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Mini-review

The redox-active nanomaterial toolbox for cancer therapy

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ABSTRACT

Advances in nanomaterials science contributed in recent years to develop new devices and systems in the micro and nanoscale for improving the diagnosis and treatment of cancer. Substantial evidences associate cancer cells and tumor microenvironment with reactive oxygen species (ROS), while conventional cancer treatments and particularly radiotherapy, are often mediated by ROS increase. However, the poor selectivity and the toxicity of these therapies encourage researchers to focus efforts in order to enhance delivery and to decrease side effects. Thus, the development of redox-active nanomaterials is an interesting approach to improve selectivity and outcome of cancer treatments. Herein, we describe an overview of recent advances in redox nanomaterials in the context of current and emerging strategies for cancer therapy based on ROS modulation.

Introduction

Reactive oxygen species (ROS) are capable of exerting different effects according to their nature, localization and levels [1]. An imbalance on ROS production and scavenging can lead to a sustained increase of ROS levels and to a pro-oxidant state that have been associated with a broad spectrum of pathological disorders, including cancer. ROS are involved in all aspects of carcinogenesis [2], as well as in non-surgical cancer treatments [3]. ROS modulation induced by conventional radio- and chemotherapy may impact on tumor outcome, although with poor selectivity and high toxicity. Thus, novel therapies are pursued in order to solve these issues. Therefore, studies on cancer treatments based on ROS modulation have grown in the last decade and, in recent years, research on nanomaterials for medical applications contributed to generate novel nanostructures with redox-active properties that may improve oncologic diagnosis and therapies.

Approaches for cancer treatment based on ROS modulation

ROS are known to have a double-edged sword property in determining cell fate, being able to increase or decrease the risk of cancer based on diverse conditions [4, 5]. Considering this, both pro- and antioxidant approaches were developed or are in development (Fig. 1 and Table 1), although nowadays, they are not clinically relevant yet. Redox alterations in cancer cells are very complex and the simple addition of ROS-generating or depleting agents may not always lead to a preferential killing of cancer cells [6, 7]. Thus, understanding the complex redox system in cancer cells is critical to achieve an adequate therapy. Under physiological conditions, normal cells maintain redox homeostasis with a low level of basal ROS by controlling the balance between ROS generation and elimination. Their reserve antioxidant capacity can be mobilized to prevent the ROS level from reaching the cell-death threshold. In contrast, cancer cells show a shift to high ROS generation and elimination, maintaining ROS levels close to the cell-death threshold. Therefore, they would be more dependent on the antioxidant system and more vulnerable to further oxidative stress induced by ROS-generating agents [8]. However, cancer cells may trigger a redox adaptive response leading to anticancer agent resistance. Thus, the potential of these therapies becomes limited. To address this issue, a therapeutic strategy that combines drugs that induce ROS generation with compounds that target the cellular redox adaptive mechanisms was

Abbreviations: ATO, arsenic trioxide; CeO_2, cerium oxide; CNTs, carbon nanotubes; GO, graphene oxide; MNPs, magnetic nanoparticles; MWCNTs, multi-walled carbon nanotubes; Nanoceria, CeO_2 nanoparticles; Nanoprodrug, nanometer-sized prodrug; NPs, nanoparticles; PCL, poly(ε-caprolactone); PCL-SS-PEEP, single disulfide bond-bridged block polymer of poly(ε-caprolactone) and poly(ethylethylene phosphate); PEG, poly-ethylene glycol; ROS, reactive oxygen species; SOD, superoxide dismutase; S-S, N,N′-bis(acryloyl)cystamine containing the cleavable disulfide-bond; SWCNTs, single-walled carbon nanotubes; TiO_2, titanium dioxide; TiO_2-1, uncoated nano-sized TiO_2 (hydrophilic); TiO_2-2, stearic acid-coated nano-sized TiO_2 (hydrophobic); TPGS, D-α-tocopheryl PEG 1000 succinate; ZnPP, zinc protoporphyrin.

