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Review

Role of DNA repair in host immune response and inflammation

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ABSTRACT

In recent years, the understanding of how DNA repair contributes to the development of innate and acquired immunity has emerged. The DNA damage incurred during the inflammatory response triggers the activation of DNA repair pathways, which are required for host-cell survival. Here, we reviewed current understanding of the mechanism by which DNA repair contributes to protection against the oxidized DNA damage generated during infectious and inflammatory diseases and its involvement in innate and adaptive immunity. We discussed the functional role of DNA repair enzymes in the immune activation and the relevance of these processes to: transcriptional regulation of cytokines and other genes involved in the inflammatory response; V(D)J recombination; class-switch recombination (CSR); and somatic hypermutation (SHM). These three last processes of DNA damage repair are required for effective humoral adaptive immunity, creating genetic diversity in developing T and B cells. Furthermore, viral replication is also dependent on host DNA repair mechanisms. Therefore, the elucidation of the pathways of DNA damage and its repair that activate innate and adaptive immunity will be important for a better understanding of the immune and inflammatory disorders and developing new therapeutic interventions for treatment of these diseases and for improving their outcome.

Contents

Abbreviations: 8-oxoG, 8-oxoguanine; AID, activation induced cytidinedeaminase; AP site, abasic sites; APE1, apurinic/apyrimidinic endonuclease 1; ATM, ataxia telangiectasia mutated; BER, base excision repair; BM, bacterial meningitis; CNS, central nervous system; CSR, class-switch recombination; D, diversity; J, Joiner; V, variable; DDR, DNA damage response; DSBs, double-stranded breaks; EBV, epstein–Barr virus; GSH, glutathione; HCV, viruses like hepatitis C; HIV-1, human immunodeficiency virus type 1; HR, homologous recombination; HSV, herpes simplex virus; IFN-γ, interferon-gamma; Ig, immunoglobulin; IgH, Ig heavy chain; IgL, Ig light chain; iNOS, inducible nitric oxide synthase; KO, knockout; LPS, lipopolysaccharide; LTA, lipoteichoic acid; MMR, mismatch repair; NER, nucleotide excision repair; NF-κB, nuclear factor kappa B; NHEJ, non-homologous end joining; PAMPs, pathogen-associated molecular patterns; PRRs, pattern-recognition receptors; RNAPII, RNA polymerase II; RNS, reactive nitrogen species; ROS, reactive oxygen species; RSS, recombination signal sequence; SCID, severe combined immunodeficiency; SHM, somatic hypermutation; SOD, superoxide dismutase; SSBs, single strand breaks; TCR, T cell receptor; TLRs, Toll-like receptors; TNF-α, tumor necrosis factor alpha; WT, wild-type.

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1. Host immune response against infectious diseases

Innate immunity is the first line of defense against pathogens, and this response is mainly composed of the activation of phagocytic cells, including professional (such as neutrophils, macrophages, and dendritic cells) and non-professional immune cells (such as epithelial cells, endothelial cells and fibroblasts) [1]. Innate immunity was previously considered to be a nonspecific response, but research has shown that the innate response has a certain specificity, with the ability to discriminate between self and foreign molecules [2]. Microorganisms produce pathogen-associated molecular patterns (PAMPs) that are recognized by germline-encoded pattern-recognition receptors (PRRs). There are many classes of PRRs, such as Toll-like receptors (TLRs), which have an important role in cellular signaling and during the initiation of the adaptive immune response [2,3].

Bacterial PAMPs and viral nucleic acid (DNA or RNA) are recognized by specific TLRs, inducing inflammatory cytokines [4,5]. In brief, TLRs activate macrophages to produce inflammatory modulators, including tumor necrosis factor alpha (TNF-α), interleukin-1beta (IL-1β) and IL-6, to coordinate local and systemic inflammatory responses. Natural killer (NK) cells are activated and begin to produce interferon-gamma (IFN-γ), which is important in the induction of phagocytic cells. In parallel, nuclear factor kappa B (NF-κB) initiates the activation of inflammatory response genes by binding to specific DNA sites, an important step in the stimulation of endothelial cells, microglia, neutrophils and astrocytes to produce and release inflammatory mediators. The ensuing steps are the recruitment of proteins and leukocytes to the infection site, the activation of the complement system and the opsonization of pathogens for phagocytosis by macrophages and neutrophils [6,7].

