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Review Article

Redox-derived damage-associated molecular patterns: Ligand function of lipid peroxidation adducts ☆

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ABSTRACT

Endogenous electrophiles, such as α,β-unsaturated aldehydes and ketones generated during lipid peroxidation, exhibit a facile reactivity with proteins, generating a variety of intra and intermolecular covalent adducts. It has been postulated that these host-derived, modified proteins with electrophiles, which constitute the products of diverse classes of oxidative reactions, represent damage-associated molecular patterns (DAMPs). The DAMPs, that occur *in vivo*, can be a ligand of multiple proteins, which in turn, may lead to the profound innate and adaptive immune responses and mediate homeostatic functions consequent to inflammation and cell death.

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Introduction

Electrophiles, in addition to being noncovalently bound to a protein, have the potential to undergo nucleophilic substitution or addition reactions with the protein. The important endogenous electrophiles that give rise to the modification of a protein may be represented by α,β-unsaturated aldehydes and ketones, such as 2-alkenals, 4-hydroxy-2-alkenals, and 4-oxo-2-alkenals, generated during lipid peroxidation [1–3]. The α,β-unsaturated carbonyl, now conjugated to the diene, forms a powerful electron-withdrawing group. This moiety is labile to react with available nucleophiles, such as protein thiol or histidine residues, via Michael addition, generating a variety of intra and intermolecular covalent adducts (Fig. 1) and conferring an altered cellular distribution, conformation and catalytic activity. Moreover, the adduction of α,β-unsaturated carbonyls to apolipoprotein B in low-density lipoproteins (LDL) has also been strongly implicated in the mechanism by which LDL is converted to an atherogenic form that is taken up by macrophages, leading to the formation of foam cells. The biological functions of lipid peroxidation adducts generated within those modified proteins are still largely unknown. However, several recent studies have shown that the lipid peroxidation modification of proteins can be directly related to the innate immunity [4,5].

The innate immunity is stimulated by danger signals called damage-associated molecular patterns (DAMPs), which represent endogenous danger molecules as a group that is separated from pathogen-derived pathogen-associated molecular patterns. DAMPs include endogenous or self-molecules, such as the high-mobility group box 1 and heat shock proteins [6]. DAMPs also refer to a much broader group of oxidatively-modified biological molecules, including oxidized LDL [4]. In the extracellular space, DAMPs can bind to pattern recognition receptors (PRRs) (Fig. 2), which recognize conserved molecular patterns that distinguish foreign organisms, or to specialized receptors to elicit an immune response by promoting the release of pro-inflammatory mediators and recruiting immune cells to infiltrate the tissue [7]. DAMPs, possessing an exposed epitope, are also accessible for recognition by the soluble PRRs, such as natural antibodies and regulatory proteins [4,8]. DAMPs stimulate the adaptive immunity and participate in

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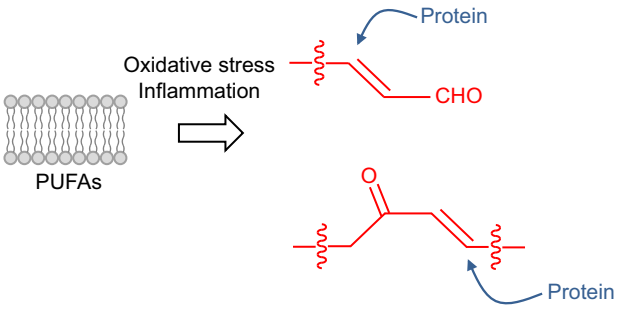

Fig. 1. Electrophilic reactivity of lipid peroxidation-derived α,β-unsaturated carbonyls with proteins. The polyunsaturated fatty acids in cholesterol esters, phospholipids, and triglycerides are subject to free radical-initiated oxidation and can participate in chain reactions that amplify damage to biomolecules. A key feature of lipid peroxidation is the breakdown of these polyunsaturated fatty acids to yield a broad array of smaller fragments, 3–9 carbons in length. The important fragments that give rise to the modification of proteins may be represented by electrophilic carbonyls, such as α,β-unsaturated aldehydes and ketones.

