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Review

Cyclopentenone-containing oxidized phospholipids and their isoprostanes as pro-resolving mediators of inflammation☆

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ABSTRACT

Inflammation represents a powerful innate immune response that defends tissue homeostasis. However, the appropriate termination of inflammatory processes is essential to prevent the development of chronic inflammatory disorders. The resolution of inflammation is actively induced by specialized pro-resolving lipid mediators, which include eicosanoids, resolvins, protectins and maresins. The responsible pro-resolution pathways have emerged as promising targets for anti-inflammatory therapies since they mitigate excessive inflammation without compromising the anti-microbial defenses of the host. We have recently shown that the lipid peroxidation of membrane phospholipids, which is associated with inflammatory conditions, generates oxidized phospholipid (OxPL) species with potent pro-resolving activities. These pro-resolving OxPLs contain a cyclopentenone as their common determinant, and are structurally and functionally related to endogenous pro-resolving prostaglandins. Here, we review the regulation of inflammatory responses by OxPLs with particular focus on the bioactivities and structural characteristics of cyclopentenone-OxPLs, and discuss the impact of the responsible signaling pathways on inflammatory diseases. This article is part of a Special Issue entitled: Lipid modification and lipid peroxidation products in innate immunity and inflammation edited by Christoph J. Binder.

1. Introduction

In order to survive, our organism has to maintain and defend a constant internal milieu while being exposed to continuously changing environmental influences. Inflammation represents a physiological response of the innate immune system to perturbations of this internal balance, irrespective of whether they originate from microbial infection, traumatic injury or metabolic dysfunction [1]. The inflammatory response aims to eliminate or sequester the injuring agent, to mount appropriate wound healing and repair programs and to restore tissue homeostasis. Inflammatory responses are initiated by innate sensing mechanisms that detect barrier breach, loss of cellular integrity or the presence of microbial infection. For this purpose, tissue-resident sentinel cells of the immune system express a panel of specialized pattern recognition receptors (PRRs). These receptors respond to pathogen-associated molecular patterns (PAMPs) that are shared between different microbes, yet are usually not expressed by mammalian cells [2]. In addition, PRRs may also recognize damage-associated molecular patterns (DAMPs), e.g. self-molecules that are produced or released only by stressed or dying cells to alarm the immune system [3]. Activation of PRRs triggers the secretion of diverse inflammatory mediators, including vasoactive substances, pro-inflammatory cytokines, chemokines and phospholipid-derived lipid mediators, which orchestrate the resulting innate immune response. Provided that the immune response succeeds to eliminate the infectious agent or to repair the initial tissue injury, the inflammatory process will be terminated and thus affects tissue function only transiently. However, in cases where the inflammation fails to resolve, for example due to the persistence of a pathogen or the failure to repair the initiating injury or tissue dysfunction [4], the powerful effector functions of the inflammatory response may inflict severe damage on the host tissue. As a result, a sustained inflammatory process develops which can permanently compromise tissue function. Accordingly,

Abbreviations: 15d-PGJ2, 15-deoxy-$\Delta^{12,14}$-prostaglandin J2; ARE, antioxidant response element; COX, cyclooxygenase; DAMP, damage-associated molecular pattern; DC, dendritic cell; EC, epoxycyclopentenone; EI, epoxyisoprostane; ICAM, intercellular adhesion molecule; IFN-γ, interferon-gamma; IL, interleukin; iNOS, inducible nitric oxide synthase; KOdiAPC, 1-palmitoyl-2-(5-keto-6-octene-dioyl)-*sn*-glycero-3-phosphocholine; Nrf2, nuclear factor E2-related factor 2; OxLDL, oxidized low density lipoprotein; OxPAPC, oxidized PAPC; OxPL, oxidized phospholipid; PAMP, pathogen-associated molecular pattern; PAPC, 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine; PECPC, 1-palmitoyl-2-(5,6-epoxyisoprostane A2)-*sn*-glycero-3-phosphocholine; PEIPC, 1-palmitoyl-2-(5,6-epoxyisoprostane E2)-*sn*-glycero-3-phosphocholine; PG, prostaglandin; PGD2S, prostaglandin D2 synthase; PGPC, 1-palmitoyl-2-glutaroyl-*sn*-glycero-3-phosphocholine; POVPC, 1-palmitoyl-2-(5-oxovaleroyl)-*sn*-glycero-3-phosphocholine; PPAR-γ, peroxisome proliferator activated receptor-gamma; PRR, pattern recognition receptor; RSV, respiratory syncytial virus; SPM, specialized pro-resolving mediator; Th, T helper; TLR, Toll-like receptor; TNFα, tumor necrosis factor alpha; VCAM, vascular cell adhesion molecule.

