Redox Biology 2 (2014) 430–435

Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

Review Article

Redox regulation of protein damage in plasma

Helen R. Griffiths *, Irundika H.K. Dias, Rachel S. Willetts, Andrew Devitt

Life & Health Sciences and Aston Research Centre for Healthy Ageing, Aston University, Aston Triangle, Birmingham B4 7ET, UK

ARTICLE INFO

Article history:
Received 31 December 2013
Accepted 11 January 2014
Available online 20 January 2014

Keywords:
Oxidation
Nitration
Glycosylation
Ageing
Thioredoxin
Peroxiredoxin

ABSTRACT

The presence and concentrations of modified proteins circulating in plasma depend on rates of protein synthesis, modification and clearance. In early studies, the proteins most frequently analysed for damage were those which were more abundant in plasma (e.g. albumin and immunoglobulins) which exist at up to 10 orders of magnitude higher concentrations than other plasma proteins e.g. cytokines. However, advances in analytical techniques using mass spectrometry and immuno-affinity purification methods, have facilitated analysis of less abundant, modified proteins and the nature of modifications at specific sites is now being characterised. The damaging reactive species that cause protein modifications in plasma principally arise from reactive oxygen species (ROS) produced by NADPH oxidases (NOX), nitric oxide synthases (NOS) and oxygenase activities; reactive nitrogen species (RNS) from myeloperoxidase (MPO) and NOS activities; and hypochlorous acid from MPO. Secondary damage to proteins may be caused by oxidized lipids and glucose autooxidation.

In this review, we focus on redox regulatory control of those enzymes and processes which control protein maturation during synthesis, produce reactive species, repair and remove damaged plasma proteins. We have highlighted the potential for alterations in the extracellular redox compartment to regulate intracellular redox state and, conversely, for intracellular oxidative stress to alter the cellular secretome and composition of extracellular vesicles. Through secreted, redox-active regulatory molecules, changes in redox state may be transmitted to distant sites.

Contents

Abbreviations: BH4, tetrahydrobiopterin; CRP, C-reactive protein; COX, cyclo-oxygenase; ER, endoplasmic reticulum; ERO1, endoplasmic reticulum oxidoreductin 1; EV, extracellular vesicles; FX1, factor XI; GPI, glycoprotein 1; GPX, glutathione peroxidase; GRX, glutaredoxin; GSH, glutathione; MIRNA, microRNA; MPO, myeloperoxidase; NO, nitric oxide; NOS, nitric oxide synthase; NOX, NADPH oxidase; $O_2^{\cdot -}$, superoxide anion radical; ONOO-, peroxynitrite; PDI, protein disulphide isomerase; Prx, peroxiredoxin; RNS, reactive nitrogen species; ROS, reactive nitrogen species; Trx, thioredoxin; VWF, von Willebrand factor; XO, xanthine oxidase

* Corresponding author. Tel.: +44 121 204 3950.
E-mail address: h.r.griffiths@aston.ac.uk (H.R. Griffiths).

http://dx.doi.org/10.1016/j.redox.2014.01.010

Introduction

Plasma proteins perform a range of important physiological functions such as maintaining homeostatic blood volume, transporting other molecules for delivery at distant sites, through to regulating endocrine systems and inflammatory responses. With half-lives ranging from minutes to a month (Table 1) and with biosynthetic and turnover rates decreasing during ageing, their potential to accumulate damage differs markedly by protein and over time [1,2]. Consequently, modifications to plasma proteins may exert a range of diverse effects according to the sites of damage and are reported to increase in frequency with age, acute and chronic diseases. Therefore, modified proteins have the potential to serve as important biomarkers and may in turn signpost aetiological mechanisms [3]. An improved understanding of factors that influence the steady state concentrations of damaged proteins is important for evaluating their sensitivity as biomarkers and also their potential as targets for therapeutic interventions that prevent or repair or modifications. The focus of this review is on the role of redox regulation of steady state protein damage in plasma.

In reviewing the redox regulation of protein damage in plasma, we will consider (1) errors introduced in biosynthesis e.g. during ER stress that affect glycosylation, folding and secretion: (2) redox control of myeloperoxidase (MPO), NAPH oxidase isoforms (NOX), nitric oxide synthases (NOS), xanthine oxidase (XO) which increase protein exposure to reactive oxygen and nitrogen species (ROS, RNS) in the plasma and result in chlorination, nitration, nitrosylation, chlorination, methionine oxidation, disulphide formation, HNE-protein adducts: and (3) regulation of hepatic and macrophage receptors, extracellular reducing enzymes and proteins such as protein disulphide isomerase (PDI), thioredoxin1 (Trx1), peroxiredoxins (Prx) and oxidoreductases that affect steady state level of plasma protein damage.

