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Review

Redox stress and signaling during vertebrate embryonic development: Regulation and responses☆

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ABSTRACT

Vertebrate embryonic development requires specific signaling events that regulate cell proliferation and differentiation to occur at the correct place and the correct time in order to build a healthy embryo. Signaling pathways are sensitive to perturbations of the endogenous redox state, and are also susceptible to modulation by reactive species and antioxidant defenses, contributing to a spectrum of passive vs. active effects that can affect redox signaling and redox stress. Here we take a multi-level, integrative approach to discuss the importance of redox status for vertebrate developmental signaling pathways and cell fate decisions, with a focus on glutathione/glutathione disulfide, thioredoxin, and cysteine/cystine redox potentials and the implications for protein function in development. We present a tissue-specific example of the important role that reactive species play in pancreatic development and metabolic regulation. We discuss NFE2L2 (also known as NRF2) and related proteins, their roles in redox signaling, and their regulation of glutathione during development. Finally, we provide examples of xenobiotic compounds that disrupt redox signaling in the context of vertebrate embryonic development. Collectively, this review provides a systems-level perspective on the innate and inducible antioxidant defenses, as well as their roles in maintaining redox balance during chemical exposures that occur in critical windows of development.

Contents

Abbreviations: ARE, antioxidant response element; BSO, buthionine sulfoximine; E_h, redox potential; GCL, glutamylcysteinyl ligase; GRX, glutaredoxin; GSH, glutathione; GSR, glutathione reductase; GSS, glutathione synthetase; GSSG, glutathione disulfide; Keap1, Kelch-like ECH-associated protein 1; NAC, *N*-acetyl cysteine; Nrf2, nuclear factor (erythroid-derived 2)-like 2; OSR, oxidative stress response; PDX1, pancreatic and duodenal homeobox 1; ROS, reactive oxygen species; TRX, thioredoxin.

☆ When referring to gene and proteins we adhere to the Zebrafish Nomenclature Guidelines (https://wiki.zfin.org/display/general/ZFIN+Zebrafish+Nomenclature+Guidelines#ZFINZebrafishNomenclatureGuidelines-2). Briefly, genes and proteins from different organisms are presented as such: zebrafish *gene*/Protein, mouse *Gene*/PROTEIN, and human *GENE*/PROTEIN. In cases where no specific model system is being addressed we use the human nomenclature.

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1. Introduction

Embryonic development is a complex and highly choreographed process, requiring exquisite temporal and spatial regulation. The challenge to the embryo is not only to control this process but also to shield it from being disrupted by internal or external stressors. Vertebrate embryos have evolved to be especially resilient to perturbation, through what has been called the "intrinsic robustness of developmental programs" in the face of a variable environment [1]. At the same time, experimental studies often show that embryonic and larval stages are among the most sensitive to adverse effects of chemicals (reviewed in [2–6]). The sensitivity of developing animals to chemical toxicants likely results from the complex nature of developmental processes combined with innate and inducible mechanisms that protect against toxic outcomes; for example, xenobiotic-metabolizing and anti-oxidant enzyme systems) are typically not yet fully functional in developing animals [2].

Redox signaling is an important component of developmental processes, and redox status is tightly regulated during development [7–10]. Consequently, disruption of redox status through generation of reactive oxygen species (ROS) or otherwise altering the control of intracellular redox potential (i.e. causing redox stress [11–15]) can interfere with these developmental processes. These disruptions can include altered cell fate decisions that can lead to structural and functional changes in developing animals [9], including in specific tissues such as the pancreas [16].

In this review, we take a multi-level, integrative approach to discuss the roles and regulation of redox signaling during development and its disruption by xenobiotic chemicals. We first summarize the importance of redox signaling and the consequences for developmental outcomes. We provide an overview of biochemical redox systems and modifications, and discuss a class of transcription factors important in the molecular regulation of redox signaling. While there are numerous redox-sensitive cell types, we examine a tissue-level example in which redox modulations affect the development and function of the pancreas. Finally, we provide specific examples of agents that disrupt redox signaling and control in developing vertebrates that result in adverse outcomes. Overall, this review provides a systems-level perspective on innate and inducible antioxidant defenses and their roles in helping to maintain redox balance in the face of chemical threats during the developmental period.

2. Redox signaling vs. stress during development

Intracellular ROS are important components of signaling cascades and regulate numerous physiological processes critical to embryonic development [17–19]. ROS are classically defined as oxygen-containing molecules with an unpaired electron such as hydroxyl radicals ($^{\bullet}OH$) and superoxide ($O2^{\bullet}-$). However, this definition has been expanded to include nonradical oxygen-containing molecules such as hydrogen peroxide (H_2O_2). The realm of ROS is further expanded when one considers interactions with other molecular structures containing nitrogen or sulphur. For a detailed discussion of the classification of ROS and free radicals we refer the interested reader to the excellent review by Sies et al. [12]. We consider here the impact of reactive species, i.e. oxidants, on redox signaling and the adaptive and adverse outcomes that can result from oxidant stress.

The effects of reactive species are modulated by the presence of robust and diverse antioxidant defenses and the homeostatic redox state of these systems. These vary depending upon the source of the oxidant, the cellular compartment in which they occur, and the proximity of a favorable electron donor. Glutathione, among other antioxidant defenses, has been shown to have specific and sometimes compartmentalized characteristics. For example, GSH redox potential (E_h) in the cytoplasm is different from that in the mitochondria and that in the nucleus [20,21]. Another critical component that determines the fate of a reactive species is whether the reactive species is a primary vs. secondary oxidant [22]. Primary oxidants are regulated by catalase, peroxidases, and superoxide dismutase; this regulation allows for specific functions within signaling pathways. Secondary oxidants are defined as those that are not well mitigated or controlled, such as the actions of hydroxyl radicals and protein or lipid-based radicals [22]. Collectively, the nature of the reactive species along with the state of antioxidant defenses determines what kind of redox stress or signaling effects will occur.

Redox signaling and redox stress [12–15] can either be active (specific) or passive (non-specific) in nature, with active effects targeting specific signaling pathways, and passive effects causing damage to macromolecules [7]. Taking this idea a step further (Fig. 1), reactive species can cause physiologic effects such as prompting cell fate decisions [23] or stimulating insulin secretion in pancreatic beta cells [24], among numerous other effects. Responses can also be adaptive in nature, such as the upregulation of enzymes involved in GSH synthesis and utilization, or through induction of other cytoprotective systems. On the other end of the spectrum, passive damage to macromolecules can cause adverse or toxic responses including cell death or loss of function. It is therefore important to distinguish between redox signaling and redox stress in these effects, particularly in the context of embryonic development.

In the context of embryonic development, it may be more appropriate to use the term "redox stress" [12–15] instead of "oxidative stress." Often it is the change in redox status of a specific couple, not necessarily whether it is oxidative or reductive, that is important in causing stress in the embryo. For example, the GSH E_h changes dynamically at specific stages of development [25,26], it is not a

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