Molecular Aspects of Medicine xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Molecular Aspects of Medicine

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

Redox control in cancer development and progression

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ARTICLE INFO

Keywords:
Reactive oxygen species
Cancer development
Cancer progression
Redox-sensitive transcription factor
Antioxidants
Redox dependent epigenetic modifications

ABSTRACT

Cancer is the leading cause of death worldwide after cardiovascular diseases. This has been the case for the last few decades despite there being an increase in the number of cancer treatments. One reason for the apparent lack of drug effectiveness might be, at least in part, due to unspecificity for tumors; which often leads to substantial side effects. One way to improve the treatment of cancer is to increase the specificity of the treatment in accordance with the concept of individualized medicine. This will help to prevent further progression of an existing cancer or even to reduce the tumor burden. Alternatively it would be much more attractive and efficient to prevent the development of cancer in the first place. Therefore, it is important to understand the risk factors and the mechanisms of carcinogenesis in detail. One such risk factor, often associated with tumorigenesis and tumor progression, is an increased abundance of reactive oxygen species (ROS) arising from an imbalance of ROS-producing and -eliminating components. A surplus of ROS can induce oxidative damage of macromolecules including proteins, lipids and DNA. In contrast, ROS are essential for an adequate signal transduction and are known to regulate crucial cellular processes like cellular quiescence, differentiation and even apoptosis. Therefore, regulated ROS-formation at physiological levels can inhibit tumor formation and progression. With this review we provide an overview on the current knowledge of redox control in cancer development and progression.

Introduction

According to the World Health Organization (WHO), cancer burden and cancer-related death will rise by 70% within the next two decades (World Health Organization). Cancer is a hyper-proliferative and complex disease which arises from a multistep process called carcinogenesis in which the initiation phase is followed by a promotion and a progression phase (Berenblum and Shubik, 1947). The initial step is induced by an accumulation of unrepaired genomic mutations or epigenetic modifications such as DNA methylation or histone acetylation (Franco et al., 2008). Mutations, which initiate cancer, can develop spontaneously through replication defects (W. H. Freeman, 2000) or chemical and physical carcinogens, which are able to facilitate the production of reactive oxygen species (ROS). An uncontrolled increase of ROS formation can induce damage of macromolecules including DNA, proteins and lipids resulting in genomic instability and changes in cell growth. ROS can modulate cell cycle progression by influencing the activity of proteins such as cyclin-dependent kinase inhibitor p21 (Barnouin et al., 2002) or the serine/threonine protein kinase *ataxia telangiectasis mutated* (ATM) (He et al., 2011). ATM, in turn, is essential for DNA repair and influences cellular signaling important for proliferation and apoptosis such as the Akt (Halaby et al., 2008) or p53 pathway (Cheng and Chen, 2010).

Despite the obvious influence of ROS on cancer development and progression, treatment of cancer patients with antioxidants failed to improve and, in some cases, even impaired the outcome of the disease (DeNicola et al., 2011). Additionally, it is extremely important to distinguish between progression of an existing tumor and the formation of a new tumor when discussing the role of ROS in cancer. In fact, it appears that ROS play a dual role: increased ROS-levels can result in DNA damage and thereby lead to malignant transformation, whereas physiological levels seem to be essential for the prevention of cancer formation.

With this review we aim to provide an overview on how ROS influence cancer development and progression.

Sources of reactive oxygen species and anti-oxidative systems

Quantitatively, mitochondria generate the highest level of ROS (Holmström and Finkel, 2014). In the course of ATP generation by these organelles, superoxide anions ($\bullet O_2^-$) are produced as a byproduct, depending on the electron load and efficacy of the individual complexes of the respiratory chain. Besides mitochondria, many enzymes exist that produce ROS. Those are, namely, xanthine oxidase, cytochrome P450

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https://doi.org/10.1016/j.mam.2018.02.003
Received 26 January 2018; Received in revised form 26 February 2018; Accepted 26 February 2018

monooxygenases, cyclooxygenase and NADPH oxidases (Nox). Among them the family of NADPH oxidase is the only one having ROS formation as its sole function. The family of Nox enzymes consists of 7 members, Nox1-Nox5 and Duox1/2. Those 7 members; all of which produce ROS at distinct sites in the cell and are specialized to produce certain kinds of ROS. While Nox1-3 and 5 produce $\bullet O_2^-$, Nox4 directly forms hydrogen peroxide (H_2O_2) as well as the Duoxes (Deken et al., 2014; Schröder, 2010). This mixed bunch of ROS producing enzymes implies that ROS, depending on their species and site of formation, fulfill useful tasks, such as serving as second messengers.

Besides a more or less controlled physiological ROS formation, exogenous stimuli contribute to an increased ROS production in stress conditions and in the course of host defense. For example; UV radiation increases the amount of mitochondria derived $\bullet O_2^-$ (Yamamori et al., 2012) and pattern recognition patterns on pathogens induce Nox2 derived $\bullet O_2^-$ production and the oxidative burst in phagocytic cells (Torres et al., 2006).

