The International Journal of Biochemistry & Cell Biology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

The International Journal of Biochemistry & Cell Biology

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

Review

Redox balance in cystic fibrosis☆

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ARTICLE INFO

Article history:
Received 20 January 2014
Received in revised form 28 February 2014
Accepted 11 March 2014
Available online xxx

Keywords:
Oxidative stress
CFTR
Nrf2 dysfunction
Antioxidants

ABSTRACT

The homeostatic balance between oxidants and antioxidants in biological systems is known as redox balance, and is regulated by complex processes. Redox balance regulates many of the known cellular pathways and disease processes. The dysregulation of redox balance can lead to acute or long-term oxidative or reductive stresses that are associated with many of the abnormalities observed in cystic fibrosis (CF). Over the past 5 decades researchers have examined contributors to redox dysregulation, their molecular products, and their impact on ion transport, cell proliferation, inflammation, bacterial killing, and the metabolism of nucleic acids, proteins, and lipids in CF. CF patients exhibit elevated markers of oxidative stress when compared to non-CF healthy controls; however, whether the reported redox imbalance is sufficient to produce pathology has been controversial. In addition, comparisons between CF and non-CF disease controls have been lacking. To better understand the mechanisms which mediate the generation of oxidants and antioxidants in CF and the importance of their balance in effecting oxidative or reductive stress, we will review the determinants of redox balance in the blood, lumen, and cellular compartments. From the perspective of methodological application, we will focus on the approaches most often used to study oxidant and antioxidants in CF, including biochemical, proteomic, metabolomic, and lipidomic studies, with a discussion of the few transcriptomic analyses that predict changes in the expression of regulators of redox. Finally, we will discuss the utility of oxidants and antioxidants as biomarkers of disease and the use of antioxidant therapy in CF.

This article is part of a Directed Issue entitled: Cystic Fibrosis: From o-mics to cell biology, physiology, and therapeutic advances.

Contents

Abbreviations: GSH, glutathione; GSSG, glutathione disulfide; Cys, cysteine; Cys–Cys, cystine; CFTR, cystic fibrosis transmembrane conductance regulator; Nrf2, nuclear factor erythroid 2 – related factor 2; Trx, thioredoxin; PRDX, peroxiredoxin; H_2O_2, hydrogen peroxide; ROS, reactive oxygen species; RNS, reactive nitrogen species.

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http://dx.doi.org/10.1016/j.biocel.2014.03.006
1357-2725/

Please cite this article in press as: Ziady AG, Hansen J. Redox balance in cystic fibrosis. Int J Biochem Cell Biol (2014), http://dx.doi.org/10.1016/j.biocel.2014.03.006

1. Introduction

The importance of the impact of oxidative stress on disease pathology has been steadily demonstrated over the past 5 decades. Increasingly, researchers have determined that a number of disease processes are very sensitive to oxidants and changes in redox balance (the homeostatic balance between oxidizing and reducing (antioxidant) equivalents, as discussed below under the *Redox balance* section). Even in the absence of disease, most known cellular pathways are significantly modulated (or regulated) by changes in redox balance. Cystic fibrosis is caused by mutations in a gene that codes for the cystic transmembrane conductance regulator, and is marked by abnormalities in ion transport, cell proliferation, inflammatory signaling, bacterial killing, and the metabolism of lipids, proteins, and nucleic acids. Many of these disease-causing processes are modulated by oxidants and antioxidants. Therefore, the study of oxidants, antioxidants, and the mechanisms that regulate redox balance in CF is logical.

In the context of CF, many studies have reported significant increases in the products of oxidation in patients and laboratory models since the late 1970s. These findings have encouraged the notion of redox imbalance in CF, which was first reviewed by Winklhofer-Roob (1994), and continues to be an area of interest. However, acute changes in oxidants and antioxidants are part of normal physiology, and do not necessarily entrain disease. In order to precipitate a pathological condition, such as oxidant-induced chronic inflammation, biological systems have to experience a sustained imbalance between oxidants and antioxidants. For example, oxidative stress can be caused by acute events such as infection or exposure to toxins which resolves with termination of the threat to homeostasis. In the case of progressive diseases such as chronic obstructive pulmonary disease (COPD) and CF, chronic redox imbalances favor an oxidizing environment which is hypothesized to precipitate the disease state. In the chronic state, an oxidizing environment can cause oxidation of DNA, proteins, lipids, and other metabolites, which subsequently alter signaling cascades and change the levels of oxidizing and reducing equivalents. Although these Gestalt level interactions precipitate the disease state, to improve detail and focus scope the majority of studies in CF have investigated individual molecules (oxidants, antioxidants, or products of oxidation), and have not examined the complex regulation of intracellular and extracellular redox balance. Consequently, the question of whether persistent oxidative stress exists in CF has not been definitively answered.

