayed barrier to carcinogenesis, responding to escalating oncogenic stress and being

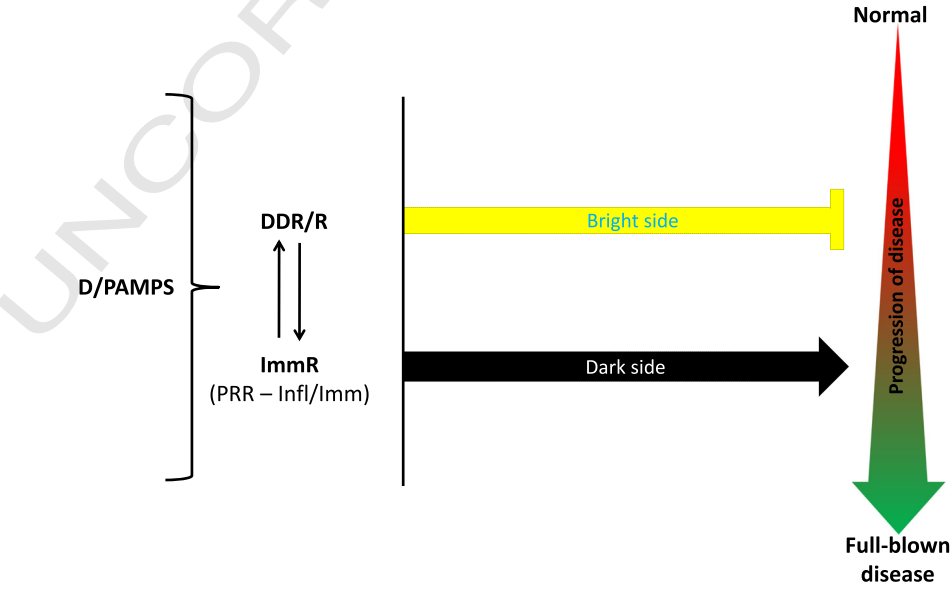


**Fig. 5.** A unifying model emerges with DDR/R and ImmR (including PRR and Inflammatory/Immune mediators) activated in concert as a response to D/PAMPs. The DDR–ImmR cross talk prevents disease development at early stages (bright side), whereas it promotes disease progression at later stages (dark side). DDR/R: DNA Damage Response/Repair; ImmR: Immune Response; D/PAMPs: Damage/Pathogen-Associated Molecular Patterns.

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robustly activated when the DDR/R kinase ATM is disabled. In view of this, it is interesting to examine the effect of ARF, along with the DDR/R, in relation to the ImmR during cancer development (Evangelou et al., 2013; Velimezi et al., 2013).

From the evidence presented so far, it follows that the DDR/R and ImmR pathways can be proposed as representing two branches of a common network that, in many cases, underlies both neoplastic and immunological disorders. However, the way these branches act in cancer and immune-related diseases may differ. For example, if immunoregulation of pro-inflammatory $T_{h1}$ activity is disrupted (Ellyard et al., 2007) failure of homeostasis of the immune system and in turn self-tolerance results, leading to what Paul Ehrlich termed as "horror autotoxicus" (harmful immune reactions against self). In general, such a state is antitumorigenic, as immunoregulation of $T_{h2}$ activity is mediated by type 2 immunity including $T_{h2}$, and by M2 macrophages, which play a pro-cancerous role as potent immunosuppressive cells (Fig. 1Bii). In a similar vein, blockage of the immune-checkpoint receptors cytotoxic T lymphocyte-associated antigen 4 (CTLA4) and programmed death ligand 1 (PDL1/CD274/B7-H1) has promising results in various types of cancer by boosting antitumor immunity (Pardoll, 2012) (Fig. 1Biii). Likewise, *CLTA4*$^{-/-}$ as well as *PDL1*$^{-/-}$ mice develop spontaneous autoimmune pathologies (Tivol et al., 1995; Ansari et al., 2003; Fife et al., 2006; Keir et al., 2006; Fife et al., 2009). However, the latter course of action is not always clear. For instance, the role of regulatory T cells ($T_{regs}$) in human neoplasia remains to be clarified. There is evidence supporting an adverse effect of $T_{regs}$ in fatal malignancies, such as ovarian and pancreatic cancer, but their role in colorectal cancer remains obscure (Műzes et al., 2008; Pages et al., 2010). Within this context, the role of the DDR/R network in the pathogenesis of autoimmune diseases needs to be investigated. Gunther et al. (2015)) recently demonstrated a functional role of Trex1 in the initiation of autoimmunity in AGS, implying that the DDR/R network emerges as a new player in the autoimmunity field. Whether prolonged DDR/R activity can trigger PRR signaling and vice versa also remains unanswered.

