JOURNAL OF PROTEOMICS 92 (2013) 239–247

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/jprot

Review

Pathophysiological relevance of aldehydic protein modifications☆

Neven Zarkovic[a,*], Ana Cipak[a], Morana Jaganjac[a,b], Suzana Borovic[a], Kamelija Zarkovic[c]

[a]Laboratory for Oxidative Stress, Rudjer Boskovic Institute, Zagreb, Croatia
[b]Toxicology and Multipurpose Labs, Anti Doping Laboratory Qatar, Sports City Str., Doha, Qatar
[c]University of Zagreb, Department of Pathology, Medical Faculty, Clinical Hospital Centre Zagreb, Croatia

ARTICLE INFO

Article history:
Available online 22 February 2013

Keywords:
Non-enzymatic protein modifications
Oxidative stress
4-Hydroxy-2-nonenal (HNE)
Malondialdehyde (MDA)
Acrolein (ACR)
Immunochemistry

ABSTRACT

There is growing body of evidence that oxidative stress, i.e. excess in production of reactive oxygen species, can lead to covalent modification of proteins with bioactive aldehydes that are mostly produced under lipid peroxidation of polyunsaturated fatty acids. Thus generated reactive aldehydes are considered as second messengers of free radicals because they react with major bioactive macromolecules, in particular with various humoral and cellular proteins changing their structure and functions. Therefore, the aldehydic-protein adducts, in particular those involving 4-hydroxy-2-nonenal, malondialdehyde and acrolein can be valuable biomarkers of numerous pathophysiological processes. The development of immunochemical methods is increasing the possibilities to study such non-enzymatic protein modifications, on the one hand, while on the other hand the increase of knowledge on bioactivities of the aldehydes and their protein adducts might lead to better prevention, diagnosis and treatments of pathophysiological processes associated with lipid peroxidation and oxidative stress in general.
This article is part of a Special Issue entitled: Posttranslational Protein modifications in biology and Medicine.

Contents

☆ This article is part of a Special Issue entitled: Posttranslational Protein modifications in biology and Medicine.

* *Corresponding author at:* Division of Molecular Medicine, Rudjer Boskovic Institute, Bijenicka 54, 10000 Zagreb, Croatia. Tel.: +385 14560937; fax: +385 14561010.
E-mail address: zarkovic@irb.hr (N. Zarkovic).

1874-3919/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jprot.2013.02.004

1. Introduction

The most versatile macromolecules in organisms are proteins. They vary in structure and function, and are involved in essentially all biological processes. Some proteins are involved in immune protection or coordinate bodily activities, while others function as contractile, structural, storage and transport proteins or they act as catalysts. In most cells, synthesis of proteins and their degradation is tightly controlled. However, various factors (e.g. environmental) can lead to protein turnover. Modification of proteins can alter their structure and consequently also their function (e.g., protein–protein interactions, subcellular protein compartmentalization, changes in signaling pathways). Protein modifications include cleavage and formation of peptide bonds, modifications of amino acids at amino or carboxyl terminus or modification of specific amino acid side chain moieties [1]. There is growing body of evidence that oxidative stress, i.e. excess in production of reactive oxygen species (ROS), can lead to covalent modification of proteins with bioactive aldehydes that are mostly produced under lipid peroxidation (LPO) of polyunsaturated fatty acids [2], while oxidation and reduction of protein amino acid side chains occur in processes of cellular redox signaling and metabolic processes. Low levels of oxidative stress are usually associated with oxidation of sulfhydryl groups to mixed disulfides [3], which are, after the return of oxidative–reductive balance, reduced back to sulfhydryls, while in case if the proteins cannot be repaired they are destroyed by proteasomes and lysosomes [4]. However, higher levels of oxidative stress mainly lead to altered proteins that cannot be repaired. Such modified proteins accumulate in the cell, and consequently can lead to numerous pathological conditions and aging. Although oxidative stress associated diseases have been widely studied little is known about the protein chemistry that is involved. Madian and Regnier have reviewed that proteins can be oxidized in more than 35 different ways [3]. Roughly, these posttranslational modifications can be divided into three groups: (i) oxidative cleavage of protein backbone or amino acid side chains, (ii) adduction of proteins with end products of lipid peroxidation and (iii) carbonyl group formation in proteins by oxidation of advance glycation end products [3]. In this review we will focus on protein modification by lipid peroxidation derived reactive aldehydes, among which the most relevant because of their bioactivities and/or usefulness as pathophysiological biomarkers are 4-hydroxynonenal (HNE), malondialdehyde (MDA) and acrolein (ACR).

2. Lipid peroxidation

Pathophysiology of numerous diseases is associated with oxidative stress considered as disturbed cell homeostasis especially affecting cell redox status. Among molecules affected are also lipids, which undergo peroxidation; thereby changing membrane structure [5]. Consequently, altered lipids in cell membrane change its permeability and fluidity [6]. The end-products of lipid peroxidation are reactive aldehydes, which can further propagate oxidative damage [5]. These aldehydes, in particular HNE, are considered as second messengers of free radicals, because they bind to major biomolecules, especially proteins changing their structure and functions [7]. Indeed, proteins modified by LPO products are associated with numerous pathological processes associated with oxidative stress, such as cardiovascular, metabolic, autoimmune (neuro)degenerative and metabolic processes as well as with cancer [8]. Lipid peroxidation is often referred as autocatalytic non-enzymatic free-radical process, yet LPO can actually involve other mechanisms such as enzymatic and non-enzymatic non-radical peroxidation [9]. Accordingly, LPO can be induced by both, endogenous and exogenous factors: radical species, radical-initiating substances, metal ions, UV radiation, ROS, reactive nitrogen species (RNS), drugs (especially tumor chemotherapeutics) and enzymes [10]. Yet, the most extensively studied LPO mechanism is the free radical mediated non-enzymatic pathway. Among the most affected lipids by radical induced LPO are cholesterol and polyunsaturated fatty acid moiety of phospholipids. Peroxidation of lipids usually occurs in three phases: initiation, propagation and termination [11]. The first step is initiation, where radical species attack PUFA and abstract hydrogen, resulting in lipid radical. Here it should be noticed that PUFAs are in particular favorable as lipid radical formed is resonance stabilized. Next, propagation occurs, where reactive and unstable intermediates are formed. The chemistry follows: lipid radical reacts with oxygen giving lipoperoxyl radical, which in turn reacts with lipid resulting in formation of new lipid radical and lipid hydroperoxide. Lipid hydroperoxide is highly unstable and generates new peroxyl and alcoxyl radicals, which are further degraded to secondary products. As mentioned, oxysterols, hydroperoxides and endoperoxides are produced by LPO process. The latter are further fragmented into a variety of reactive α,β aldehydes (4-hydroxy-2-nonenal, HNE and acrolein, ACR), dialdehydes such as malondialdehyde (MDA), and glyoxal, and keto-aldehydes (4-oxo-trans-2-nonenal, ONE and isoketals) [5]. The biological relevance of these LPO end-products is reflected by the fact that linoleic acid (n−6 PUFA, C18:2), essential in mammals, and the most abundant in plants, and arachidonic acid (n−6 PUFA, C20:4), with a crucial role in inflammation, are both sources of HNE. Finally, the LPO end with the third phase, when radical species reacts with other radical giving non-radical or non-propagating species.

It should be mentioned that peroxidation of lipids can be both inhibited and prevented by antioxidative defense mechanisms in the cell [12]. Briefly, cells evolved enzymatic and non-enzymatic systems to prevent oxidative damage. Enzymatic cascades detoxify oxidants completely, with elimination of potentially harmful conjugates formed from the cell. The most