Historically, the proteins analysed most frequently for damage were the more abundant plasma proteins (e.g. albumin and immunoglobulins) occurring at up to 10 orders of magnitude higher concentrations than other proteins found in plasma; more recently improved purification methods and higher sensitivity mass spectrometry techniques have enabled less abundant proteins to be examined [4].

Redox regulation in protein synthesis

There is little protein specificity for ROS and RNS, with reactions often proceeding at diffusion controlled rates, such that the proteins most likely to be damaged by ROS are those in closest proximity to their sites of production and at the highest concentrations.

During protein synthesis, secretory and membrane proteins co-translationally enter and are folded in the endoplasmic reticulum (ER) and Golgi. Oxidative disulphide bond formation and glycosylation facilitate correct protein folding prior to transport to the plasma membrane for export; misfolded ER proteins are recognised and unfolded by ER resident reductases and chaperones before undergoing retrotranslocation to the cytosol [5].

Oxidative maturation is achieved by highly regulated enzymatic transfer of two electrons [6]. The first conserved ER-resident oxidase in the pathway to be identified that generates disulphide at the expense of reducing oxygen is oxidoreductin 1 (Ero1) which occurs in two discretely regulated and distributed forms, alpha and beta; however, in contrast to observations in yeast, double Ero1 knockout animals show little phenotype. Indeed, normal ER redox conditions can be established after a strong reductive challenge, although this occurs more slowly than in wild-type cells, suggesting a role for other oxidative enzymes in disulphide formation [7]. One candidate family is the protein disulphide isomerases (there are 20 reported family members in mammalian cells) that include PDI, glutathione peroxidase (GPx) 7, GPx8 and which interact with Ero1alpha [8]. Ero1alpha activity is inhibited by an intramolecular disulphide switch between the active-site Cys94 and Cys131 and is re-activated by available reduced PDI. In support of this regulatory mechanism, overexpression of the mutant Ero1alpha-Cys131Ala which does not have a disulphide switch, leads to ER overoxidation [9]. In one of the first studies to identify specific oxidised thiol sites on intracellular proteins, using methoxypolyethylene glycol 5000 maleimide, Herzog-Appenzeller et al. showed that PDI is found in two semi-oxidised forms suggesting that either domain in human PDI can catalyse substrate oxidation and reduction [10]. Both isoforms of Ero1 facilitate the propagation of disulphides via PDI to nascent proteins and hence are crucial for oxidative maturation [11] in a process that is modulated by the glutathione (GSH)-oxidised GSH (GSSG) redox pair [12]. Other redox regulated enzymes that have been implicated in control of protein folding include; (a) Prx4 which can use luminal hydrogen peroxide to oxidise PDI and thereby favour oxidative folding but limit oxidative stress; and (b) vitamin K epoxide reductase in cooperation with membrane-bound Trx-like redox partners [13]. The extent of redundancy in the pathways for oxidative protein folding supports the importance of effective redox control in the biosynthesis of secreted proteins.

There are very few examples of loss of redox control in the ER which impact on the secretome. An early study by Lodish used DTT to explore the effect of a strongly reducing environment on the secretion of different proteins and found that only secretion of those with disulphide bonds was reversibly inhibited by DTT [14]. In contrast, a recent study describes that in astrocytes overexpressing mutant SOD1, total protein secretion was decreased although increased mutant SOD1-containing exosome release was observed, possibly to prevent intracellular aggregate formation [15]. It remains to be determined how the conventional ER secretory pathway is affected by SOD1 mutant and whether this is due to excess ROS. The extent to which exosome and microparticle (extracellular vesicles; EV) formation can influence protein damage or transport modified proteins is unknown, however, a few intriguing reports suggest that EV can induce redox signalling at distant sites [16–18] and that their

Table 1
Major plasma protein characteristics.

Plasma protein	Normal level	(%)	Function	Half-life
Albumin	3.5–5 g/dl	60	Create oncotic pressure Carry other molecules	17d
Immunoglobulins	1–1.5 g/dl	18	Acquired immune response	19–24 d in healthy subjects
Fibrinogen	0.2–0.45 g/dl	4	Blood clotting	3.5–5.5 d
α-globulins	0.15–0.35 g/dl	3	Anti-trypsin	62 h
	0.03–0.2 g/dl	2	Haptoglobin	8 h
β globulins	0.2–0.36 g/dl	4	Transferrin,	$<$ 24 h
	0.06 g/dl	1	High Density Lipoprotein	
	0.1 g/dl	2	Low density lipoproteins	
Hormones (e.g. norepinephrine)	0.6 NM		Promote stress response	2.5 min