The outcome of these emerging potentially pathogenic links should always be evaluated within a spatiotemporal frame. IL-4, a prototype mediator of the $T_{h2}$ response that favors experimental autoimmune myocarditis, is an interesting example related to organ/cell specificity, whereas IFNγ produced by $T_{h1}$ cells limits this pathology. Contrary observations have been made in other sites and settings, such as experimental autoimmune encephalomyelitis and type 1 diabetes, with respect to the $T_{h1}/T_{h2}$ immunoregulatory function (Afanasyeva et al., 2001). Within the frame of topology, the two immune-privileged organs, namely the testis and thymus, can also additionally support the DDR/R–ImmR concept. The natural development of germ cells and lymphocytes is highly dependent on the continuous function of the DDR/R network, which could lead to host immunity under non-tolerant conditions possibly by upregulating the NKG2D and DNAM ligands (Jackson & Bartek, 2009; Fijak et al., 2011; Nunes-Alves et al., 2013). Similarly, this may also explain the features shared by both the cancer microenvironment and the immune-privileged sites (Swartz & Lund, 2012). Cancer cells exhibit an unremitting cycle of DSB formation and repair, which could render them susceptible to the immune system if the protective shield of immune tolerance was absent (Halazonetis et al., 2008; Hanahan & Weinberg, 2011). Time, the second element of the "spatiotemporal" parameter, determines the situation in many cases. For instance, prolonged activity of activated macrophages, conventionally classified as antitumor cells, favors tumor promotion through the production of ROS and RNS (Biswas & Mantovani, 2010; Lawrence & Natoli, 2011; Murray & Wynn, 2011). Similarly, a "timing"-dependent dual role of p38α signaling, a key pathway implicated in immunity, inflammation, and recently DDR/R (Phong et al., 2010), was shown during colorectal carcinogenesis (Gupta et al., 2014, 2015). p38α suppresses tumorigenicity at the initial developmental stages of colon cancer, while subsequently fostering tumor progression by promoting proliferation and inhibiting apoptosis of cancer cells. Recently, the activation of mutant H-Ras in mouse epidermis was report to trigger a different response in aged mice compared with young mice (Golomb et al., 2015, in press). In aged mice, H-Ras activation resulted in a neoplastic phenotype that correlated with senescence, most probably via DDR/R activation (Di Micco et al., 2006; Gorgoulis et al., 2006, 2010), and an ImmR that was more extensive than in young mice, in addition to delayed tissue recovery. The aged mice showed an increase in pro-inflammatory mediators along with a robust anti-inflammatory response tending towards $T_{h2}$ polarization, accompanied by the upregulation of PDL1(CD274). Investigating the mediators implicated in the DDR/R–PRR–inflammatory/immune signaling network after exerting the same insult in both young and old counterparts will further our understanding of (multi)cellular responses during aging.

