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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; PD1, Programmed death 1; 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; RIPK1,3, Receptor-interacting protein kinase 1,3; 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_h1,2, 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; Trex1, Three prime repair exonuclease 1; 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 mutated (ATM), which alerts and recruits mainly natural killer (NK) cells at