Inflammation-induced DNA damage and damage-induced inflammation: a vicious cycle

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Abstract

Inflammation is the ultimate response to the constant challenges of the immune system by microbes, irritants or injury. The inflammatory cascade initiates with the recognition of microorganism-derived pathogen associated molecular patterns (PAMPs) and host cell-derived damage associated molecular patterns (DAMPs) by the pattern recognition receptors (PRRs). DNA as a molecular PAMP or DAMP is sensed directly or via specific binding proteins to instigate pro-inflammatory response. Some of these DNA binding proteins also participate in canonical DNA repair pathways and recognise damaged DNA to initiate DNA damage response. In this review we aim to capture the essence of the complex interplay between DNA damage response and the pro-inflammatory signalling through representative examples.

1. Aetiology and molecular consequences of inflammation

Inflammation, from the latin *inflammare*: set on fire, in mammals is the natural defence mechanism of the immune system in response to the constant challenges it is exposed to including injury, toxins and microorganisms, low level cosmic or medical quality radiations (X-ray, γ-irradiation or UVA/B), drugs and air pollutants (e.g. asbestos or cigarette smoke) [1,2]*. Inflammation is a hallmark of aging and many chronic diseases such as obesity, Chron's disease, Parkinson's disease and autoimmune diseases just to name a few [3-7].

**Additional on-line references are marked by superscript numbers*

The first phase of a complex defence mechanism is acute inflammation instigated by the infiltrated peripheral polymorphonuclear leukocytes (neutrophils), granulocytes (eosinophils) and tissue resident phagocytes (macrophages) at the site of insult. The pro-inflammatory signal is transmitted through the PRRs that can identify danger through DAMPs (e.g. ROS, circulating DNA fragments), cytokines or chemokines released by the damaged tissue or PAMPs from pathogens [1] [8]. The initial role of these cells is to remove the invading pathogen and initiate tissue repair [9].

One of the major defence mechanisms of the activated neutrophils and macrophages is the production of a vast spectrum of endogenous reactive oxygen (ROS) and nitrogen (RNS) species [10] in a process termed "respiratory burst" [11] (see below). However, ROS, as well as the more stable and less reactive by-product of ROS production, hydrogen-peroxide (H_2O_2), are more than toxic products of respiratory burst, they are also effectors for a plethora of signalling pathways inducing innate and adaptive immune cell recruitment, proliferation, tissue healing, cell survival or apoptosis [12-14]. As a secondary messenger ROS are essential contributors to the signalling cascade of receptors (e.g. members of the Toll-like [TLRs] or Nucleotide-binding oligomerisation domain [NOD]-like receptors [NLRs]) that induce pro-inflammatory innate immune response via an array of functionally diverse down-stream signalling elements (e.g. NFκB, STAT1, IRF3 and caspase-1 activation) [2] [15-20].

Inflammation is self-limiting and normally subsides following the removal of the insulting particles and completion of tissue repair. However, if the loss of tissue homeostasis is prolonged it may ultimately lead to chronic inflammation with increased recruitment of macrophages, enhanced senescence and suspended apoptosis, unregulated growth and tissue repair. The overwhelming persisting ROS production by inflammatory cells damages macromolecules (DNA, as well as RNA, lipids, carbohydrates and proteins) of the host cells [21,22] inducing genomic instability and tipping the balance of the antitumour activity of ROS to a tumour promoting one. Chronic inflammation is viewed as a susceptibility factor for many chronic diseases including asthma, cardiovascular, autoimmune, neurodegenerative and age-related disorders [23-30] and cancer [31-33].Oxidative burst-

produced inflammatory ROS damage both nuclear (nuDNA) and mitochondrial (mtDNA) DNA causing genome instability and loss of homeostasis. Mammalian cells and the immune system have evolved an arsenal of receptors recognising molecules of pathogen- or host-origin, including DNA. Damaged host DNA, similar to bacterial DNA, signals danger and induces a wealth of signalling pathways to induce DNA damage response, DNA repair, inflammatory and immune response or cell death to restore tissue homeostasis and maintain host genomic integrity and survival.

1.1 Generation of inflammation-induced ROS and RNS

The chemical components of inflammatory response are ROS and RNS, molecules with free radicals (containing one unpaired electron) or other non-radical oxidants generated from oxygen or nitrogen [14]. Oxidative stress mediating ROS can typically arise from exogenous sources such as UVA or γ-irradiation, drugs, heavy metals [34-36], or from endogenous sources e.g. oxidative metabolism, apoptosis, bystander cells or enzymatic activity [31,37-39]. Extracellular ROS and RNS are produced by migrating neutrophils and macrophages at the site of injury or inflammation, while the intracellular sources are mostly biochemical processes through enzymatic reactions or autooxidation related to oxidative metabolism [40]. An array of oxidants is generated by neutrophils and macrophages at the site of infection including superoxide ($O_2{*}^-$), H_2O_2, hypochlorous acid (HOCl), nitric oxide (NO*) and nitrogen dioxide radicals (NO_2*). These reactive species mostly arise from the enzymatic action of NADPH oxidases (NOXs), SOD, MPO and nitric oxide synthase (NOS) or non-enzymatic homolytic scissions, respectively.