Another parameter to be considered is the type of insult that dictates and orchestrates the proper defense mechanism. Taking for example the immunological branch of the DDR/R–ImmR network, elimination of phagocytosed microbes is promoted by a committed $T_{h1}$ response, whereas $T_{h2}$ polarization favors the defense against helminthic infections (Fig. 1Bii) (Jankovic et al., 2001). Likewise, the DDR/R limb reacts in a manner similar to that presented in detail in Fig. 1A. Nevertheless, if and how both branches of the DDR/R–ImmR network are coordinated in response to the same exogenous or endogenous insults remain to be examined.

All of these parameters provide plasticity to the interaction between the DDR/R pathway and the ImmR, sculpturing the end effects. Most importantly, this cross talk promotes inflammation, an emerging characteristic feature of cancer as mentioned earlier (Hanahan & Weinberg, 2011). Although inflammation is considered a protective host response to danger signals, maintaining harmony in both growing and adult animals according to Metchnikoff (Tauber, 2003), aberrant activation of the inflammatory response disrupts (multi)cellular homeostasis, favoring the pathogenesis of chronic diseases including neoplasms and autoimmune diseases (Karin & Greten, 2005; de Visser et al., 2006; Tzioufas et al., 2012; Elinav et al., 2013; Holmdahl et al., 2014). In tumor biology, chronic inflammation does not merely foster tumor initiation, but it might also be an "active component of the cancerous play," favored by full-blown cancers, in order to support their self-aggrandizement. The latter may be achieved by promoting several cancer hallmarks including genomic instability, angiogenesis, invasion, metastasis, and possibly immune evasion, by favoring T cell exhaustion, and potentially others such as deregulated metabolism. In cancer, abnormal activity of PRR and DDR can promote an inflammatory reaction; the physiological counterpart of this counterpart is still unknown. Therefore, what are the key features of cancer-associated inflammation? Some of these features may be explained by the concept of parainflammation/SIR (Medzhitov, 2008; Lasry & Ben-Neriah, in press) and the "over-healing wound" hypothesis (Schäfer & Werner, 2008). Cooks and colleagues recently proved the significance of the DDR/R–ImmR functional interplay in this scenario by the promotion of chronic inflammation and colitis-associated carcinogenesis by certain p53 mutant proteins through prolonged NF-κB activation (Cooks et al., 2013; Cooks et al., 2014a, 2014b). Taking into consideration that *TP53* mutations are among the most frequent in human malignancies (Olivier et al., 2004; Oren & Rotter, 2010), the GOF activity of p53 mutants (mt) p53 may play a significant role in supporting the unique inflammatory environment of different malignancies. It is also worth noting that loss of wild-type p53 activity by itself causes a critical breach in cellular homeostasis (Vousden & Prives, 2009). This is proved by its protective role against inflammatory stress (Cooks et al., 2014a, 2014b). Hence, when considering the GOF of mt p53 in addition to the wild-type p53 loss, a highly inflammation-prone environment is favored. The p53 "symphonic orchestra" is also known for performing a lesser-known function, described by Herkel et al. (2001) a decade ago, which further supports the functional connection between DDR/R and autoimmune disorders. Patients with SLE produce Ab's against the carboxy-terminal DNA-binding domain of p53, whereas patients with tumors produce anti-p53 Ab's that



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recognize the amino terminus (Lubin et al., 1993). This could possibly be explained by the varying exposure to p53 in malignancies versus autoimmune diseases, including SLE (Herkel, et al., 2001). It is worth considering that the Ab's against p53 are usually related to mutant p53 in tumors (Davidoff et al., 1992), whereas no p53 mutations are found and anti-p53 Ab's are directed against wild-type p53 in SLE (Kovacs et al., 1997). Yet, the functional consequences of the anti-p53 Ab's in different settings need to be clarified. This becomes even more challenging because of the ongoing trials with drugs targeting p53, either with reactivation of mutant p53 (Lambert et al., 2009) or with activation of wild-type p53 (Brown et al., 2009). Noticeably, murine double minute 2 (MDM2) blockage with nutlin-3 attenuates inflammation in various settings, through suppression of NF-κB signaling (Liu et al., 2009; Hashimoto et al., 2011; Mulay et al., 2012), suggesting that the potential therapeutic effect of this drug is mediated by regulating both p53-dependent and p53-independent pathways (Thomasova et al., 2012).