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non-resolved inflammation has been identified as an important etiologic factor in the pathogenesis of many chronic diseases, including obesity, atherosclerosis, inflammatory bowel disease, neurodegenerative disorders and certain cancers [4]. Therefore, not only the induction of the inflammatory process requires appropriate regulation; also its timely resolution has to be guaranteed in order to avoid the detrimental consequences of chronic inflammation. It is now evident that the resolution of inflammation represents a well-controlled process already programmed during the initiation phase of the inflammatory response and the underlying molecular pathways are currently being elucidated at the molecular level [5].

2. The resolution of inflammation

The termination of inflammatory responses has been long regarded a passive event that automatically occurs with the removal of the injuring agent and the resulting cessation of pro-inflammatory signals. However, the resolution of inflammation is now recognized as an actively induced process, which is directed by a family of specialized pro-resolving lipid mediators (SPMs) [5,6]. Analogous to the inflammation-inducing prostaglandins and leukotrienes, these pro-resolving mediators are enzymatically generated from phospholipid-derived polyunsaturated fatty acids. They include eicosanoids, such as the lipoxins, but also the more recently discovered resolvins, protectins and maresins that are synthesized from essential omega-3 fatty acids, including eicosapentaenoic acid and docosahexaenoic acid [5,6]. Physiological inflammation comprises a sequence of events that begins with the initial release of pro-inflammatory mediators, followed by the subsequent endothelial activation, edema formation and infiltration of polymorphonuclear neutrophils into the injured tissue. The nonphlogistic recruitment of monocytes then supports the clearance of apoptotic neutrophils via efferocytosis and initiates wound repair programs to facilitate the return to tissue homeostasis. Synthesis of pro-resolving lipid mediators is mediated by cell-cell interactions within the inflammatory exudates. Intriguingly, the generation of these pro-resolving signals appears to be already instructed early during the inflammatory process. This prepares the lipid mediator class switch from the predominant production of pro-inflammatory mediators during the initiation phase towards the production of a pro-resolving mediator profile at later stages, which heralds the resolution of inflammation [6]. Importantly, while SPMs specifically influence different levels of the inflammatory process to promote its resolution, their activity does not compromise host resistance to infection [5]. On the contrary, SPMs have been shown to increase host survival in models of bacterial [7–9], fungal [10] and viral [11] infections. This is a clear difference to conventional anti-inflammatory therapies, which usually also mediate certain immunosuppressive effects. In this regard the pro-resolution mediators are considered particularly advantageous since they could provide novel therapeutic approaches for inflammatory diseases that do not interfere with anti-infectious immune defenses [12,13]. Accordingly, the discovery of these resolution-inducing pathways has sparked great interest in identifying the involved lipid species and the molecular mechanisms mediating their signaling. Recent studies suggest that not only the lipid mediators generated by enzymatic reactions, but also certain oxidized phospholipid (OxPL) species that are formed by radical-mediated lipid peroxidation in the context of inflammation exert potent pro-resolving activities in vitro and in vivo. Here, we will summarize the current knowledge of the regulation of inflammatory responses by OxPLs with a particular focus on cyclopentenone-containing OxPLs, which have emerged as powerful pro-resolving lipid mediators with high therapeutic potential.

