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Review

The innate immune response to products of phospholipid peroxidation ☆

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ABSTRACT

Lipid peroxidation occurs in the context of many physiological processes but is greatly increased in various pathological situations. A consequence of phospholipid peroxidation is the generation of oxidation-specific epitopes, such as phosphocholine of oxidized phospholipids and malondialdehyde, which form neo-self determinants on dying cells and oxidized low-density lipoproteins. In this review we discuss evidence demonstrating that pattern recognition receptors of the innate immune system recognize oxidation-specific epitopes as endogenous damage-associated molecular patterns, allowing the host to identify dangerous biological waste. Oxidation-specific epitopes are important targets of both cellular and soluble pattern recognition receptors, including toll-like and scavenger receptors, C-reactive protein, complement factor H, and innate natural IgM antibodies. This recognition allows the innate immune system to mediate important physiological house keeping functions, for example by promoting the removal of dying cells and oxidized molecules. Once this system is malfunctional or overwhelmed the development of diseases, such as atherosclerosis and age-related macular degeneration is favored. Understanding the molecular components and mechanisms involved in this process, will help the identification of individuals with increased risk of developing chronic inflammation, and indicate novel points for therapeutic intervention. This article is part of a Special Issue entitled: Oxidized phospholipids—their properties and interactions with proteins.

Contents

Abbreviations: 4-HNE, 4-hydroxynonenal; AMD, age-related macular degeneration; AGE(s), advanced glycation end product(s); ApoE, apolipoprotein E; BSA, bovine serum albumin; C#, complement component #; CEP, carboxyethylpyrrole; CFH, complement factor H; CFHR, complement factor H related protein; CL, cardiolipin; CHD, coronary heart disease; CPS, capsular polysaccharide; CRP, C-reactive protein; CuOx-LDL, copper-oxidized LDL; DAMP(s), damage-associated molecular pattern(s); FAAB, 2-formyl-3-(alkylamino) butanal; HBGM1, high-mobility group box 1; HSP(s), heat shock protein(s); IL-#, interleukin-#; LDL, low-density lipoprotein; MAA, malonacetaldehyde; MDA, malondialdehyde; MDHDC, 4-methyl-1,4-dihydropyridine-3,5-dicarbaldehyde; MFG-E8, Milk fat globule epidermal growth factor 8 (lactadherin); NAb(s), Natural antibodies; OSE(s), oxidation-specific epitope(s); OxCL, oxidized cardiolipin; OxLDL, oxidized LDL; OxPS, oxidized phosphatidylserine; PAMP(s), pathogen-associated molecular pattern(s); PC, phosphocholine; PE, phosphatidylethanolamine; POVPC, 1-palmitoyl-2-(5-oxovaleroyl)-sn-glycero-3-phosphcholine; PRR(s), pattern recognition receptor(s); PUFA(s), polyunsaturated fatty acid(s); RAG, recombinase activating gene; TLR#, toll-like receptor.

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1. Introduction

Living in an aerobic environment brings along constant oxidative modification of biomolecules as part of normal tissue turn over. Our organism is usually well equipped to provide an adequate response to this physiological process and maintain homeostasis. However, during certain situations such as inflammation, this oxidative pressure is even more enhanced, which may cause the accumulation of oxidized proteins and lipids [1]. To prevent this and to ensure an appropriate response, mechanisms need to be in place that recognize and bind such modified molecules. Several proteins of the innate immune system have evolved to fulfill this function. They respond to oxidatively damaged molecules, thereby alarming the host while at the same time protecting it from overwhelming or chronic inflammation by triggering clearance mechanisms. A detailed understanding of the molecular structures that identify "biological waste" and the proteins interacting with them will provide fundamental insights into physiological house keeping mechanisms of innate immunity and help understand pathologies that may result from an impairment of these responses.