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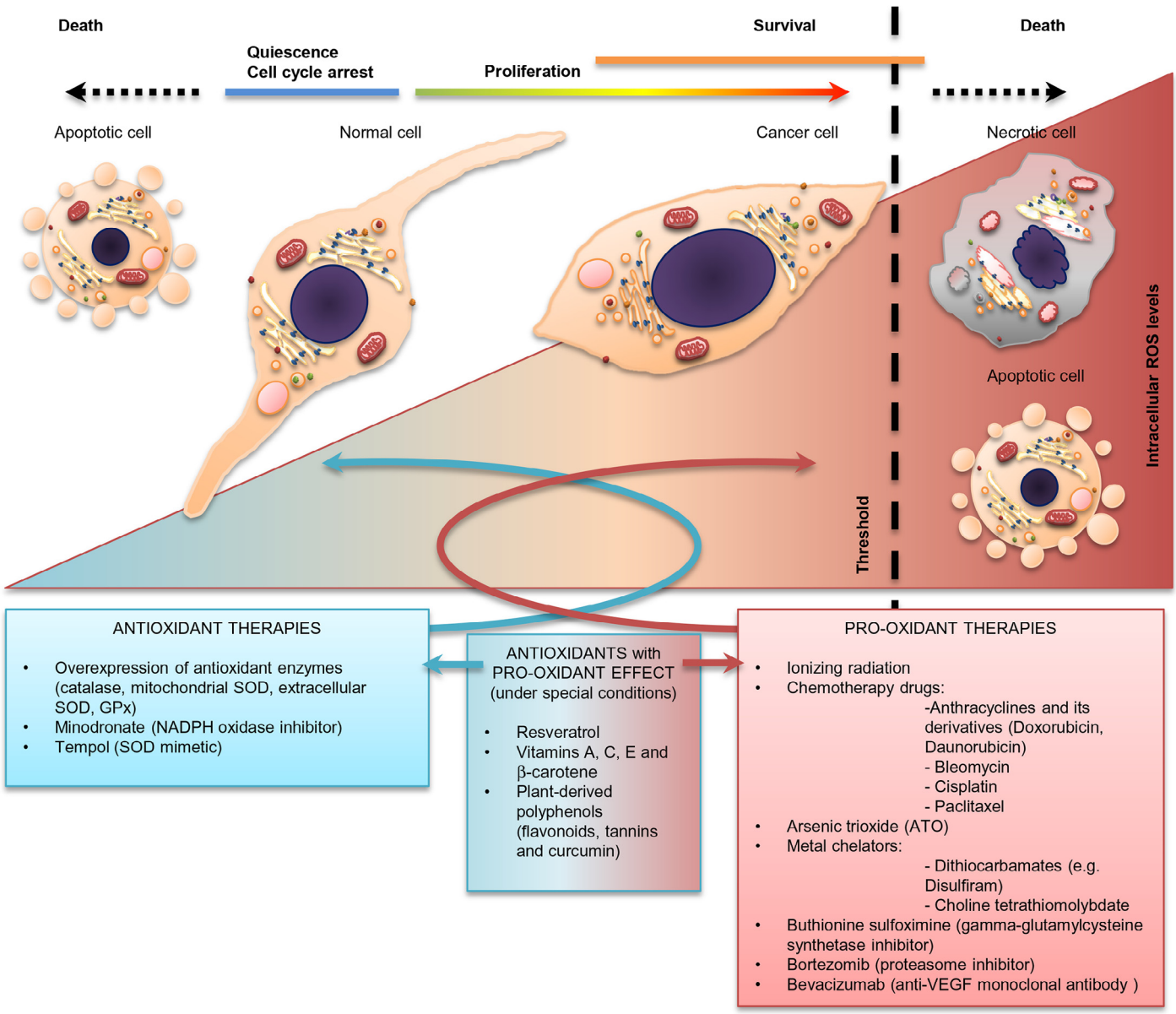

Fig. 1. Anti-cancer therapies based on ROS modulation. The scheme shows the fate of cancer cells exhibiting high levels of ROS that can be altered by anti- or pro-oxidant agents in order to reacquire growth control of normal cells or induce death by apoptosis or necrosis. Some antioxidants which might become pro-oxidants under special conditions are also listed.

proposed [8]. The upregulation of thiol-based antioxidants glutathione, thioredoxin and peroxiredoxin is probably the biochemical basis of redox adaptation and is also involved in drug resistance, being these molecules, as well as other antioxidant enzymes, potential targets for these combined therapies [5, 8]. A more detailed research on the effect of drugs that affect cancer cell oxidative metabolism will help to define better-tailored therapies, decreasing side effects and propensity to develop drug resistance [5].

In order to overcome the limiting tumor hypoxia on cancer therapy, hypoxia-selective redox drugs are also in study (Fig. 2) [9].

Redox therapies based on nanostructures

Nanostructures development for cancer diagnosis and treatment has impacted in the field of medicine. Nanomaterials (Fig. 3) have unique properties given their small size and large surface with high area-to-volume ratio, allowing them high efficiency to bind, absorb and carry compounds such as drugs and biomolecules. The combination of different functions in nanostructure-based delivery systems enables them to have high stability, targeting capacity, stimuli sensitivity and compatibility with different administration routes, thereby making them highly attractive [56, 57]. Moreover, chemotherapeutics bound as nanoconjugates or encapsulated into nanoparticles cannot be recognized as substrates by the ATP-binding cassette efflux systems, thus evading this drug-resistance mechanism. Nanomedicines to overcome resistance were reviewed in Ref. 58. Approved/commercialized nanomaterials/nanomedicines for cancer treatment and detection as well as others at the various stages of clinical trials are reviewed in Nazir et al. [59].

Different nanomaterials exhibit intrinsic redox properties or may be assembled in complexes with drugs or enzymes for this purpose.

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