ROS themselves are a group of oxygen derivatives, produced by the partial reduction of oxygen (Ray et al., 2012). Depending on their site of production and surrounding environment, the produced ROS can interact with each other and various other molecules (Fig. 1). Some ROS e.g. H_2O_2, are relatively stable and can diffuse within and between cells (Bienert et al., 2006). Additionally a transport via aquaporins has been described for H_2O_2 (Hara-Chikuma et al., 2015). Other reaction products such as $\bullet O_2^-$ or hydroxyl radicals (•OH) hold one unpaired electron, which limits their diffusion across cell membranes. These free radicals are relatively unstable and highly reactive, resulting in their potential harmful characteristics. One of the best characterized reactions of $\bullet O_2^-$ is the reaction with nitric oxide (•NO) derived from NO-Synthases (NOS). The subsequently formed peroxynitrite ($ONOO^-$) oxidizes tetrahydrobiopterin, the cofactor of endothelial nitric oxide synthase. Consequently, NOS is uncoupled which favors the production of $\bullet O_2^-$ by this enzyme (Harrison et al., 2010). In the Haber-Weiss reaction, catalyzed by free transition metal ions, the H_2O_2 and $\bullet O_2^-$ are reduced to •OH which has the highest oxidative potential (Manea, 2010).

The potential harm induced by ROS is prevented by their tightly controlled and highly efficient degradation. $\bullet O_2^-$ is processed into H_2O_2 either spontaneously or enzymatically catalyzed by superoxide dismutase (SODs: soluble Copper/Zinc-SOD (SOD1), mitochondrial Manganese-SOD (SOD2) and extracellular Copper/Zinc-SOD (SOD3)). H_2O_2 is further decomposed by catalase or glutathione peroxidase (GPX) that oxidizes glutathione (GSH) which is reduced back by glutathione reductase under NADPH consumption (Brigelius-Flohé and Maiorino, 2013). Peroxiredoxins (Prx) reduce H_2O_2 to water using NADPH, thereby becoming oxidized themselves (Rhee et al., 2012). Thioredoxins (TRX) facilitate the reduction of oxidized Prx (Fig. 1). In addition to the enzymatic systems, there exist non-enzymatic compounds (so called anti-oxidants) such as α-Tocopherol, ascorbate and lipoic acid that undergo oxidation when reacting with the substrate.

Regulation of gene expression in cancer

Normal somatic cells strongly differ with regards to their metabolic demand, motility and proliferative capacity amongst many other cellular functions. Cancer cells can boost their anti-apoptotic mechanisms to evade cell death by activating a specialized gene expression profile. Accordingly, those cancer gene profiles differ from the ones of the originating or precursor cells. The following section will highlight some redox-sensitive mechanisms related to gene expression.

Redox-sensitive transcription factors in cancer

One important transcription factor in cancer is hypoxia-inducible-factor-1α (Hif-1α). Hif1α is constantly produced and immediately degraded by the proteasome. Elevated levels of ROS in prostate and ovarian cancer cells maintain Hif-1α and the expression of its major downstream target vascular endothelial growth factor (VEGF) (Xia et al., 2007). Although it remains uncertain how ROS regulate Hif1α activity, Nox4 is a potential candidate for keeping Hif1α abundance stable (Zhang et al., 2010). An increase in the Hif1α/VEGF axis enables more efficient angiogenesis in an existing tumor, such as a fibro sarcoma (Helfinger et al., 2016).

NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex that controls transcription of DNA, cytokine production and cell survival. NF-κB is a transcription factor which becomes activated upon dissociation from its inhibitor IκB, which is then degraded through the proteasome. Prevention of NF-κB activation by the proteasome inhibitor bortezomib induces apoptosis in gastric cancer cells and simultaneously induces ROS generation (Nakata et al., 2011). Activation of NF-κB in turn can be facilitated in a redox dependent manner via pyruvate dehydrogenase kinase 1 (PDK1). By that mechanism epithelial growth factor receptor (EGFR) facilitates proproliferative effects, which forces the formation of pancreatic precancerous lesions in a KRas mouse model (Liou et al., 2016). Nox4 is described to contribute to NF-κB activation in melanoma cells, thus combating apoptosis and promoting cancer development (Fried and Arbiser, 2008). In addition to cell survival/proliferation, invasion can also be affected by NF-κB. Bonner et al. demonstrated that Nox1-derived ROS contribute to cancer cell invasion by increasing NF-κB translocation into the nucleus and subsequent expression of the matrix metalloprotease-9 (MMP-9) (Bonner and Arbiser, 2012).

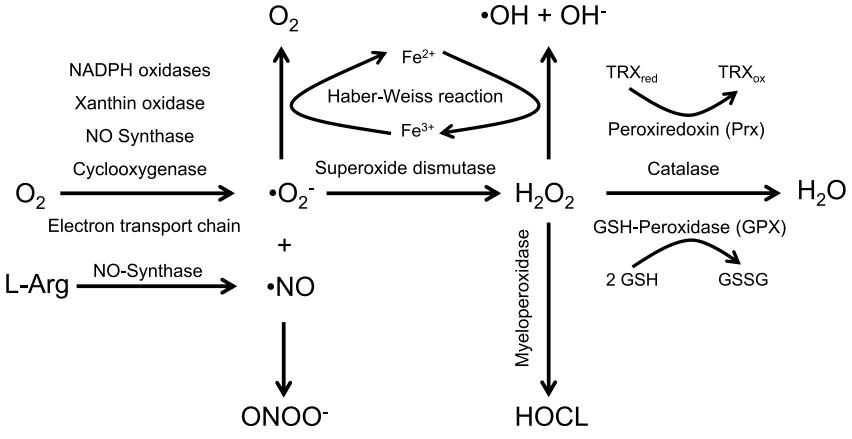

Fig. 1. Sources of reactive oxygen species and their conversion.
The figure shows endogenous and exogenous sources of various reactive oxygen species and their possible interaction partners or conversion. Additionally antioxidant systems and the Haber Weiss reaction are introduced. Details of the figure are listed and explained in the text.