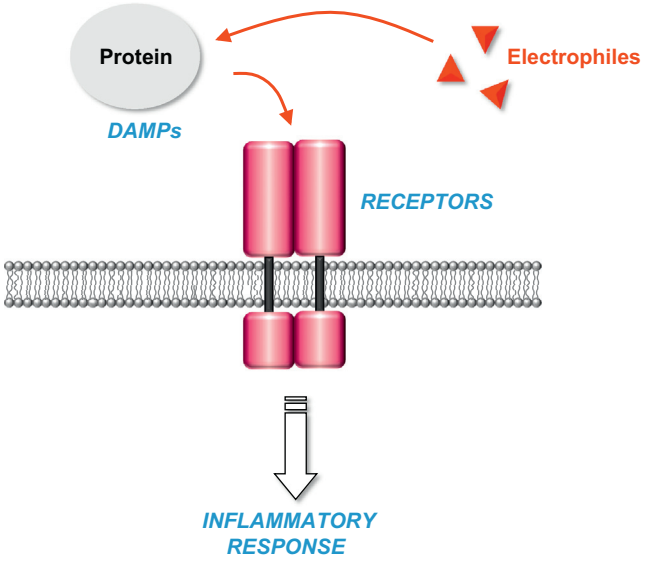

Fig. 3. Electrophile-derived DAMPs as a ligand of the PRRs. Electrophile-modified proteins represent DAMPs and trigger proinflammatory responses through binding to cellular PRRs.

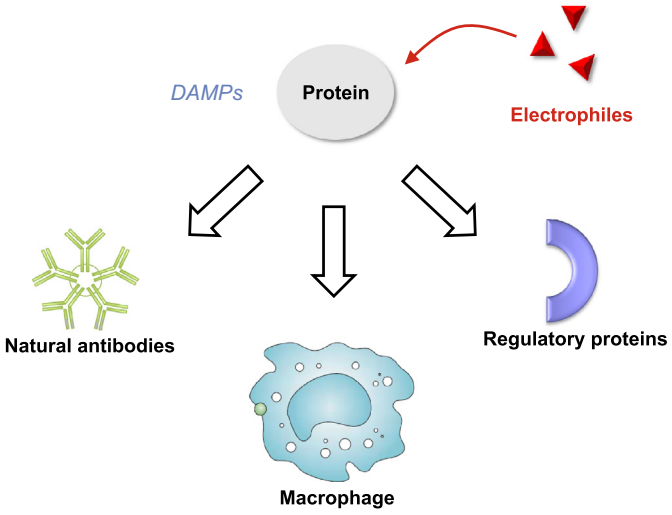

Fig. 2. Recognition of electrophile-derived DAMPs. This illustration is based on the hypothesis by Miller et al. Ref. [4], demonstrating that covalent modification of proteins by electrophiles yields DAMPs, accessible to recognition by natural antibodies, macrophage scavenger receptors, and regulatory proteins.

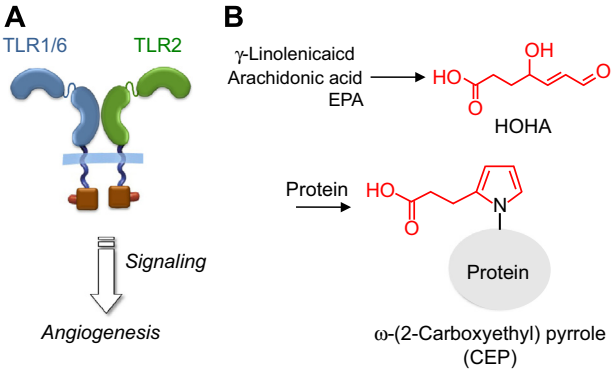

Fig. 4. A new function of TLR2 as an electrophile-derived DAMP, providing a key link connecting inflammation, oxidative stress, innate immunity and angiogenesis Ref. [10]. (A) Involvement of TLR signaling in angiogenesis. TLRs are PRRs that have a unique and essential function in animal immunity and has been shown to be involved in the recognition of a broad range of microbial products. The formation of heterodimers between TLR2 and either TLR1 or TLR6 dictates the specificity of ligand recognition. (B) Formation of ω-(2-carboxyethyl)pyrroles during lipid peroxidation modification of proteins. Oxidative stress generates lipid peroxidation products, including hydroxy-ω-oxoalkenoic acids (HOHA) and their esters. Reaction of unesterified HOHA with proteins gives rise to a family of carboxyalkylpyrrole protein adducts, among them ω-(2-carboxyethyl)pyrroles and similarly modified compounds.

autoimmune responses and tissue repair. It has been suggested that the DAMPs-mediated activation of the innate immune system has an important role in the pathogenesis of various immune and inflammatory diseases [9].