The adaptive immune response has the function of eliminating the pathogen during the late phase of the infection, generating immune memory that is mediated by T and B cells that are able to respond to a wide range of potential antigens through their receptors, which are generated via DNA rearrangement [3,8]. Antigens are coupled in peripheral tissues by antigen-presenting cells and are delivered to the lymph nodes or spleen, followed by recognition by conventional lymphocytes. The differentiation of lymphocytes into an effector cell type and their localization in the infection site is regulated by the innate immune system [9]. These responses vary with age: the immunoglobulin (Ig) level, such as IgG and IgA, is lower in children than in adults, which is based on the fact that the activation of B cells for Ig production and maturation is dependent on antigen exposure [10]. Fig. 1 summarizes the involvement of the host immune response against infectious microorganisms.

Recently, much progress has been made toward discovering the interaction between the mechanisms of DNA repair and the immune response because it has great importance during the infectious process due to both the protective role against oxidative stress and the regulation of inflammation [11–15]. In addition, V(D)J recombination, class-switch recombination (CSR) and somatic hypermutation (SHM) are three processes of DNA damage and repair that are required for effective humoral adaptive immunity, creating genetic diversity in developing T and B cells. Deficiency in these DNA repair pathways is associated to several immunological disorders [16].

This review focuses on recent advances in the understanding of how DNA repair contributes to the development of innate and acquired immunity. In the next section, the processes that lead to DNA damage during infection and the involvement of DNA repair pathways with the development of the host immune response are described.

2. Role of oxidative stress in immune response

Oxidative stress resulting from excess reactive oxygen species (ROS) and/or reactive nitrogen species (RNS), which are generated by several mechanisms, including normal metabolism and exposure to exogenous agents. ROS and RNS are potent chemicals that play important roles under normal physiological conditions; in addition, they may be both beneficial and detrimental to cells within the cellular context. ROS are directly involved in protein, DNA and lipid oxidation, which may cause direct tissue injury or induce a variety of cellular responses. Furthermore, oxidative stress has been related to diseases associated with inflammation (for a review, see [17]). Thus, the development of adjuvant therapies based on anti-inflammatory and/or antioxidant molecules is important [18–21].

The mitochondria are the major source of ROS, which can be formed under physiological conditions as a consequence of ATP formation via the respiratory chain [22]. Indeed, respiratory chain dysfunction in mitochondria is responsible for most of the production of ROS because molecular oxygen is incompletely reduced during redox reactions [23]. During cellular dysfunction, an excess of superoxide ions promotes the activation of NF-κB, the key regulator of tissue inflammation, leading to a subsequent increase in the expression of cytokines, chemokines, eicosanoids, inducible nitric oxide synthase (iNOS) and adhesion molecules [24].

During infection, oxidative stress has an important role in host protection against invading microorganisms. In activated immune cells, enzymes such as (NADPH)-oxidase and myeloperoxidase lead to the production of ROS, which are effective at killing pathogens. A deficiency in these enzymes leads to recurrent infection by bacteria and fungi. However, excessive oxidative stress may induce cellular and tissue damage via the oxidation of proteins, lipids and DNA, triggering cell death, mainly through apoptosis or necrosis [25]. The consequences of oxidative stress are especially important in chronic infections, such as those caused by *Helicobacter pylori* and hepatitis C virus (HCV), which are correlated with cancer development in the stomach and liver, respectively [26]. In the central nervous system (CNS), the oxidative stress induced by inflammatory processes caused by infectious or neurodegenerative diseases is related to the main events that lead to functional loss and neurological sequelae [27].

The DNA damage induced by ROS are directly involved in cell death. Among the lesions generated, oxidized bases, such as 8-oxoguanine (8-oxoG), 2,6-diamino-4-hydroxy-5-formamidopyrimidine (Fapy-G), 2-hydroxyadenine, 5-hydroxycytosine, 5,6-dihydroxy-5,6-dihydrothymine (thymine glycol), abasic sites (AP site) and DNA double-strand breaks (DSBs) or single-strand breaks (SSBs) are the most frequent. 8-oxoG is the major lesion formed in purines and is associated with several diseases, inflammatory processes, accelerated telomere shortening and aging. Therefore, 8-oxoG is often used as a biomarker for oxidative stress [28,29].

The oxidized lesions generated during inflammation may cause mutations that lead to an increased risk for diseases such as cancer, neurodegeneration and atherosclerosis. The DNA damage response (DDR) pathway coordinates cell cycle arrest, DNA repair and the activation of transcription factors, including p53 and NF-κB [30–33]. DNA strand breaks are formed in bacterial infection, such as with *P. aeruginosa* and *H. pylori*, and histone H2AX is phosphorylated (γH2AX), constituting a marker of DSBs. In these cases, damage signaling and repair response dependent on ataxia telangiectasia mutated protein (ATM) and p53 have been described [34,35]. In response to DNA damage, the best understood nuclear process converges toward the "classical" pathway via activation of the IKK/NF-κB transduction pathway. Numerous DNA-damaging agents that induce DSBs also activate NF-κB [36–38].