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Mini-review

Dual role of hydrogen peroxide in cancer: Possible relevance to cancer chemoprevention and therapy

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Abstract

Accumulating evidence suggests that hydrogen peroxide (H_2O_2) plays an important role in cancer development. Experimental data have shown that cancer cells produce high amounts of H_2O_2. An increase in the cellular levels of H_2O_2 has been linked to several key alterations in cancer, including DNA alterations, cell proliferation, apoptosis resistance, metastasis, angiogenesis and hypoxia-inducible factor 1 (HIF-1) activation. It has also been observed that the malignant phenotype of cancer cells can be reversed just by decreasing the cellular levels of H_2O_2. On the other hand, there is evidence that H_2O_2 can induce apoptosis in cancer cells selectively and that the activity of several anticancer drugs commonly used in the clinic is mediated, at least in part, by H_2O_2. The present report discusses that the high levels of H_2O_2 commonly observed in cancer cells may be essential for cancer development; these high levels, however, seem almost incompatible with cell survival and may make cancer cells more susceptible to H_2O_2-induced cell death than normal cells. An understanding of this dual role of H_2O_2 in cancer might be exploited for the development of cancer chemopreventive and therapeutic strategies.

Keywords: Reactive oxygen species; Hypoxia-inducible factor; Apoptosis; Carcinogenesis; Antioxidant; Prooxidant

1. Introduction

Reactive oxygen species (ROS) are generated by all aerobic organisms and their production seems to be needed for signal-transduction pathways that regulate multiple physiological processes. Excessive amounts of ROS, however, can start toxic and lethal chain reactions, which oxidize and disable structures that are required for cellular integrity and survival. ROS are generated in multiple compartments and by multiple enzymes within the cell. Important contributions include proteins within the plasma membrane, such as the growing family of NADPH oxidases; lipid metabolism within the peroxisomes; as well as the activity of various cytosolic enzymes such as cyclooxygenases. Although all these sources contribute to the overall ROS production, the vast majority of cellular ROS can be traced back to the mitochondria [1–4].

Most of the energy that our cells need to live depends on a mitochondrial process that requires oxygen (O_2). In this process, called oxidative phosphorylation, ATP generation is coupled with

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a reaction in which O_2 is reduced to H_2O. Under certain conditions, O_2 can also be reduced to H_2O via the ROS superoxide anion ($O_2^{\cdot-}$) and hydrogen peroxide (H_2O_2) [2,5]. It is recognized that the cellular production of $O_2^{\cdot-}$ and H_2O_2 favors the formation of other reactive oxygen and nitrogen species – such as hydroxyl radical ($OH^{\cdot}$) and peroxynitrite ($ONOO^-$) – and that an excessive production of these species causes oxidative stress and may play an important role in carcinogenesis [6]. It is not clear, however, which species is directly responsible for each of the biological activities in which ROS have been implicated. For instance, several studies have demonstrated that the overexpression of the enzymes superoxide dismutases (SOD) in tumor cells can reduce tumor cell growth, metastasis and other malignant features of cancer cells [7–12]. Since these enzymes catalyze the conversion of $O_2^{\cdot-}$ to H_2O_2, the anticancer effects induced by SOD overexpression may be mediated by a decrease in the cellular levels of $O_2^{\cdot-}$ or by an increase in the cellular concentrations of H_2O_2. Experimental data suggest that the anticancer effects produced by overexpression of manganese SOD can be reverted by overexpression of two enzymes involved in H_2O_2 catabolism, catalase and glutathione peroxidase; this supports that the anticancer effects induced by SOD overexpression are mediated by an increase in H_2O_2 [13,14].

The present report discusses evidence that suggests that an increase in the cellular levels of H_2O_2 may play, directly or indirectly, a key role in malignant transformation, but can also sensitize cancer cells to H_2O_2-induced cell death. An understanding of this dual role of H_2O_2 in cancer might be exploited for the development of cancer chemopreventive and therapeutic strategies.

2. Key role of hydrogen peroxide in carcinogenesis

Many researchers consider that cancer is a genetic disease caused by the acquisition of multiple mutations in genes that control cell proliferation, cell death and genomic instability [15]. This hypothesis – called the somatic mutation theory of cancer – has been the prevalent paradigm to explain the process of carcinogenesis in the last several decades. There is growing experimental evidence, however, that contradicts or cannot be explained by this hypothesis, and other theories are being developed or revisited [16–23]. It is currently accepted – even by those who challenge the somatic mutation theory of cancer – that cells must develop several acquired capabilities in order to become a malignant cancer: increased cell proliferation (caused, in part, by resistance to growth inhibition and independence from mitogenic stimulation), apoptosis resistance, cellular immortalization, increased angiogenesis and invasion/metastasis. Besides, it is considered that genetic instability is a key event that enables the acquisition of these capabilities [24,25].

Accumulating experimental data suggest that an increase in the cellular concentrations of H_2O_2 can explain all these hallmarks of cancer. It is known that H_2O_2 is associated with DNA damage, mutations and genetic instability [26–31]; H_2O_2-induced DNA damage seems to be mediated by $OH^{\cdot}$ generated from H_2O_2 by the Fenton reaction [26,30,31]. Several studies have also demonstrated that H_2O_2 can induce cell proliferation [2,32,33], apoptosis resistance [34,35], increased angiogenesis [36,37] and invasion and metastasis [33,38,39]. Indeed, these studies showed that an increase in the levels of H_2O_2-detoxifying enzymes could reduce cell proliferation, promote apoptosis, and inhibit invasion, metastasis and angiogenesis. The activation of hypoxia-inducible factor 1 (HIF-1) by H_2O_2 can contribute to explain these hallmarks of cancer. There is evidence that the most important oncogenes and tumor-suppressor gene pathways may culminate in HIF-1 activation [15] and that HIF-1 activation plays an important role in apoptosis resistance, invasion/metastasis, angiogenesis and immortalization [5,40–43]. It is not surprising, therefore, that HIF-1 overexpression is observed in many human cancers and has been associated with increased patient mortality [40,41,44]. Interestingly, recent research has established that an increase in the cellular concentrations of H_2O_2 can activate HIF-1, and that overexpression of the H_2O_2-detoxifying enzyme catalase prevents the activation of HIF-1 induced by different stimuli [5,45–49].

The key role of H_2O_2 in carcinogenesis is supported by experimental data that have shown that cancer cells commonly have increased levels of H_2O_2 [2,50–52]. For instance, Szatrowski and Nathan reported that several tumor cell lines, representing a variety of tissue types, constitutively produced large amounts of H_2O_2. They observed that the cumulative amount of H_2O_2 produced after 4 h by these tumor cells was comparable to the amount of H_2O_2 produced by similar numbers of phorbol ester-triggered neutrophils [50]. It has also