2. Innate immunity

The innate immune system represents an evolutionary old defense strategy that is present in all multicellular organisms [2]. Based on cellular and humoral responses, it provides a first line of defense against invading microbes. Following a pathogenic insult, an inflammatory response is initiated, which involves the rapid recruitment of innate immune cells, particularly neutrophils and macrophages. These cells engulf invading microbes and start producing a number of cytokines and chemokines that eventually activate lymphocytes, thereby triggering adaptive immune responses. Unlike the highly specific adaptive immunity the innate immune system typically recognizes foreign invaders by a set of pathogen-associated molecular patterns (PAMPs), which bind to various evolutionary conserved pattern recognition receptors (PRRs) and act as danger signals alarming the innate immune system. Prototypic examples for a PAMP are bacterial lipopolysaccharides that bind to the prototypic PRR toll like receptor 4 (TLR-4). Apart from cell surface receptors, PRRs can also be represented by soluble pattern recognition proteins, like the plasma reactant C-reactive protein, which binds phosphocholine (PC) conjugated to (lipo)teichoic acid on capsular polysaccharides of *Streptococcus pneumoniae*.

An inflammatory response can also be triggered by endogenous self-structures in the absence of microbes, and such a response is generally referred to as "sterile inflammation" [3]. Sterile inflammation is part of normal wound healing and tissue repair, which rely on an appropriate inflammatory response to the tissue damage, as the newly recruited leukocytes remove cellular debris and secrete proteases, thereby allowing tissue remodeling. If the inflammatory insult remains unresolved, this can result in chronic inflammation, inappropriate tissue destruction, or fibrosis. In analogy to PAMPs, sterile inflammation is triggered by damage-associated molecular patterns (DAMPs), which are generated by tissue injury or break down [4]. DAMPs can be either newly generated, damage-associated structures like advanced glycation end products (AGEs) or host molecules that are typically sequestered inside the cells under physiological conditions and only released as a result of cellular stress, such as necrosis following trauma, ischemia reperfusion, or chemically induced injury. Prototypic DAMPs include epitopes found on intracellular proteins like the chromatin-associated protein high-mobility group box 1 (HMGB1) or heat shock proteins (HSPs), and have also been shown to bind and/or activate PRRs.

3. Oxidation-specific epitopes are DAMPs

Research of the last years has shown that specific structures generated as a result of lipid peroxidation are recognized by various arcs of innate immunity and thereby can modulate many physiological and pathological processes [5]. The peroxidation of phospholipids occurs during a plethora of biological processes, including cellular senescence and apoptosis [6,7]. Moreover, this is greatly enhanced during inflammation. As a result a number of highly reactive phospholipid peroxidation products that can modify autologous proteins and lipids are generated. For example, phosphatidylcholine, which is present in cell membranes and low density lipoprotein (LDL) particles, contains an sn-2 polyunsaturated fatty acid (PUFA) that makes it particularly prone to oxidation, which results in the generation of highly reactive breakdown products, such as malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), and the remaining core-aldehyde, 1-palmitoyl-2-(5-oxovaleroyl)-sn-glycero-3-phosphocholine (POVPC). These reactive aldehydes can generate covalent adducts with primary amines of proteins and amino groups of lipids such as phosphatidylethanolamine (PE), and thereby form so-called oxidation-specific epitopes (OSEs) that are recognized by different immune receptors in a hapten-specific manner. Because many OSEs possess strong pro-inflammatory properties they have been proposed as novel kind of DAMPs. A conceptual review on this topic has been recently published elsewhere [5]. This review will cover primarily OSEs that result from oxidation of PUFAs in phospholipids and novel PRRs that have recently been identified in this context.

Lipid peroxidation occurs as a physiological process that is greatly accelerated during certain pathologies. Indeed, oxidation products such as oxidized phosphatidylcholine, MDA, 4-HNE and others have been documented in virtually all inflammatory diseases including atherosclerosis, pulmonary, renal, and liver diseases, as well as diseases affecting the central nervous system like multiple sclerosis and Alzheimer's disease [8–14]. Studies on the pathogenic role of oxidized LDL (OxLDL) have been instrumental in the identification of a variety of lipid peroxidation derived structures that may act as DAMPs [5,15]. An excellent historical perspective on this has recently been published by Steinberg and Witztum [16]. Once LDL gets trapped in the intimal layer, it can undergo oxidation via enzymatic as well as non-enzymatic mechanisms. The first includes among