Upon activation of neutrophils and macrophages, membrane bound NADPH oxidases (NOXs) are assembled in the phagosomal, endosomal or cellular membrane (NOX2) [3] [41], or in the mitochondrial membrane (Complex I and III in the mitochondrial respiratory chain). NOXs catalyse the conversion of NADPH to $NADP^+$ while leaking one electron that can be captured by dissolved O_2 to produce $O_2{*}^-$, which is subsequently converted to additional anti-microbial and cytotoxic ROS. The $O_2{*}^-$ is released to the cytosol or the extracellular milieu where it is protonated to H_2O_2 and O_2 by

superoxide dismutase (SOD) [42,43]. H_2O_2 diffuses within the cell and through the aquaporins crosses the membrane into the extracellular space. Outside the cells it can travel long distances, which makes it a distant effector of phagocytic cellular killing [44]. Hence, it is also recognised as a distant effector of phagocytes when transformed to more potent oxidising radicals by myeloperoxidase (MPO) [45,46]. H_2O_2 is the substrate of MPO producing HOCl in neutrophils [4] [47], or HOBr in eosinophils [5]. H_2O_2 is highly stable and less electrophilic in vivo, however, is also a source of more reactive hydroxyl radicals (OH*) when it is reduced in the Fenton reaction by ferrous or copper ions [14,48,49].

The enzyme responsible for NO* production in macrophages and less abundantly in neutrophils is inducible nitric oxide synthase (iNOS) or i-mtNOS in the mitochondria [6] [50]. Electron leaking from NADPH via NOS-mediated oxidation of L-arginine can also produce O_2^{*-}. The reaction of NO* with O_2^{*-} generates peroxynitrite ($ONOO^-$). $ONOO^-$ is highly unstable and quickly autooxidates to nitrous anhydrate (N_2O_3) or converted to OH* and NO_2*. NO_2* and carbonate radical anion (CO_3^{*-}) are the by-products of the reaction of $ONOO^-$ with CO_2 followed by homolysis. Neutrophils also contribute to the NO_2* pool via MPO-mediated reduction of nitrite (NO^{2-}) to NO_2* [7] [46,51,52].

Under non-inflammatory conditions, low level ROS are intracellular signal transducers contributing to physiological activation of adaptive mechanisms maintaining cellular homeostasis. Low concentration of NO* has been observed to promote cell survival and proliferation, while non-physiological levels can induce DNA damage, cell cycle arrest and apoptosis [53]. Controlling non-activated cellular ROS levels within physiological range is the delicate balance of the catalytic and scavenger action of a wealth of enzymatic and non-enzymatic (small molecule antioxidants) reactions. Enzymes catalysing ROS metabolism include SOD, catalases, glutathione peroxydases, and thioredoxin, glutathione, methionine sulphoxide or peroxinitrite reductases [54-57], while ascorbate, oxaloacetate and pyruvate are a few examples of small molecule antioxidants [13,58,59].

1.2 Mutator ROS: ROS-induced DNA damage and repair

The spectrum of genotoxic effects of ROS and RNS are ranging from nucleobase modification such as oxidation (OH*, HOCl), halogenation (HOCl), alkylation, methylation, nitration (N_2O_3, $ONOO^-$), depurination and deamination, and abasic sites that can be present as isolated tandem or clustered lesions. In addition to this, more complex modifications of the DNA structure can also be catalysed by these chemical mediators of inflammation (inter- and intra-strand crosslinks, DNA-protein crosslinks, single strand breaks (SSB) and double strand breaks (DSB) [8] [60,60-62]. In addition, ROS can inhibit key proteins of the DNA repair machinery [63]. The balance between ROS induced DNA damage and repair is responsible for the relatively low level of lesions in normal cells and tissues [9]. However, this rate of damage increases with age, chronic diseases or cancer [10] [64,65].

Isolated oxidative DNA lesions and abasic sites are repaired with relatively high efficiency via base excision repair (BER) [66-68], while nucleotide excision repair (NER) removes intrastrand crosslinks [69] and bulky nucleotide lesions. Mismatched bases and small insertion/deletion loops are repaired by mismatch repair (MMR). The pathway choice to repair DSBs depends on the cell cycle state and can utilise homologous recombination (HR) or non-homologous end joining (NHEJ). Furthermore, DSBs (induced by e.g. γ-irradiation) are repaired by NHEJ [70,71] and replication-induced DSBs are repaired by HR [11] [72].

1.2.1. Isolated single nucleobase lesions, clustered DNA damage, SSB and DSB

Inflammation-mediated halogenisation by HOCl or HOBr [73] and nitration by N_2O_3 [74-79] can damage all four nucleotides in vivo giving rise to an abundant variety of nucleobase lesions. From all four canonical nucleotides, the most frequently identified oxidised guanine products in vivo are 8-oxodG and FapydG (2,6-diamino-4-hydroxy-5-formamidopyrimidine), while the most abundant oxidised pyrimidine lesions are thymine glycol (Tg; 5-,6-dihydroxy-5,6dihidrothymidine) and cytosine glycol (5-,6-dihydroxy-5,6dihidrocytosine) [1,60,61,80,81]. In addition to the above, OH*-mediated hydrolysis of

the deoxyribosyl moiety can result in SSBs [82]. Abasic sites, inter- and intrastrand G-G/G-A crosslinks can arise from nitrosation of purines [74]; while oxidised guanines can lead to 8-oxodG:dC or 8-oxodG:dA pairing, the latter leading to G→T transversions [83] [8].