3. Oxidative stress and the generation of oxidized phospholipids

The generation of reactive oxygen species (ROS) represents an essential innate effector function of phagocytic cells that is required for the successful immune defense against microbial pathogens. In non-phagocytic cells, ROS serve as important intracellular signaling molecules that modulate the activity of biological processes. For instance, transient increases in cellular ROS levels are involved in the regulation of cellular proliferation, differentiation, migration and angiogenesis responses, as well as the induction of cell death programs [14]. Likewise, the intracellular redox balance also influences the activity of signaling pathways via the reversible modification of ROS-sensitive cysteine residues [14]. Nevertheless, conditions in which the generation of ROS exceeds the protective capacity of the cellular antioxidant defense mechanisms, as may occur during inflammation, are associated with oxidative stress. The excessive ROS production and an imbalanced redox homeostasis are especially harmful due to the ensuing oxidative modification of self-molecules, such as lipids, proteins or nucleic acids. Accordingly, oxidative stress has been identified as an important etiologic factor in the pathogenesis of chronic inflammatory diseases, metabolic diseases and cancer [15,16].

The exposure of biological membranes to ROS rapidly leads to the oxidative modification of membrane phospholipids (Fig. 1). Particularly the polyunsaturated fatty acid side chains of phospholipids are highly susceptible to radical-mediated oxidation. Importantly, this lipid peroxidation is non-specific, and thus generates a complex mixture of distinct oxidized phospholipid species with diverse bioactivities [17]. The radical-mediated oxidation of membrane phospholipids can produce two major categories of OxPLs (Fig. 2) [17,18]. OxPLs of the first category are characterized by a truncated oxidized fatty acid at the *sn2* position that contains hydroxyl or carbonyl groups. These OxPLs are generated due to a fragmentation of the oxidized fatty acid, which also releases highly reactive short-chain aldehydes, such as 4-hydroxynonenal or malondialdehyde. OxPLs belonging to the second category are a result of intra-molecular cyclization, rearrangements and further oxidation; they may contain isoprostanes, isothromboxanes or isofurans at their *sn2* position [17,18]. Examples for each category of OxPLs have been detected in vivo and characterized as synthetic compounds. While common effects shared by several OxPLs exist, these studies also indicated distinct biological activities for structurally diverse OxPLs. OxPLs have been demonstrated in a range of disease settings with a prominent inflammatory component. Importantly, the pathophysiological relevance of OxPLs to such disease conditions, including acute and chronic infections [19–21], atherosclerosis [22] and neurodegenerative disorders [23] appears to be directly related to their ability to modulate the underlying inflammatory processes (Fig. 1).

4. Pro- and anti-inflammatory activities of oxidized phospholipids

Although both pro- and anti-inflammatory bioactivities of OxPLs have been described, OxPLs are generally considered to exert strong pro-inflammatory effects and to promote pathogenic inflammation in a range of disease settings [17]. Indeed, many studies have reported such pro-inflammatory activities of OxPLs, which can be attributed to the direct recognition of OxPLs by different PRRs of the innate immune system. In particular, OxPLs have been shown to interact with Toll-like receptors [21,24,25], scavenger receptors [26–28], complement components [23], C-reactive protein [29] and natural antibodies [30,31]. For example, in the acute respiratory distress syndrome caused by acid-induced lung injury or infection with highly pathogenic influenza viruses, locally generated OxPLs initiate the pathogenic cytokine storm by activating TLR4 signaling [21]. In the context of atherosclerosis, vascular inflammation is driven by OxPL species present on oxidized low-density lipoprotein (OxLDL). These OxPLs have been shown to provoke the secretion of pro-inflammatory cytokines and chemokines by activating a hetero-dimeric complex of TLR4 and TLR6 on macrophages [24]. Moreover, this process required the co-operation of the dimeric TLR4/6 with scavenger receptor CD36, which in addition supported the internalization of OxLDL for the subsequent priming of IL-1beta secretion [32]. A similar co-operation in the recognition of OxPLs has been reported for CD36 and TLR2. This interaction was shown to induce

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