MicroRNAs (miRNAs) have also emerged as modulators of the DDR/R–ImmR interplay, which are also considered critical players in inflammation-associated pathologies (Kapsogeorgou et al., 2011; Singh et al., 2013). This type of noncoding RNAs is indispensable for T cell homeostasis implicated in the development of $T_{regs}$ (Yan et al., 2014). Strong evidence supports their involvement in inflammation-driven cancer (Schetter et al., 2010). Because miRNAs have been shown to be more abundant at common fragile sites (CFSs), representing the preferential target sites for oncogene-mediated replication stress from the earliest stages of cancer (Gorgoulis et al., 2005a, 2005b; Halazonetis et al., 2008; Tsantoulis et al., 2008; Aqeilan, 2014; Georgakilas et al., 2014; Ozeri-Galai et al., 2014), the extent to which DDR/R-mediated miRNA deregulation affects immune signaling can be investigated further. Similarly, miRNAs target the 3′-untranslated region (UTR) of NKG2DL including MICA, MICB, and ULBP1-3, reducing their cell surface expression and leading to evasion of malignant or virus-infected cells from immunosurveillance (Jasinski-Bergner et al., 2014). Furthermore, p53 enhances the posttranscriptional maturation of miRNAs, particularly those that suppress growth (Suzuki et al., 2009).

The players and biochemical interactions that surface from examining the interplay between the DDR/R and ImmR modules not only boost future therapeutic applications but also increase the modes of new therapeutic interventions, targeted more optimistically and with lesser side effects than the existing one. For instance, it was recently shown that the vasculature of solid tumors selectively expresses FasL (CD95L), which kills effector CD8+ T cells, thus establishing immune tolerance. Blockage of vascular endothelial growth factor A (VEGF-A) attenuated endothelial FasL expression, leading to an increase in the influx of CD8+ cells and in turn tumor growth suppression (Motz et al., 2014). An alternative approach could be based on FasL induction by the DDR/R pathway (Mo & Beck, 1999). If VEGF-A cannot be targeted directly (Breccia et al., 2014), then a differential option by inhibiting ATM can be followed. This would lead to downregulation of FasL and concurrently ARF induction by hindering ATM activity (Velimezi et al., 2013), which can eventually suppress VEGF-A, as previously reported (Kotsinas et al., 2014). Therefore, the latter therapeutic strategy may offer a better result because it targets three pathogenic factors (ATM, FasL, and VEGF-A) instead of the two (FasL and VEGF-A) inhibited in the former strategy. It is worth noting that several of the data produced were obtained from mice models, and they must be extrapolated to humans and vice versa with caution (as an example, see Suppl. Fig. 1).

As the ImmR has a memory of its own (Fig. 1Bi) (Crotty, 2011) it appears that DNA can also "remember" its damage. The latter was reported in yeast, with the evidence showing the marked influence of DDR/R on the state of a cell for many generations (Burrill & Silver, 2011). If this holds true in humans, then the DDR/R–ImmR functional interplay has further implications for potential therapeutic applications, as cells with "DNA damage memory" will be much more resistant to DNA-damaging interventions.

Overall, the DDR/R–ImmR concept broadens our insight into the pathogenesis of many diseases that were previously considered "unrelated," with the emergence of common underlying mechanisms. Previously isolated biomedical fields are now being linked by commonalities detected between different entities, allowing us to join forces for a better and more prosperous world. Besides, previous studies have already provided us with the concept of (multi)-cellular organisms espousing the motto of the Three Musketeers: "unus pro omnibus, omnes pro uno."

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## Conflict of interest

The authors declare no conflict of interest.

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