Apart from direct nucleotide lesions generated by inflammatory ROS, secondary mutagenic radicals (aldehydes, epoxides, lipid hydroperoxides) can also arise from ROS-mediated oxidation of other cellular macromolecules and can induce further DNA lesions [84,85]. Clustered DNA lesions or non-DSB clusters are two or more DNA lesions within one helical DNA turn, which can be either on one strand or on both strands of the DNA helix (tandem or bistranded, respectively). Clustered DNA lesions are almost exclusively generated by ionizing radiation rather than inflammatory ROS, however, it is also reported that single pyrimidine radicals generated by reaction with OH* can attack the complementary or neighbouring purine bases [86,87] [8].

Typically, non-ionising radiation mediated oxidative stress induces SSBs, while DSBs arise as secondary lesions. Incomplete repair of a single lesion by BER (typically a nucleobase lesion or an abasic site generated by the AP endonuclease or glycosylase and more frequently by the long-patch BER) or by the NER pathways can induce SSBs and two adjacent SSBs (essentially arising from the repair of two bistranded clustered lesion) can lead to a DSB [88]. When the replication fork collides with unrepaired abasic sites or single strand breaks it can results in collapsed replication forks and DSBs (replication induced DSB) [72,89].

1.2.2. mtDNA damage

The circular mtDNA constitutes 1% of total cellular DNA, is of symbiotic bacterial origin, and compared to nuDNA has a very different molecular organisation and regulation. mtDNA has no histones and the methylation of CpG repeat motifs is under-represented, therefore it is particularly vulnerable to damage by endogenous ROS generated by the oxidative electron transport chain during ATP synthesis [90-92]. The major nascent mitochondrial ROS molecule is $O_2{}^{*-}$, which is quickly dismuted to H_2O_2. Under physiological conditions $O_2{}^{*-}$ and H_2O_2 are considered less reactive to

mtDNA directly than the OH* radicals generated from H_2O_2 in the Fenton reaction [93,94]. Due to the abundance of the GC-rich repeats e.g. in the ribosomal genes, the most frequent oxidative DNA adducts are 8-oxodG [95], however, thymine glycol is also frequent [96,97]. Additional mtDNA lesions include abasic sites (from OH*-mediated hydrolysis), cytosine alkylation by S-adenosylmethionine (SAM) [95], replication-mediated mismatch of modified nucleotides [98] and repair- or replication-induced SSBs [99] or DSBs [100] [12]. Abundant expression of mitochondrial NO* and secondary radicals are also responsible for mtDNA damage.

The most active pathway in the mitochondria to repair oxidative mtDNA lesions is BER [101]. SSBs are repaired by the joined BER/SSBR (single strand break repair) pathway [102] while DSBs are by HR, albeit at low frequency [103,104], or with NHEJ [13]. mtDNA degradation is another pathway to eliminate unrepaired oxidative DNA lesions [93], which is supported by the abundant cellular copy number of mtDNA and observations of cellular tolerance to extensive mtDNA loss in vitro [105] [106] and in vivo [107] [108,109] [13].

2. Oxidised DNA as a pro-inflammatory signal

Inflammation and ROS-mediated damage modulates the DNA damage response signalling and repair pathways resulting in an increase in expression of genes involved in repair and the inflammatory response [110]. On the other hand, ROS can directly damage or inhibit proteins of these processes as well [111,112]. In chronic inflammation, persistently high ROS level, reduced repair efficiency and dysfunctional mitochondrial respiration can lead to the accumulation of DNA damage [113]. If oxidative DNA lesions are unrepairable or repair is incomplete, prolonged DNA damage induces permanent cell-cycle arrest, senescence, eventually apoptosis or necrosis, during which DNA enters the degradation pathway. Under normal physiological circumstances DNA is sequestered in the nucleus and the mitochondria away from immune surveillance. Upon apoptosis [14,15] [114] necrosis or tissue damage fragmented cellular DNA can enter the vascular circulation and the intracellular space,

however, it is not recognised as antigenic for the unchallenged immune system. Failed clearance of apoptotic debris, excess circulating extracellular DNA (also known as cell free DNA; ecDNA/cfDNA) from necrosis or tissue damage, and increased level of DNA modifications are stimuli for immune response and inflammatory pathways, and pathological processes such as atherosclerosis [16], deep vein thrombosis [17], thrombotic microangiopathies [18], primary Sjögren's syndrome or systemic lupus erythematosus (SLE) [19] [115]. DNA is present in the extracellular milieu (ecDNA) and the vascular system of healthy as well as diseased individuals. Increase in its concentration and the level of oxidative damage correlates with tissue damage and disease severity. It is important to note that normal physiological processes such as ageing, stress and exercise can also lead to increased ecDNA levels [20] [116,117].

There are two sources of circulating ecDNA: 1) virtosomes; newly synthesised DNA/RNA/lipopolysaccharide complexes from living cells [21] or 2) cell death; apoptosis, necrosis and oncosis [15] [118]. Circulating ecDNA can be taken up by neighbouring or distant cells and could act as a messenger to exert biological bystander effect [22] [119].