The key question is whether the lipid peroxidation modification of proteins plays a role in the innate immunity, especially, if any specific lipid peroxidation-derived adducts could function as DAMPs. Some of the adducts have been recently identified as a candidate ligand of PRRs, leading to downstream inflammation (Fig. 3). West et al. [10] reported that ω-(2-carboxyethyl)pyrrole and other related pyrroles, generated upon the reaction of proteins with unesterified hydroxy-ω-oxoalkenoic acids, are recognized by the Toll-like receptor 2, possibly in a complex with the Toll-like receptor 1/6, and promote angiogenesis *in vivo*, thereby contributing to accelerated wound healing and tissue recovery (Fig. 4). Kumano-Kuramochi et al. [11] recently demonstrated that the 4-hydroxy-2-nonenal (HNE)-histidine Michael adduct is formed as the major product in the oxidized LDL and that it has a significant affinity to one of the PRRs, i.e., the lectin-like oxidized LDL receptor-1 (LOX-1) (Fig. 5). Notably, the HNE-histidine adduct has been detected in the *in vitro* oxidized LDL as the major product (about 6 molecules per LDL molecule), suggesting the possibility that LOX-1 recognizes the adduct as the ligand in the oxidized LDL. LOX-1 has also been identified as a potential binding protein for other lipid peroxidation adducts, such as the 4-oxo-2-nonenal-lysine and 2-nonenal-lysine adducts [12,13]. On the other hand, Weismann et al. [14] identified the plasma complement factor H as a soluble PRR that could bind malondialdehyde (MDA)-modified proteins and block both the uptake of the MDA-modified proteins by macrophages and MDA-induced pro-inflammatory effects *in vivo* (Fig. 6). These studies suggest that the innate immunity has a pivotal role in providing homeostatic responses against lipid peroxidation-specific DAMPs.

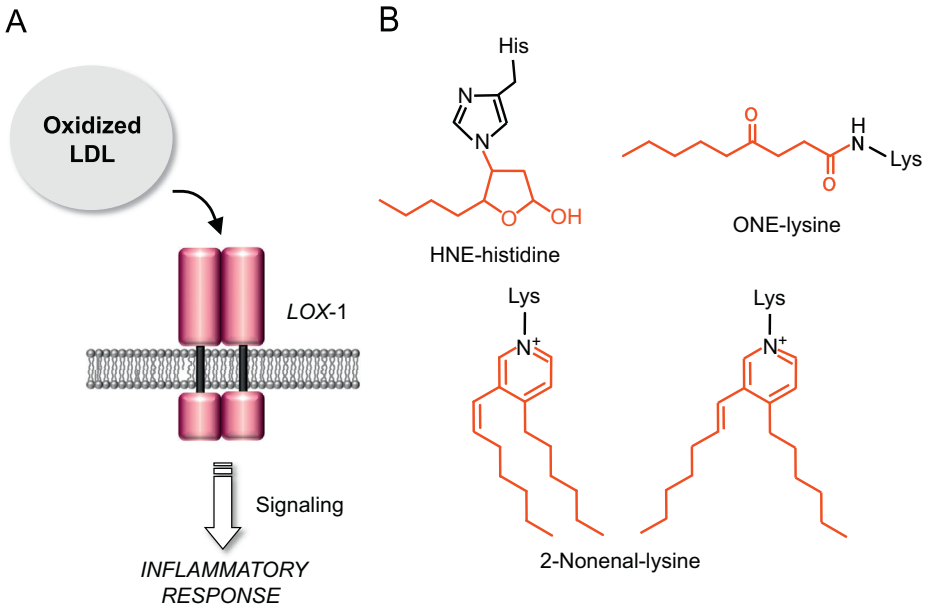

Fig. 5. Identification of electrophile-derived DAMPs as a ligand of LOX-1. (A) Activation of LOX-1 signaling by oxidized LDL. LOX-1 is an endothelial scavenger receptor that is important for the uptake of oxidized LDL and contributes to the pathogenesis of atherosclerosis. (B) The lipid peroxidation adducts identified as the ligand of LOX-1 Ref. [11–13].

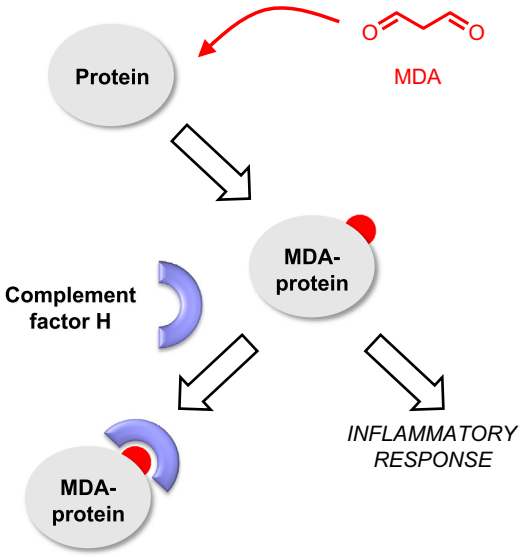

Fig. 6. Identification of electrophile-derived DAMPs as the ligand of a regulatory protein. MDA, among lipid peroxidation products, is the most abundant individual aldehyde resulting from lipid peroxidation. MDA occurs in biological materials in various covalently bound forms, such as protein-bound forms, which have been known to induce inflammatory responses and are recognized by innate immunity. Weismann et al. [14] recently identified complement factor H as a major regulatory protein that specifically binds MDA-modified proteins.

