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Review Article

Reactive Oxygen Species (ROS) in Cancer: Review Article

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Abstract

Background

Cancer is one of the major heterogeneous disease with high morbidity and mortality with poor prognosis. Elevated levels of reactive oxygen species (ROS), alteration in redox balance, and deregulated redox signaling are common hallmarks of cancer progression and resistance to treatment. Mitochondria contribute mainly in the generation of ROS during oxidative phosphorylation. Elevated levels of ROS have been detected in cancers cells due to high metabolic activity, cellular signaling, peroxisomal activity, mitochondrial dysfunction, activation of oncogene, and increased enzymatic activity of oxidases, cyclooxygenases, lipoxygenases, and thymidine phosphorylases. ROS, now appreciated for their cellular signaling capabilities, have a dual role in cancer. On the one hand, ROS can promote protumorigenic signaling, facilitating cancer cell proliferation, survival, and adaptation to hypoxia. On the other hand, ROS can promote antitumorigenic signaling and trigger oxidative stress–induced cancer cell death. To hyperactivate the cell signaling pathways necessary for cellular transformation and tumorigenesis, cancer cells increase their rate of ROS production compared with normal cells. Concomitantly, in order to maintain ROS homeostasis and evade cell death, cancer cells increase their antioxidant capacity. Compared with normal

cells, this altered redox environment of cancer cells may increase their susceptibility to ROS-manipulation therapies. In this article, we discuss the role of ROS in cancer, the mechanisms underlying ROS signaling, and the opposing cancer therapeutic approaches to targeting ROS.

Introduction

Oxidative stress is closely related to all aspects of cancer, from carcinogenesis to the tumor-bearing state, from prevention to treatment. The human body is constantly under oxidative stress arising from exogenous origins (e.g., ultraviolet rays) and endogenous origins (at the cellular level where mitochondria are involved) [1].

When such oxidative stress exceeds the capacity of the oxidation- reduction system of the body, gene mutations may result or intracellular signal transduction and transcription factors may be affected directly leading to carcinogenesis. The tumor-bearing state is also said to be under oxidative stress associated with active oxygen production by tumor cells and abnormal oxidation-reduction control. One of the mechanisms by which anticancer agents and radiation therapy exert their effects is through apoptosis of cancer cells. Oxidative stress is also involved in the problem of resistance to these treatments [1].

ROS are broadly defined as oxygen-containing chemical species with reactive properties. These include the superoxide (O2•–) and hydroxyl (OH•) free radicals as well as non-radical molecules such H_2O_2. These molecules are principally derived from the oxygen that is consumed in various metabolic reactions occurring mainly in the mitochondria, peroxisomes and the endoplasmic reticulum (ER). It is estimated that about 2% of the oxygen consumed by mitochondria is reduced to form superoxide; mitochondria are therefore considered to be a major source of ROS [2,3]. Peroxisomes are involved in both the scavenging of ROS (through catalase-mediated decomposition of H_2O_2) and in the production of ROS (through β-oxidation of fatty acids and flavin oxidase activity) [4]. The ER constitutes an oxidizing environment that favours disulphide bond formation and protein folding, and increases ROS levels through protein oxidation [5].

ROS are closely related to tumorgenesis. Under hypoxic environment, increased levels of ROS induce the expression of hypoxia inducible factors (HIFs) in cancer stem cells (CSCs), resulting in the promotion of the upregulation of CSC markers and the reduction of intracellular ROS level, thus facilitating CSCs survival and proliferation. Although the ROS level is regulated by powerful antioxidant defense mechanisms in cancer cells, it is observed to remain higher than that in normal cells. Cancer cells may be more sensitive than normal cells to the accumulation of ROS; consequently; it is supposed that increased oxidative stress by exogenous ROS generation therapy has an effect on selectively killing cancer cells without affecting normal cells [6].

The regulation of oxidative stress is an important factor in both tumor development and responses to anticancer therapies. Many signalling pathways that are linked to tumorigenesis can also regulate the metabolism of ROS through direct or indirect mechanisms. High ROS levels are generally detrimental to cells, and the redox status of cancer cells usually differs from that of normal cells. Because of metabolic and signalling aberrations, cancer cells exhibit elevated ROS levels. The observation that this is balanced by an increased antioxidant capacity suggests that high ROS levels may constitute a barrier to tumorigenesis [7].

At high levels, ROS promote cell death and severe cellular damage. Cancer cells need to combat high levels of ROS, especially at early stages of tumor development. The conditions that induce oxidative stress also increase the selective pressure on pre-neoplastic cells to develop powerful antioxidant mechanisms [8]. High ROS levels are also induced by detachment from the cell matrix. This aspect represents a challenge for metastatic cancer cells that need to survive during migration to distant organs [9].

Therefore, cancer cells regulate ROS to levels that are compatible with cellular biological functions but still higher than in normal cells. It is believed that targeting these enhanced antioxidant defence mechanisms represent a strategy that can specifically kill cancer cells, including CSCs (also known as tumor-initiating cells), while sparing normal cells [9].

Conclusion

Most chemotherapeutics elevate intracellular levels of reactive oxygen species (ROS), and many can alter redox-homeostasis of cancer cells. It is widely accepted that the anticancer effect of these chemotherapeutics is due to the induction of oxidative stress and ROS- mediated cell injury in cancer. However, various new therapeutic approaches targeting intracellular ROS levels have yielded mixed results. Since it is impossible to quantitatively detect dynamic ROS levels in tumors during and after chemotherapy in clinical settings, it is of increasing interest to apply mathematical modeling techniques to predict ROS levels for understanding complex tumor biology during chemotherapy.

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