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Mini Review

The redox biology network in cancer pathophysiology and therapeutics

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ABSTRACT

The review pinpoints operational concepts related to the redox biology network applied to the pathophysiology and therapeutics of solid tumors. A sophisticated network of intrinsic and extrinsic cues, integrated in the tumor niche, drives tumorigenesis and tumor progression. Critical mutations and distorted redox signaling pathways orchestrate pathologic events inside cancer cells, resulting in resistance to stress and death signals, aberrant proliferation and efficient repair mechanisms. Additionally, the complex inter-cellular crosstalk within the tumor niche, mediated by cytokines, redox-sensitive danger signals (HMGB1) and exosomes, under the pressure of multiple stresses (oxidative, inflammatory, metabolic), greatly contributes to the malignant phenotype. The tumor-associated inflammatory stress and its suppressive action on the anti-tumor immune response are highlighted. We further emphasize that ROS may act either as supporter or enemy of cancer cells, depending on the context. Oxidative stress-based therapies, such as radiotherapy and photodynamic therapy, take advantage of the cytotoxic face of ROS for killing tumor cells by a non-physiologically sudden, localized and intense oxidative burst. The type of tumor cell death elicited by these therapies is discussed. Therapy outcome depends on the differential sensitivity to oxidative stress of particular tumor cells, such as cancer stem cells, and therefore co-therapies that transiently down-regulate their intrinsic antioxidant system hold great promise. We draw attention on the consequences of the damage signals delivered by oxidative stress-injured cells to neighboring and distant cells, and emphasize the benefits of therapeutically triggered immunologic cell death in metastatic cancer. An integrative approach should be applied when designing therapeutic strategies in cancer, taking into consideration the mutational, metabolic, inflammatory and oxidative status of tumor cells, cellular heterogeneity and the hypoxia map in the tumor niche, along with the adjoining and systemic effects of oxidative stress-based therapies.

Contents

Abbreviations: BER, base excision repair; CSC, cancer stem cells; DAMPs, danger-associated molecular patterns; DDR, DNA damage response; EGFR, epidermal growth factor receptor; HMGB1, high-mobility Group Box 1; HR, homologous recombination repair; IR, ionizing radiation; LET, linear energy transfer; PDT, photodynamic therapy; PS, photosensitizer; ROS, reactive oxygen species; SNP, single-nucleotide polymorphism; Treg, T regulatory cell

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1. Introduction

Cancer is one of the main causes of death worldwide (see WHO database at http://www-dep.iarc.fr/WHOdb/WHOdb.htm). It brings a considerable economic and social burden despite intensive research for deciphering its molecular mechanisms, and for developing targeted therapeutic strategies using the personalized medicine concept.

This review aims to summarize currently operational concepts on the critical role of the intrinsic and microenvironmental oxidative stress in sustaining cancer development and spreading. We are particularly highlighting that reactive oxygen species (ROS) may not only act as supporters of tumor cells, but can be turned into their enemy that may be highly efficacious in cancer treatment.

It has been long proven that cancer cells display a pro-oxidative shift [1] generated by: (1) chronic activation of various metabolic sources of ROS, related to NADPH oxidases (NOXs 1–5 and dual oxidases DUOX1/2) [2], alterations of mitochondrial DNA, oxidative phosphorylation and energy metabolism, accompanied by enhanced aerobic glycolysis [3]; (2) a dysfunctional antioxidant response that is unable to counteract sustained production of ROS during tumorigenesis [4]. This intracellular oxidative turmoil is complemented by constant exposure of cancer cells to exogenous ROS derived from anoxia-reoxygenation cycles [5], and from the oxidative activity of tumor-infiltrating monocytes and neutrophils [6].

Starting from the insidious oxidative stress in the tumor microenvironment, the review pinpoints without aiming to be exhaustive key genetic alterations and repair mechanisms, along with critical turning points in redox signaling pathways, that confer a survival advantage to cancer cells. Cancer is not a "all-or-none" process, but integrates various cues into a pathologic network of events and cellular responses in the tumor niche under the pressure of multiple stresses (oxidative and inflammatory).