Lipid peroxidation plays a role in the pathogenesis of many types of tissue injuries and especially in the tissue damage induced by several toxic substances. In addition, lipid peroxidation has been implicated in the pathogenesis of numerous diseases including atherosclerosis. Several lipid peroxidation products, such as oxidized phosphatidylcholine, cardiolipin, and phosphatidylserine, have been identified as DAMPs [8]. They could be generated in the oxidized LDL and have been suggested to function as a ligand of the PRRs. However, a limited number of lipid peroxidation-derived adducts has been characterized as DAMPs. This may be a matter of primary concern, which represents an important direction to pursue involving lipid peroxidation in redox biology.

References

[1] E. Esterbauer, R.J. Schaur, H. Zollner, Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes, Free Radical Biology and Medicine 11 (1991) 81–128.
[2] K. Uchida, Role of reactive aldehyde in cardiovascular diseases, Free Radical Biology and Medicine 28 (2000) 1685–1696.
[3] K. Uchida, 4-Hydroxy-2-nonenal: a product and mediator of oxidative stress, Progress in Lipid Research 42 (2003) 318–343.
[4] Y.I. Miller, S.H. Choi, P. Wiesner, L. Fang, R. Harkewicz, K. Hartvigsen, A. Boullier, A. Gonen, C.J. Diehl, X. Que, E. Montano, P.X. Shaw, S. Tsimikas, C.J. Binder, J.L. Witztum, Oxidation-specific epitopes are danger-associated molecular patterns recognized by pattern recognition receptors of innate immunity, Circulation Research 108 (2011) 2348–2352.
[5] M.Y. Chou, L. Fogelstrand, K. Hartvigsen, L.F. Hansen, D. Woelkers, P.X. Shaw, J. Choi, T. Perkmann, F. Bäckhed, Y.I. Miller, S. Hörkkö, M. Corr, J.L. Witztum, C.J. Binder, Oxidation-specific epitopes are dominant targets of innate natural antibodies in mice and humans, Journal of Clinical Investigation 119 (2009) 1335–1349.
[6] D.L. Rosin, M.D. Okusa, Dangers within: DAMP responses to damage and cell death in kidney disease, Journal of the American Society of Nephrology 22 (2011) 416–425.
[7] C.A. Janeway Jr., R. Medzhitov, Innate immune recognition, Annual Review of Immunology 20 (2002) 197–216.
[8] D. Weismann, C.J. Binder, The innate immune response to products of phospholipid peroxidation, Biochimica et Biophysica Acta 1818 (2012) 2465–2475.
[9] M. Karin, T. Lawrence, V. Nizet, Innate immunity gone awry: linking microbial infections to chronic inflammation and cancer, Cell 124 (2006) 823–835.
[10] X.Z. West, N.L. Malinin, A.A.M. Merkulova, M. Tischenko, B.A. Kerr, E.C. Borde, E.A. Podrez, R.G. Salomon, T.V. Byzova, Oxidative stress induces angiogenesis by activating TLR2 with novel endogenous ligands, Nature 467 (2010) 972–976.
[11] M. Kumano-Kuramochi, Y. Shimozu, C. Wakita, M. Ohnishi-Kameyama, T. Shibata, S. Matsunaga, Y. Takano-Ishikawa, J. Watanabe, M. Goto, Q. Xie, S. Komba, K. Uchida, S. Machida, Identification of 4-hydroxy-2-nonenal-histidine adducts that serve as ligands for human lectin-like oxidized LDL receptor-1, Biochemical Journal 442 (2012) 171–180.
[12] T. Shibata, Y. Shimozu, C. Wakita, N. Shibata, M. Kobayashi, S. Machida, R. Kato, H. Itabe, X. Zhu, L.M. Sayre, K. Uchida, Lipid peroxidation modification of protein generates N^{ε}-(4-oxononanoyl)lysine as a pro-inflammatory ligand, Journal of Biological Chemistry 286 (2011) 19943–19957.
[13] K. Ishino, C. Wakita, T. Shibata, S. Toyokuni, S. Machida, S. Matsuda, T. Matsuda, K. Uchida, Lipid peroxidation generates a body odor component trans-2-nonenal covalently bound to protein in vivo, Journal of Biological Chemistry 285 (2010) 15302–15313.
[14] D. Weismann, K. Hartvigsen, K.N. Lauer, K.L. Bennett, H.P. Scholl, P. Charbel Issa, M. Cano, H. Brandstätter, S. Tsimikas, C. Skerka, G. Superti-Furga, J.T. Hand, P.F. Zipfel, J.L. Witztum, C.J. Binder, Complement factor H binds malondialdehyde epitopes and protects from oxidative stress, Nature 478 (2011) 76–81.