The 8-oxodG content of genomic DNA (gDNA) in necrotic cells is enriched and its concentration in the ecDNA pool is elevated by oxidative stress or disease [23] [120]. Serum from patients with chronic diseases contains high levels of cell free oxidamaged DNA [24], while mice treated with antigenic oxidised gDNA ($gDNA^{ox}$) show induced inflammation and high anti-DNA^{ox} antibody levels [25]. Furthermore, similar to oxidised extracellular DNA ($ecDNA^{ox}$) released from damaged cultured cells [26] [120], $gDNA^{ox}$ generated in vitro [22] is a stress signal and can induce ROS production, causes decreased expression, nuclear localisation and transcription of NFκB in cultured fibroblasts; DNA damage, apoptosis or adaptive response in cells at sites far from the initial oxidative stress. This suggests that $gDNA^{ox}$ is a potential mediator of bystander effect that is observed following damage from both physical (irradiation) and chemical (ROS) sources [22,23,26] [120,121]. Low-LET radiation also induces ROS-mediated oxidative damage and inflammation in normal non-irradiated tissues [27]

[122,123]. Naïve cells exposed to either ecDNA from irradiated cells or gDNA extracted from H_2O_2 stressed cells show spatial and structural rearrangement of chromosomes within the nucleus, facilitating repair and transcription of ribosomal genes and genes involved in repair- and signalling processes [28].

2.2. Oxidised mtDNA as a stress signal

Circulating mtDNA is passively released to the extracellular space together with other mitochondrial macromolecules (e.g. lipids, formyl-peptides) by direct injury to tissue or programmed cell death mechanisms [124,125], and is present in measurable amounts with higher 8-oxodG content relative to nuDNA [23,29]. The importance of mtDNA in host defence is demonstrated by its active release via another immune response mechanism, called neutrophil extracellular traps (NETs): mtDNA and ROS are launched by activated eosinophils [30] [126] and neutrophils [31] [127,128] in response to bacterial lipopolysacharide induced IFN-γ and IL-5 [129].

The immune response to mitochondrial DAMP (e.g. mtDNA and ROS) is similar to PAMP induced PRR signalling and inflammatory immune response. One might surmise that despite the two billion year old symbiosis, mitochondria still possess immunogenic properties reminiscent of bacteria, and together with ROS these mitochondrial signals are an additional level in host immune defence (stress induced adaptive response) to maintain or restore homeostasis or if it is beyond that induce cell death. This may not be too far-fetched from the bacterial SOS response to ROS-induced damage from host cells. Invading bacteria activate pathogen recognition receptors, incite chronic inflammation and host DNA damage to hijack host DNA repair processes in order to repair their own DNA and gain bacterial resistance and survival. However, prolonged inflammation inhibits DNA repair, eventually leading to cancer. *Helicobacter pylori* infection downregulates MMR and BER and consequently induces carcinogenesis [32] [130-132], especially if *H. pylori* infection is associated with underlying metabolic syndromes such as diabetes or obesity [33] [133]. Exposure of cultured MEFs and HCT116 cells to oxidative stress showes much higher frequency of SSBs, but only a marginal increase

of 8-oxodG load in mtDNA [34]. On the other hand 8-oxodG level is increased in the fragmented mtDNA population in tissues [23,29], which implicates that if repair is overwhelmed mtDNA degradation is a potential pathway to maintain mitochondrial genomic integrity by clearing out damaged copies. Released extracellular or intracellular oxidamaged mtDNA ($mtDNA^{ox}$) fragments than act as mediators of immune response via DAMP activated TLR9 receptor signalling (see below). A large body of in vitro and in vivo data supports that 8-oxodG DNA fragments with high GC content promote local as well as distant inflammation. Exposure of cultured murine macrophages to such DNA induces TNFα secretion [35], while bystander effect has been demonstrated in a murine model: when the liver was injected with isolated mtDNA it also induced lung inflammation [36]. mtDNA binding to TLR9, subsequent p38MAPK phosphorylation and IL-8 secretion are diminished in vivo in cultured neutrophils that are incubated with oligonucleotides complementary to CpG repeats of mtDNA [36]. Bacterial-like non-methylated CpG rich mtDNA, therefore, can influence inflammation that is found to increase lung injury and arthritis in murine models in vivo, which is further enhanced by oxidative mtDNA damage [36,37]. Furthermore, cell free oxidised mtDNA is found in arthritic joint fluids [37] [134].

Oxidative stress induces elevated mitochondrial respiration and translocation of thioredoxin-interacting protein (TXNIP) from the nucleus to the mitochondria [38]. In the mitochondria TXNIP inhibits the antioxidant thioredoxin 2 (TRX2) [39], which leads to mtDNA damage, elevated ATP synthesis, amplified ROS production and dysfunctional mitochondria to culminate in inflammation or cell death [135-137] [40]. A genuine cellular response to eliminate dysfunctional mitochondria is mitophagy (mitochondrial autophagy) [138], which blocks NLRP3 inflammasome activation and the inflammatory response [2,41]. NLRP3 (NLR family, pyrin domain containing 3) is a molecular monitor of the metabolic status of mitochondria and the cytosol for DAMPs and PAMPs [42] [20] e.g. various radiation-generated ROS [43], asbestos and silica [44], β-amyloid plaques [45], extracellular ATP [46], oxidised mtDNA [47] and double-stranded RNA [48]. Depletion of mtDNA also inhibits inflammasome activation [41]. In the absence of mitophagy, augmented ROS can activate the

