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Minireview

Post-translational modifications disclose a dual role for redox stress in cardiovascular pathophysiology

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ABSTRACT

Although some of the redox changes that occur in biological components may result in deleterious events, this process has recently been tackled as a modulatory event. Advances in our understanding regarding the role of some oxidative/nitrosative reactions revealed that proteins can be structurally and functionally modified by chemical reactions, an epigenetic event known as post-translational modification (PTM). PTMs can function as an "on–off switch" for signaling cascades, and are dependent on the specific generation of redox components such as reactive oxygen species (ROS) and nitric oxide (NO). NO-driven modifications regulate a wide range of cellular processes and have been highlighted as an epigenetic event that protects proteins from proteolytic degradation. On the other hand, ROS-driven modifications are implicated in cell damage in a number of pathological conditions, especially in the cardiovascular system. Therefore, while mitochondrial uncoupling yields the massive production of ROS in the heart, some cellular redox-sensitive pathways trigger PTMs that may play a cardioprotective role. In this review, we present an overview of the oxidative/nitrosative milieu in cardiac pathologies and address the role of the main redox-driven PTMs as epigenetic events in cardioprotection, as well as its regulatory function in cardiomyocyte signaling. Improved understanding of the role of these PTMs in cardiovascular disease can help direct some approaches for future clinical research regarding health risk assessment, as well as inform strategies for disease treatment and prevention.

Contents

Post-translational modifications as regulatory epigenetic events

The human genome consists of about 21,000 genes; however, the number of distinct proteins produced is in the range of 1,000,000. This incompatible number is explained through the process of alternative splicing and, mainly, as a consequence of post-translational modifications (PTMs) [1, 2]. In general, protein modifications can be subdivided into two classes: amino acid modification and group attachment. Modifications in amino acids are in the form of small chemical moieties added to such residues, giving rise to PTMs, such as phosphorylation, acetylation, amidation, formylation, hydroxylation, farnesylation and sulfation.

Phosphorylation is the most common PTM. The phosphorylation process involves the reversible attachment of a phosphate ester in amino acid residues such as serine (Ser), threonine (Thr), and tyrosine (Tyr) [4]. Phosphorylation is a predominant process that drives

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intracellular signaling, in which phosphate is located in groups of protein families involved in specific responses to cellular stimuli. This signaling event usually begins with extracellular signal recognition by receptors coupled across the cell membrane, but can also occur by autophosphorylation [3]. Following exogenous stimuli, cell receptors can dimerize and promote cross phosphorylation of the cytosolic domain. Therefore, the phosphate groups are allowed to pass through by intracellular proteins known as signaling mediators, and generally end in effector proteins that function in metabolic processes, cytoskeleton modification, and transcriptional factors [5,6].

The life span of proteins is also regulated by PTMs, which assist in protein turnover and renewal. In some cases, protein degradation is essential for turn-off of a signaling pathway, such as in hypoxia signaling [7]. Ubiquitin (Ub), a 76-amino acid globular protein, is added to the proteins, resulting in their degradation [68]. This process in known as ubiquitination, and involves a family of Ub-conjugating proteins, represented by the letter E. An initial step in this method is the ATP-dependent activation of free Ub, allowing for formation of a thiol-ester linkage between the protein E1 (Ub-activating enzyme) and the carboxyl terminus of Ub. This is transferred to one of the 35 existing E2 (Ub-conjugating enzyme) enzymes. E2s associate with E3 (Ub protein ligase) enzymes, which direct the transfer to a final target protein. In cases where this does not occur, the Ubs in E3s are first transferred to the active-site cysteine of the HECT domain (homologous to the E6-AP carboxyl terminus), followed by transfer to the final protein substrate. This process drives mono- and multiple-Ub attachments to the target protein, and prepares it for degradation by proteasome [8]. Although ubiquitination mainly affects protein degradation, it is also known to participate in translation, activation of transcription factors, and assist in DNA repair protein function [9,10].

Some PTMs are derived from the attachment of chemical components produced physiologically inside the cells, such as the nitric oxide molecule (NO). NO-driven reactions give rise to several PTMs. S-nitrosylation is a PTM where the NO moiety is covalently attached to the free cysteine residues of the target protein. NO itself acts as an intracellular messenger, originating a wide range of reactive nitrogen species (RNS) [11]. S-nitrosylation is a reversible event, presenting a fast turnover, and is involved in many cellular processes such as gene expression control, protein stabilization, apoptosis, and autophagy. In addition, the S-nitrosylated proteins work as a source of NO for intracellular signaling [12].