The therapeutic use of the cytotoxic face of ROS is exemplified by oxidative stress-based therapies, such as the radiotherapy and photodynamic therapy. The mechanisms underlying the resistance to an oxidative attack of particular cancer cells, such as cancer steam cells, are highlighted. Finally, we show that the effects of oxidative stress-based therapies go beyond local cytotoxicity, being propagated in the close vicinity and having even a systemic echo mediated by the immune response.

2. Oxidative stress-induced genetic alterations and repair mechanisms in cancer cells

Depending on its intensity and intracellular localization, oxidative stress can alter mitochondrial and nuclear DNA. DNA damage may include point mutations and single or double DNA strand breaks. When the oxidative error is incorporated into critical genes, such as those involved in cell cycle control, important cellular changes of metabolic rate and/or cellular response occur. Accordingly, point mutations that occur in cancer-associated genes result in defective DNA repair, apoptosis and cell cycle deregulation that sustain the malignant phenotype [7].

The most common forms of DNA alterations mediated by oxidative stress are 8-oxoguanine and/or guanosine, induced by deregulated intracellular metabolism and uncontrolled oxidative stress, as well as by injurious environmental factors, such as ionizing radiation.

mtDNA is more susceptible to oxidative damage than nuclear DNA and basically contains a higher level of base damage, commonly 8-oxoguanine [8]. It has been shown that hydrogen peroxide or menadione-mediated 8-oxoguanine foci do not co-localize with y-H2AX$^{(S139)}$ foci that are a hallmark of DNA strand breaks in the nuclear genome [9]. It is possible that these two types of DNA damage are not inter-connected, or that exposure to hydrogen peroxide or menadione may not always lead to single or double strand breaks. This is consistent with previous studies showing that 8-oxoguanine occurs more frequently in mitochondrial (mtDNA) than in nuclear DNA [7], but both genomes are accumulating 8-oxoguanine with increasing age [10].

Oxidative phosphorylation in mitochondria is an important source of ROS, with up to 4–5% of molecular oxygen picking up electrons directly from the flavin dehydrogenases and ubiquinol to generate superoxide anion. Since mitochondrial DNA is not covered by histones, DNA-associated proteins are directly exposed to ROS. Moreover, as mtDNA is intronless and has high transcription rates, the probability of oxidative modification of the coding region is increased [11–13]. Because mitochondrial respiration and consequent production of ATP are key cellular events, oxidative stress-induced damage of mitochondria and mtDNA may result in reduced energy production, compromised cellular functions and defective repair mechanisms. Therefore, oxidative damage of mtDNA has been linked to the onset of various pathologic conditions, such as neuronal degeneration, cardiovascular disorders, reproductive malfunctioning, cancer and aging.

Divergences in cellular function can cause cycles of oxidative damage that could contribute to cancer-related changes of physiological functions. Genome variation can induce an important shift of cellular responses towards oxidative damage. These pathologic changes are induced by critical single-nucleotide polymorphisms (SNPs) that affect cell susceptibility to defective or malfunctioning of encoded proteins. Most of the available data on SNPs in cancer are provided by follow up studies focused on SNPs that can predict the response or resistance of particular cancers to chemotherapy. Some of these include ERCC polymorphisms in non-small cell lung cancer, BRCA1 in mammary cancer, TMPRSS-ERG in prostate cancer, certain phase II and III ABC transporters, along with polymorphisms of oxidative damage response genes (OGG1, GPX2/3 and SOD2/3) in renal cell carcinoma, lung, mammary and prostate cancers [14,15].

The consequences of toxic and mutagenic stresses are minimized in normal cells by specific repair mechanisms that continuously monitor DNA for maintaining genome integrity. Normal cells respond to intracellular ROS generation by activating specific