opening of mitochondrial permeability transition pores (mPTP) and the release of cytochrome c, ATP and Ca^{2+} to the cytosol. This in turn induces the intrinsic (mitochondrial) apoptotic pathway through the activation of the apoptosome [138,139] and a subsequent release of ROS, TXNIP, non-oxidised and 8-oxodG rich oxidised mtDNA to the cytosol, which then directly bind to NLRP3 [2,41,47] [18,140]. Priming of the NLRP3 inflammasome requires a pro-inflammatory signal likely provided by ROS [141]. Oxidamaged mtDNA binds to the pyrine domain of NLRP3, which then interacts with the cytosolic apoptosis-associated spec-like protein (ASC) component and induces the assembly and activation of the NLRP3-ASC adaptor-procaspase-1 complex (inflammasome). The active NLRP3 inflammasome relocates from the ER to the perinuclear space and binds to the mitochondrial outer membranes via the mitochondria-associated adaptor molecule, MAVS (mitochondrial antiviral signalling) [2] [142]. Mitochondrial membrane-bound NLRP3 instigates inflammatory caspase-1 autocatalysis [143], which interlinks pathways of cell death and the inflammatory response [139] (Fig. 1A). Active caspase-1 enhances proteolytic cleavage and secretion of pro-inflammatory cytokines (IL-1β, IL-33 and IL-18) [42] [144,145], which in turn result in the expression of TNFα and IFN (α/β and γ) instigating further immune cell recruitment. These pro-inflammatory cytokines activate the IL-1 or TNF receptors, and downstream NFκB signalling [146]. Activated caspase-1 also instigates the pyroptosis pathway: an inflammatory form of apoptosis characterised by cellular 'rapture' that releases its pro-inflammatory content, including oxidised DNA fragments [124,147]. NLRs are also involved in and regulate mtDNA-mediated inflammation and apoptosis in concert with TLR9 [47,49].

Recent in vivo and in vitro studies show that intact or oxidised mtDNA is a danger signal [1] [129,148], and induces pro-inflammatory cytokine (TNFα, IL-6 and IL-10) expression. This in turn promotes recruitment of activated macrophages, age related low level inflammation [20], or sepsis-like non infection associated, sterile SIRS (systemic inflammatory response syndrome) via the DAMP activated TLR9/NFκB pathway following trauma and lung injury [50]. However, other DNA sensors are likely involved in mtDNA and ROS mediated damage signalling [26] [120] as well.

In vivo and in vitro studies show that the effect of mtDNA as a damage signal is much more adverse than that of nuDNA [1] [148,149]. As protein coding in mtDNA is restricted to elements of the electron transport chain, many functions (replication, repair and transcription) in mitochondria rely on products encoded in the nuclei that are transported to the mitochondria [150,151]. As a consequence, nuDNA damage is also an important contributing factor to dysfunctional mitochondria [152].

3. Transduction of damaged DNA induced stress signal

Several different proteins have been identified to date (including MRE11 [153], PARP-1, Ku70, DNA-PK [154] IFI16 [155], DDX41 [156], RNA Pol-III [157], cGAS [158], DAI, HMGB1, AIM2 [159], RIG-1, TLR9 and STING [160-162]) [51] [163], which bind pathogen- or host derived DNA (originating from either the mitochondria or nuclei in response to cellular stress) and initiate defensive immune-response via NLRs, TLRs or RLRs (retinoic acid inducible gene-1 [RIG-1]-like receptors) mostly in a cell-type specific fashion. These sensors bind dsDNA in a non-differentiating manner only showing some preferences to non-oxidised or 8-oxodG rich DNA structures [47]. Further investigations are required to identify a specific DNA structure for pathogen derived DNA PAMPs [164] or conditions and conformations (emerged from its processing) that designate host-derived DNA [165] as DAMPs.

3.1 TLR9

Toll-like receptor 9 (TLR9) is present in cellular, nuclear and phagosomal membranes of innate immune cells and its expression is elevated during inflammation and starvation [22]. Non-methylated bacterial CpG-DNA from phagocytosis and mtDNA with the same properties are ligand to TLR9 via the extracellular high mobility group protein-1 (HMGB1). 8-oxodG enriched ecDNA^{ox} from tissue damage, cell death (pyroptosis) or mitochondrial release as DAMPs are preferred TLR9 ligands [52] [166,167], while extracellular histones are direct TLR9 ligands [53]. Ligand activation followed by the binding of the signalling adaptor MYD88 to TLR9 [168,169] induces TLR9 translocation from the ER to the endosomes [54]. MYD88 is also a signalling adaptor of the cytokine receptor IL-1R [55] linking the

TLR-dependent and TLR-independent inflammatory response pathways. The downstream effect of TLR9/MYD88 stimulation leads to IκB degradation and nuclear translocation of the NFκB transcription factor and the simultaneous phosphorylation of p38MAPK. This subsequently induces the synthesis and release of IFN-γ and TNFα. NFκB, in combination with other transcription factors e.g. AP-1, IRFs and CREB, induces the expression of proteins like additional pro-inflammatory cytokines (IL-1β, IL-6, IL-10, IL-18), NOX2, NLRP3, TRX2, TRX3 to regulate innate (monocyte recruitment) and adaptive (T- and B cell activation) immune response, local inflammation [36,50] [170,171], inflammation in distant cells or organs (bystander effect) [36] and senescence, as well as proliferation, tissue repair and survival [49] [172-176] (Fig. 1B).

Accumulation of non-degraded mtDNA leaking from overwhelmed autophagy induces TLR9 expression and TLR9-mediated inflammation [56]. Similarly, ecDNA from cancer patients induces TLR9 expression in mesenchymal stem cells [26], while TLR9 inhibitors decrease damaged ecDNA induced TLR9-mediated DNA damage response (chromosome remodelling, nuclear rearrangement, rRNA expression) in the bystander cells [22].