Another PTM process is the oxidative modification of proteins, induced by the reaction of specific residues with reactive oxygen species (ROS) produced during situations of oxidative stress. Oxidation is a covalent PTM of the products generated by ROS, or the secondary products from oxidative stress, which are produced by the various metabolic processes. Oxidization can occur in several amino acid residues such as histidine, asparagine, lysine, tyrosine, and cysteine [13]. Depending on the type of oxidative modification (which mainly targets thiol residues), a wide range of amino acid sub-products are formed. In many cases, oxidative modifications are inhibited by enzymatic activity; it could even lead to loss of function in structural proteins. Oxidative PTMs are further associated with many chronic inflammatory diseases, including Alzheimer's disease, rheumatoid arthritis, cataracts, Parkinson's disease, and atherosclerosis [14–16].

PTMs are also facilitated by the addition of sugar molecules. While glycation and glycosylation may appear to be similar, the former is a non-enzymatic process, while the latter is enzyme-dependent [18]. Both are, however, described as covalent reactions of sugar molecules with proteins and lipids.

Glycation was first described in the Maillard reaction in the 1900s, and affects a number of pathological conditions such as diabetes, rheumatoid arthritis, and Alzheimer's disease [19]. This reaction is detected by the accumulation of advanced glycation end-products (AGEs), which are glycated residues formed in proteins and lipids after sugar exposition [20]. AGEs are formed as products of Schiff base reactions, Amadori rearrangements, as glycolytic intermediates (methylglyoxal and 3-deoxyglucosone), and lipid peroxidation (glyoxal and methylglyoxal) [17].

Glycosylation is the enzymatic adding of sugar residues to cellular molecules. This is a complex process in which multiple monosaccharides are linked to protein residues through a number of enzymatic reactions; it occurs in the Golgi complex and the endoplasmic reticulum, and is coordinated by glycosyltransferase enzymes. Glycosylated proteins (N-glycosylated) are important effectors of the structure and interactions of cell membranes and extracellular components [25,26]. Glycosylation is divided into 3 main classes: high-mannose, hybrids and complex glycans. The high-mannose glycans have unsubstituted mannose (5–9 residues) attached to the O-linked β-N-acetylglucosamine (O-GlcNac) core. Glycosylation with O-GlcNac modulates cell signaling by affecting transcription factors and cytoplasmatic proteins, such as nucleoporins and cytokeratins, and must represent the end of chain signal transduction in such cellular processes [21]. O-GlcNac has been also related with the physiopathology of chronic diseases such as neurodegeneration, cancer and diabetes [22].

Therefore, a wide range of PTMs are directly linked to oxidative stress, and little is known regarding the role of specific PTMs in the functioning of cardiac cells. Redox variations show a dual role in cardiac cells, since they can act as a source of damage, and can further promote the occurrence of cardioprotective modifications in the pivotal components of cardiac signaling. In the following sections, we review redox-mediated events in the heart as being causative agents of cardiac injury, and discuss how nitrosative PTMs help to protect the cardiac structures from damage.

Oxidative stress as a main cause of cardiac injury

Proteins are important targets of RS-driven PTMs. RS can directly attack protein residues or generate lipidic metabolites that react with proteins, resulting in reversible and irreversible PTMs. ROS-driven PTMs can be associated with loss of function via the carbonylation process; while NO-related PTMs have emerged as mechanisms for cell protection against deleterious oxidative damage [23]. Therefore, before discussing the role of PTMs in the heart, it is necessary to look deeper into the biochemistry of redox mediators involved in these processes.

The imbalance between RS production and its neutralization by antioxidant defenses is called oxidative stress. Under physiological conditions, low to moderate concentrations of ROS mediate physiological signaling. Damages to lipids, proteins, and DNA are known to occur when reactive species (RS) are not produced in an appropriate place, time, or level [27]. Therefore, oxidative stress is intimately involved in the pathogenesis of several pathologies, including cardiovascular diseases [28].

Some diseases are caused by an increase in RS generation, while in others, RS formation is secondary to the primary disease [29]. In this context, it is well known that cardiovascular complications are mainly prevalent during an advanced age [24,30]. Although the free radical theory of aging is still under debate and has not been conclusively proven [31,32], it dictates that RS production influences the lifespan [33,34]. Despite ROS regulation in normal cardiac functions [35], mitochondrial dysfunction leading to ROS overproduction is related to cardiovascular diseases [36].

For a long time, RS were only recognized as damaging species. In recent times, oxidant species have been discovered to mediate several signaling pathways and other biological processes [37,38]. The state of an oxidant must be substantial in order to define cellular fate [39], and ROS can even regulate several cellular responses. Under physiological conditions, the cells present a highly reduced potential. As RS levels rise, the cellular machinery can start some process as proliferation and phosphorylation, and conditions of greater oxidative stress there is the release of metal ions, increase in free calcium and mitochondrial