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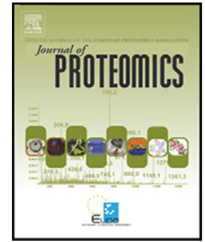

Invited Review

Redox proteomics and drug development

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ABSTRACT

As alterations of the redox homeostasis lie at the root of many pathophysiological processes in human health, redox proteomics holds the promise to shed further light on fundamental biological processes. In this review, the mechanisms of reactive oxygen species (ROS) and reactive nitrogen species (RNS) production are reviewed, mainly addressing those chemical phenomena which have already been associated with pathological conditions (of the central nervous system, cardiovascular system, or simply related to aging and altered-cell cycle regulation). From Alzheimer's to Parkinson's and Hungtinton's disease, from ageing to cancer, oxidative stress (OS) appears to represent a common trait in so many relevant biological aspects of human health, that further investments in the field of redox proteomics ought to be mandatory.
For the foreseeable future, redox proteomics will likely play a pivotal role in the quest for new therapeutical targets and their validation, in the process of determining OS-triggered cellular alteration upon drug treatments and thus in the very heart of the design and testing of new drugs and their metabolites against those pathologies relying on altered redox homeostasis.
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1. Introduction

Redox proteomics is an emerging branch of proteomics aimed at investigating oxidative-stress induced modifications of proteins. Oxidative injuries to proteins are produced by chemically reactive species. Modifications could address oxygen species and thus generate Reactive Oxygen Species (ROS), such as hydroxyl, peroxide and superoxide radicals, or produce mixed nitrogen-oxygen species (RNS), viz nitric oxide (NO) and peroxynitrite ($ONOO^{-}$).

The ROS/RNS are inevitably generated in metabolic pathways in all cells, and some of them might play important roles in cell signalling [1,2]. However, excessive levels of ROS from either the environment or aberrations in electron transport can produce such high levels of oxidative stress (OS) that large amounts of proteins can be irreparably altered [3]. Under chronic OS, damaged proteins can even accumulate up to reach toxic levels, often causing cell death as in a plethora of OS-associated physiological disorders and pathological diseases.

Among biomolecules, proteins are major targets of ROS/RNS thus complicating the whole proteome through side-chain modifications and covalent changes which have repercussions on protein activity, unfolding, degradation, as well as in cell functioning [4,5].

Thus, protein-oriented investigations upon prolonged OS-exposure, either under physiological or pathological conditions, are gaining momentum.

2. Redox proteomics: a brief look at the basics

Redox proteomics aims at detecting and analyzing redox-based changes within the proteome both in redox signalling scenarios and in OS [5]. The interested reader is referred to Table 1 for a rapid glimpse at the contents of this section, which is mainly focused on the assessment of oxidations/nitrosylations in thiol groups through gel-based and shotgun proteomic approaches and nitration on tyrosines. The basics of carbonylation-targeting redox proteomics are also briefly described.

2.1. *Oxidation/nitrosylation of cysteine thiol groups*

2.1.1. *Gel-based approaches*

To date, most of the proteomic studies of the oxidative stress response have used 2DE as a protein separation and quantification tool, coupled with mass spectrometry (MS) as a protein identification tool. Despite its weaknesses in the separation of certain protein categories (i.e. more hydrophobic and high molecular weight proteins, such as membrane proteins) and limitation in dynamic range, 2DE is still the best separation tool when dealing with redox-based protein changes. ROS/RNS add different footprints in the cells in the form of covalent modifications to proteins, thus it is often possible to reveal these changes by applying specific labelling followed by detection. A common strategy is to perform western blot analysis of proteins separated by 2DE [6].

Amongst the many kinds of amino acid residues susceptible to oxidative stress, cysteine is by far one of the most sensitive. Oxidation of its -SH groups can have functional significance by regulating protein function and can be the target of oxidative insult as well. For this reason, several experimental approaches have been developed for the systematic and exhaustive characterization of the so-called thiol proteome. One major limit in such an analysis is the chemical labile nature of Cys redox modifications, thus basically two critical steps are needed in analyzing the thiol proteome, which consist in a temporary trapping of free thiols and their subsequent reduction. Different strategies exist for quenching the thiol groups, ranging from the simple TCA (trichloroacetic acid)-based acidification [7] to the use of cell-permeable Cys-specific reagents such as the alkylating agents iodoacetamide (IAA) or N-ethylmaleimide (NEM) [8]. In this approach the subsequent use of more or less selective reducing agents will allow detection of a specific form of oxidation. For instance, cysteine residues in the sulfenic acid form are difficult to identify because of their unstable chemical nature, however this has been achieved by exclusive reduction of the sulfenic acid by sodium arsenite [9], or by its reaction with specific chemicals such as dimedone [10]. S-nitrosothiols are rather selectively reduced by ascorbate [11], whereas stronger reductants such as DTT reduce both nitrosothiols and disulfides. However, detection of protein S-nitrosylation is not easily performed with traditional gel-based methods such as immunoprecipitation and western blot analysis where the S—NO bond is broken during the electrophoresis step. On the other hand, commercially available anti-S-nitrosocysteine antibodies have been applied with good results only in immunohistochemistry studies [12,13] and little in the context of proteomics investigations.

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