3.2 AIM2

Similar to phagolysosomal pathogen entry to the cytosol, intracellular dsDNA and mtDNA can bind and activate another type of inflammasome, AIM2 (Absent in melanoma-2) and induce caspase-1 mediated activation and secretion of IL-1β and IL-18 in addition to caspase-1 induced pyroptosis [57] [177,178] (Fig. 1A). Rathinam and co-workers also showed that cytosolic dsDNA induces type I IFN and AIM2 expression. This suggests that oxidised ecDNA that escapes degradation following entry into the cell via phagosomes can induce cell death and inflammation. However, in macrophages, non-oxidised DNA preferentially activates AIM2 [57], while oxidised mtDNA induces NLRP3 inflammasome assembly and both induce IL-1β secretion [47].

3.3 STING

The presence of 8-oxodG lesions alleviates the susceptibility of DNA to degradation by the TREX1 exonuclease [58], and as a consequence it accumulates to induce immune response. Elevated ecDNA level from increased apoptosis or NETs from dying neutrophils with defect in lysosomal DNase activity are characteristic for SLE [59]. Elevated ROS production induces NET formation [179], hence ecDNA in SLE accumulates 8-oxodG lesions that are sensed by STING (stimulator of IFN genes) and induces IRF signalling [58]. Following dsDNA stimuli STING relocates from the ER membrane to perinuclear endosomal compartments and forms a complex with TANK-binding kinase 1 (TBK1) [60] (Fig. 1C). The STING-TBK1 complex activates IKK to induce the NFκB or IRF3 pathways in a TLR-independent manner and induces Type I IFN expression and release, thus overstimulation of anti-viral and inflammatory innate immune responses via membrane IFN-receptor (IFNAR) in neighbouring cells and lymphocytes. Type I IFN-mediated receptor activation initiates the Janus kinase (JAK) signal transducer and the STAT (signal transducer and activator of transcription) pathway stimulating the expression of different antiviral genes [180,181].

dsDNA also activates translocation of STING to the apoptosome where it associates with TBK1 and interacts with autophagy-related proteins (Atg-9a) promoting autophagy [61]. Although STING-dependent IFN-β production is proven to be stimulated by synthetic poly(dG:dC) and dsDNA in MEFs, binding and colocalisation of STING to DNA were not shown suggesting that STING is not a DNA binding protein [60]. However, Abe and co-workers shown low affinity dsDNA binding to STING homodimers [62]. Upstream dsDNA binding molecules that induce the STING-TBK1-IRF3 pathway are IFN-inducible protein 16 (IFI16) [63] and DEAD-box polypeptide 41 (DDX41) [64], in addition to the recently identified cyclic GMP-AMP (cGAMP) synthase (cGAS) (Fig. 1C). cGAS binds and activates STING via the secondary messenger cGAMP and triggers NFκB and IFN response [65] [182,183]. The bacterial cyclic di-adenylate monophosphate (c-di-AMP) and cyclic di-guanylate monophosphate (c-di-GMP) are directly sensed by STING [66] [184,185] as well as via DDX41 [67]. The reduced IFN-β level in

Sting$^{-/-}$ MEFs to synthetic poly(dA:dT) dsDNA was accounted for an additional Type I IFN response that is independent of both TLR and STING, and mediated by the dsDNA induced innate immune signalling receptor RIG-1 [60]. RIG-1, a member of the RLR family, is a dsRNA receptor that also triggers antiviral response to dsDNA [186-188].

3.4. DNA damage sensor and repair proteins in inflammatory immune response

Damage to the DNA induces a cascade of actions commonly termed the DNA damage response (DDR). DDR includes the activation of different transcription programs, cell cycle checkpoints to induce transient or permanent cell cycle arrest (senescence), activation of specific repair pathways and apoptosis if repair fails. While the dsDNA-mediated immune-response pathways have been well characterised, there are still new alliances being discovered between DNA damage sensors of the DNA repair pathways and DNA receptors of the immune system.

3.4.1. MRE11

The MRN complex, consisting of MRE11 (Meiotic recombination 11 homolog A), RAD50 and NBS1 (Nijmegen breakage syndrome 1), is one of the first proteins to sense and bind broken double-stranded DNA ends. MRE11 possesses 3'→5' exonuclease activity and contributes to the resection of the broken end thus facilitates and regulates HR or NHEJ depending on cell cycle [71,189]. The complex controls DDR via the CDK phosporylation-dependent binding of CtIP to NBS1 and facilitating the ATM dependent phosphorylation of CtIP [190-192]. Once activated, CtIP promotes end resection by stimulating the endonuclease activity of MRE11 in an S-phase dependent manner [68] (Fig. 1D). In addition to IFI16 and DDX41 dsDNA binding proteins, MRE11 was also implicated in stimulating dsDNA induced type I IFN mediated inflammatory signalling via the STING-dependent pathway [69]. It has been shown in MEFs and ataxia telangiectasia-like disorder (ATLD) cells treated with non-AT-rich IFN stimulating DNA sequences, that MRE11 in complex with RAD50 but independent from

NBS1, induces IFN-β expression, and activation and translocation of STING. MRE11-mediated STING activation is not induced by pathogen-derived DNA suggesting that MRE11 rather functions in host damage response [69] (Fig. 1C). ATM activation promoted by MRE11 ultimately induces the p53 and p21 checkpoint proteins and cell cycle arrest, indicating a role of MRE11 in the control of p53 dependent apoptosis and cell-cycle regulation, and a direct link between DDR and the immune response pathways [193]. While p53 is considered to be a tumour suppressor, when overexpressed or in constant activation it can promote pro-tumorigenic inflammation [194]. Yan *et al* reported that in rat liver constant genotoxic stress-induced persistent DNA damage sustained elevated p53 expression and subsequently increased HMGB1 secretion, pro-tumorigenic hepatic inflammation and apoptotic hepatic injury in wild type rats, which was less severe in heterozygous $p53^{+/-}$ rats [70] [195]. Additionally, ATM also induces a pro-survival response via activated NFκB, which in turn accelerates DNA end resection, promotes HR, and induces BRCA2 and ATM transcription [71] (Fig. 1D).