Traditionally, the study of oxidants and antioxidants in CF, which began in the late 1970s, has employed biochemical approaches. More recently, the use of gene array technology has allowed for the examination of genes that regulate redox balance. A significant methodological shift in the study of CF occurred with the advent of electrospray ionization technology that allows for direct mass spectrometric examination of oxidants and antioxidants, the proteins that regulate their production, and the various targets of redox modification (nucleic acids, lipids, proteins, and metabolites). Although mass spectrometry (MS) based approaches, such as proteomics, lipidomics, and metabolomics hold much promise for studies of oxidants and antioxidants in CF, only a small number of studies have been reported. Therefore, we will review the predominantly biochemical work as well as the MS-based studies, with the aim of giving the reader a summary of the field as well as providing a solid background of areas where omics approaches can be applied. We will begin with a discussion of redox balance to provide the critical framework for the reader to understand oxidants and antioxidants in a physiological context. Moreover, because the determinants of redox balance significantly differ in different milieus, we will review mainly animal and human studies of oxidants and antioxidants in the context of three compartments; the blood, the cell (the predominant work is in airway epithelia), and the lumen.

2. Redox balance

The production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) is a necessary physiological process that modulates many cellular functions. For example, both tumor necrosis factor (TNF) α (Li et al., 2009) and interleukin (IL)-1β (Li and Engelhardt, 2006) mediated activations of NF-κB and subsequent inflammatory signaling have been shown to be hydrogen peroxide (H_2O_2) dependent. Peroxide enhances the phosphorylation and subsequent activation of IκB kinases leading to the increased phosphorylation of IκB, its subsequent degradation, and the increased activation of NF-κB (Kamata et al., 2002). A large number of other signaling cascades, including those of AP1, MAPK, and JNK are similarly regulated. To manage signaling through these and other pathways, cells use a complex and tightly regulated balancing system to control the effects of oxidants and antioxidants. This is the system of redox balance. Normal and efficient signaling is dependent on shortly lived imbalances that result in short term oxidation or reduction of biological molecules that affect various cellular functions. However, oxidative or reductive stresses, which contribute to disease pathology, can arise when increases in the production of ROS and/or RNS are poorly balanced by antioxidants, resulting in a disruption the cellular homeostasis of oxidizing and reducing equivalents.

Generally, oxidizing and reducing equivalents are balanced in ratios to regulate appropriate cell function (Fig. 1). Balance is achieved through antioxidant systems, enzymes and metabolic processes, which are ultimately critical to cell viability. Exposure to various environmental or pharmacological insults can alter ratios to cause an imbalance of oxidizing and reducing equivalents. This observation provides much of the rationale for more classical definition of oxidative stress that was coined nearly 35 years ago by Helmut Sies: "... a disturbance in the prooxidant-antioxidant balance in favor of the former" (Cadenas and Sies, 1985). There are a number of different systems in place that actively restore balance to intracellular environments during periods of oxidative imbalance, which must occur in a timely fashion to prevent cellular dysfunction and cell death. It should be noted that prolonged periods of oxidative stress require relatively high levels of mild oxidant, such as H_2O_2, to elicit cell death, while strong oxidants such as sodium hypochlorite (NaOCl) and hydroxyl ions (•OH) can induce cytotoxicity at low levels. Physiologically, ratiometric shifts of the reducing and oxidizing equivalent (redox) balance are much more likely to cause changes to intracellular signaling before overt cytotoxicity (Fig. 2).

2.1. Advances in understanding oxidative stress

Since its original definition, oxidative stress has been primarily viewed as global changes to oxidizing and reducing equivalents

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