3.4.2. PARP-1

Persistent unrepaired DNA lesions can cause replication fork stalling. A stalled replication fork may collapse if it is processed by endonucleases like MUS81, or if a progressing fork encounters an SSB it is converted to a DSB [196]. Stalled replication forks can reverse to aid template switching, replication past a lesion and replication restart. Collapsed forks can be re-built and replication reinstated through the homologous recombination repair pathway [197,198]. This process is initiated with end-resection that is catalysed by the MRN complex. Stalled replication forks, SSBs, DSBs, DNA cross over or stem loop/cruciform structures are sensed by the DNA binding and scaffold protein poly-ADP-ribose polymerase (PARP-1) [72]. PARP-1 has a bipolar effect in oxidative stress-induced DDR: DNA repair and survival or necrotic cell death. PARP-1 directly binds and recruits several proteins of the major repair pathways (MRE11, NBS1 [199,200], Ku70 [201], DNA-PK [202], ATM [203]) and regulates chromatin remodelling, DNA replication and repair, and transcriptional activity of inflammatory factors [204-206] (Fig. 1F). PARP-1 is also involved in caspase-1 mediated [73] or caspase-independent [74] apoptosis

and autophagy [207] [75]. PARP-1 catalyses the addition of poly (ADP-ribose) (PAR) chains to its substrate proteins and facilitates DNA repair. Persistent DNA damage induced PARP-1 over-activation results in the depletion of cellular NAD^+. NAD^+ re-synthesis leads to the depletion of cellular ATP reserves, impaired energy metabolism, cellular and mitochondrial dysfunction and necrosis; known as PARP-suicide [76]. PARP-1 is implicated in many inflammatory diseases including diabetes [208], asthma [209,210], atherosclerosis [211] and hepatic fibrosis [212] [77]. PARP-1 directly interacts and activates (PARylation) p53, and NFκB [78] [213,214], while interaction with p21 inhibits PARylation activity [72] [215]. In addition, PARP-1 was shown to regulate the phosphorylation of ERK1/2, p38MAPK, and c-Jun [78]. Similar to senescence, DNA damage induced PARP-1 over-activation generates an inflammatory feedback loop. PARP-1 binding to NFκB induces NFκB-mediated inflammatory immune-response by iNOS and expression of pro-inflammatory cytokines (e.g. IL-1, TNFα), leading to inflammatory ROS production and persistent DNA damage [72] [216-219].

3.4.3. Ku70 and DNA-PK

DSB is sensed by Ku70 to facilitate the Ku-dependent non-homologous DNA end-joining pathway (NHEJ), the major cell-cycle independent repair pathway of double stranded DNA breaks [70]. Ku70 is also implicated in the triggering of inflammatory signalling by inducing IRF1 and IRF7-mediated Type III IFN expression (IFN-λ1) [79] (Fig. 1E).

DNA-dependent protein kinase catalytic subunit (DNA-PKcs) is a member of the phosphatidyl-inositol (PI3) kinase family (of which ATM and ATR are also members). DNA-PKcs is activated upon binding to the Ku70/Ku80 regulatory subunit bound to dsDNA ends. DNA-PK plays a central role in DNA repair (NHEJ) and in V(D)J recombination of programmed DNA rearrangements in lymphocyte differentiation in the nucleus [70,220,221], but it also plays a role in the cytoplasm [80] [222,223]. Macrophages expressing catalytic dead DNA-PKcs or siRNA knock down of DNA-PKcs showed that its activity is essential for transfected synthetic CpG oligonucleotide -induced expression of the anti-inflammatory cytokine IL-10 while DNA-PKcs activity inhibits the expression of the inflammatory

cytokine IL-12p70. It correlates with previous findings that unmethylated CpG oligonucleotides induce IL-6, IL-10, IL-12, type I IFN and TNFα in dendritic cells (DC), macrophages and B cells [81] [224]. DNA-PKcs-mediated cytosolic binding of CpG oligonucleotides is a pre-requisite for the regulation of IL-12p70 and IL-10 expression through the DNA-PKcs-ERK mediated pathway. Interestingly, the CpG oligonucleotide-liposome complex also induces IL-12p70 [80]. Nevertheless, IL-12p70 induction could also be a response of TLR4 receptor activation that is probably induced by the liposome itself. A recently described cytoplasmic function of DNA-PK is the cytoplasmic DNA-mediated activation of IRF-3 in vitro and in vivo via STING-TBK1 stimulation (Fig. 1C). DNA-PKcs directly binds cytoplasmic DNA, which is enhanced by Ku and DNA-PKcs catalytic activity is not required for IRF-3 signalling [82].

3.4.4. HMGB1

HMGB1 (also called alarmin) is a chromosomal scaffold protein with diverse nuclear, cytosolic and extracellular functions. In the nucleus it facilitates chromatin assembly, binding of protein-complexes, and regulates transcription [225], replication [226], chromatin remodelling upon DNA damage [227,228] and DNA repair. HMGB1 can bind to different DNA structures in vivo and promote the NER [229], BER [230,231] and MMR [232] pathways. HMGB1 enhances the binding and the activity of Ku and DNA-PK at the DSB ends in NHEJ [233] and is implicated in V(D)J recombination [234] [83]. In addition to recognising specific DNA structures: supercoiled, hemicatenated, single stranded, B- and Z-DNA, four-way junction, triplex DNA, looped structures and DNA mini circles [83] [166,235], HMGB1 has strong binding affinity to damaged DNA sequences like UV treated oxidised DNA [84] and to CpG DNA. HMGB1 promotes TLR9 translocation to the endosomes and the HMGB1-CpG DNA complex induces TLR9 mediated IL-6, IL-12 and TNFα secretion in macrophages and DCs [85] (Fig. 1B). In response to starvation induced mitochondrial ROS mediated oxidative stress, HMGB1 actively translocates to the cytosol to inhibit apoptosis and to promote autophagy and survival. Intriguingly, this process is hijacked by tumour cells by overexpressing HMGB1 [86] [236]. As an extracellular DAMP, it induces pro-inflammatory signalling when released by activated immune cells [87] [237,238] or necrotic non-immune

cells [88] [239]. It acts as a cytokine: stimulates migration of immune cells in complex with CXCL12 [89], secretion of pro-inflammatory TNFα, IL-1 and IL-6 [240], and induces secondary delayed inflammatory response [90]. HMGB1 signals through the cell surface RAGE receptor on immune and non-immune cells to activate NFκB via the Ras-MAPK pathway [91], to promote tumour invasion by activating MAP kinases p38MAPK, JNKs and ERK1/2 (p44/42 MAPK) [92], and to induce NET formation via TLR4-mediated signalling [93]. Thus, HMGB1 is a contributing factor to many pathogenic conditions including sterile inflammations [94], sepsis [95] [241]; chronic inflammatory diseases like rheumatoid arthritis [96]; autoimmune diseases like SLE [97] and tumour development and survival [98] [236,242]. As a specific example: in chronic lymphocytic leukemia (CLL) plasma HMGB1 endorses proliferation of the nurse-like cells and the tumour via the RAGE-TLR9 pathway [99]. These suggest that in addition to its active release by activated innate immune cells to mediate pathogenic PAMP (GpC DNA) activated inflammatory immune response, nuclear HMGB-1 maintains DNA repair, genome integrity and promotes survival. Once DNA damage becomes prolonged and repair fails DNA-HMGB1 structures are released by necrosis and as DAMPs induce a second wave of inflammatory response that can be hijacked by tumour cells.

4. Concluding remarks

The link between DNA mutations, genome instability and tumour development is well established, and it is also widely recognised that chronic inflammation is a cancer susceptibility factor. Understanding the interplay between DNA damage response pathways and inflammation has dominated research in recent years. Our understanding of how the genotoxic effects of inflammation induce DNA damage response, and how factors of the DDR pathway and the PRR-mediated inflammatory immune response processes interlink to maintain homeostasis have advanced significantly. It all supports the hypothesis of a global inflammation cascade propelled by ROS and DNA damage. Loss of immune homeostasis and prolonged acute inflammation generated by different sources (infection, radiation, toxins, autoimmune disease and genetic susceptibility to

inflammation, aging, dietary factors and many more) induce ROS production, elevated ROS-mediated oxidative DNA damage, reduced repair capacity launching more ROS and oxidamaged DNA (nuclear and mitochondrial) by death of damaged cells. This in turn induces secondary and subsequent inflammation in intact distant bystander cells as stress signals, which accelerates into a systemic acute inflammation or cancer. The balance between these counteracting pathways is delicate and aim to avoid chronic inflammation, loss of genomic integrity by promoting DNA repair, or induce apoptosis to eliminate cells with accumulated unrepaired pro-tumorigenic mutations. Amongst many regulatory factors, damaged DNA within the nucleus and the mitochondria, or released from dying cells seems to play a central role by signalling danger and influencing repair and inflammation-associated pathways. Hence, while developing targeted therapeutic approaches to treat inflammation-associated diseases, the complex relationship between DDR and inflammatory immune processes has to be taken into consideration.

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Figure legends

Figure 1. Complex relationship between the inflammatory and DNA damage (DDR) response pathways. Genotoxic ROS induced DNA damage is sensed at different levels during inflammation and is a contributing factor to the pro- and anti-inflammatory immune response to restore tissue homeostasis. The cytosolic dsDNA sensor (A) AIM2 and NLRP3 inflammasomes contribute via ligand activated caspase-1 to the inflammatory catabolic NFκB pathway by post-translational cytokine

activation, or if the damage is greater induce cell death programmes. (B) Other cytosolic DNA sensors (IFI16, DDX41, DNA-PK etc.) via activated STING-TBK1 integrate into the cytokine and interferon signalling pathways in a TLR- independent manner promoting pro-inflammatory innate immune processes. (C) The same response is instigated by dsDNA in different endosomal compartments via the membrane bound TLR9 receptor. Nuclear damaged DNA sensors induce the DDR response: (D) the MRN complex (MRE11-RAD50-NBS1) through activated ATM and (F) PARP-1 instigate cell cycle arrest via the p53-p21 axis, DNA repair processes and additional transcriptional activation of inflammatory and repair genes (Pro-ILs, Type I IFN, NLRP3, ATM etc.) via NFκB or (E) via IRF3 transduced from the Ku70/Ku80/DNA-PK complex to promote cell survival or cell death in case of persistent damage.

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