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BEYOND PATHOLOGIES: THE ROLE OF REACTIVE OXYGEN SPECIES IN CANCER PREVENTION AND TREATMENT IN HUMANS

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ABSTRACT

Traditionally associated with pathologies such as cardiovascular disease and ageing, Reactive Oxygen Species (ROS) have been shown to have crucial roles in tumorigenesis and cancer stem cell longevity. The multifaceted roles of ROS in the cellular processes of cancer cells, including their dual, sometimes antithetical, roles in tumorigenesis and cancer therapy, are explored here. ROS are known to mutate or deactivate tumour suppressor genes and damage homeostatic proteins, resulting in tumours. The production, function, and regulation of ROS, particularly within the context of the redox window, are also discussed. With respect to cancer therapeutics, we go over the efficacy of conventional cancer treatments, which rely on ROS-mediated cytotoxic effects. The concentration-dependent functions of ROS open avenues for therapeutics since we can modulate ROS levels for cancer cell destruction while sparing healthy cells. Additionally, we emphasise the need for further research to fully comprehend the intricate roles of ROS in cancer. We advocate for continued research into ROS mechanisms and pathways to gauge the effectiveness of therapies, especially against cancer stem cells. Given the global impact of cancer, a better understanding of the cellular mechanisms of cancer is imperative for finding better treatments.

KEYWORDS: Reactive Oxygen Species, Redox Window, Redox Homeostasis, Oxidative Stress, Mitochondria, Antioxidants, Tumorigenesis, Cancer Treatment, Mitochondria-Targeted Antioxidants, Cell Signalling.

INTRODUCTION

Reactive oxygen species (ROS) are reactive molecules or free radicals that originate from molecular oxygen. Mitochondria are the largest source of ROS in cells. Other sources include the endoplasmic reticulum, peroxisome, and cytochrome P450 reactions. Studies have shown that ROS have beneficial roles in cell signalling, maintaining redox homeostasis, immunity, and the normal functioning of the cardiovascular system (Patel et al., 2018). However, ROS have historically been implicated for their correlation with pathologies such as cardiovascular disease, ageing, and cancer. Owing to their ubiquitous nature in body tissue, misregulation or overproduction can quickly lead to disease and cell death, accelerated by high oxidative stress. Research shows that elevating ROS levels within cells is the mechanism of action of most chemotherapies (Nakamura & Takada, 2021). Hence, it is possible to use ROS as a specific target treatment for cancer.

Production, Function, and Regulation of Reactive Oxygen Species

During aerobic cellular respiration, oxygen undergoes a one-electron reduction, producing highly reactive superoxide anions (O2-). These ions are converted into hydrogen peroxide (H_2O_2) by a group of mitochondrial enzymes called 'superoxide dismutases' (SOD). H_2O_2 is less reactive than superoxide. However, H_2O_2 can react with superoxide in the Haber-Weiss reaction, leading to the formation of hydroxyl radicals (OH), which are detrimental to various tissues due to their strong chemical activity. This is exacerbated by the absence of enzymatic reactions that can eliminate them from cells.

When superoxide is produced in the presence of nitrogen monoxide (NO), it can spontaneously react to create peroxynitrite (ONOO-), a highly toxic oxidant. Peroxynitrite has the ability to penetrate cell membranes and cause damage to proteins by oxidising heme groups. It can also oxidise the sugar-phosphate backbone and nitrogenous bases of DNA. Table 1 by Patel et al. (2018) summarises the production of select reactive oxygen species.

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Reactive Oxygen Species	Mechanism of Generation
Superoxide (O_2-)	Reduction of oxygen during aerobic cellular respiration and other enzyme-catalysed reactions
Hydrogen Peroxide (H_2O_2)	Conversion of superoxide-by-superoxide dismutase
Hydroxyl radical (OH)	Reaction of hydrogen peroxide and superoxide in the Haber-Weiss reaction
Peroxynitrite (ONOO-)	Reaction between superoxide and nitrogen monoxide

Table 1: Synthesis of select ROS
Source: Patel et al. (2018)

In most cells, there is a basal level of ROS production, i.e., a certain amount of ROS is produced in various redox reactions that occur in healthy mitochondria and the cell cytosol. At basal levels, ROS are indispensable to cell cycle modulation, cell signalling, innate immunity activation, and vascular development. These levels of ROS production lie within a certain range dubbed the "redox window," which is the optimal level required for proper functioning of the body. Too much ROS causes oxidative stress and triggers a mitochondrial apoptosis pathway through the caspase cascade. Too little ROS hinders cell growth by blocking many signalling pathways.

ROS are self-regulatory and activate a robust antioxidant defence system when levels deviate from the redox window. This defence mechanism includes the Superoxide Dismutase (SOD) family discussed above and other redox proteins, together called ROS scavengers. The difference between ROS production levels and the cell's ability to eliminate them is termed "oxidative stress." When oxidative stress is high yet below apoptotic levels, the cell turns tumorigenic. Figure 1 by Galadari et al. (2017) shows the redox window and the processes associated with relative intracellular ROS concentrations.

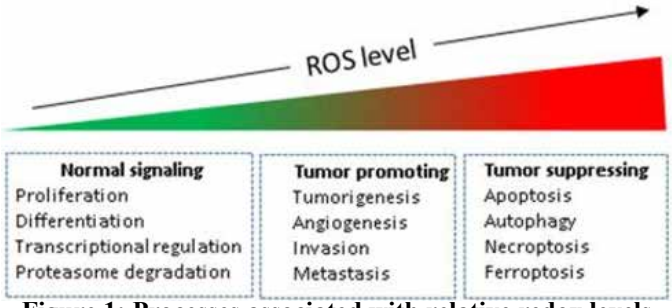

Figure 1: Processes associated with relative redox levels
Source: Galadari et al. (2017)

ROS in Tumorigenesis

High intracellular and extracellular ROS levels are a common observation in many cancers, because of which ROS can be used as biomarkers for cancer. Exogenous carcinogens, such as tobacco and radiation, generate ROS during their metabolism. Many oncogenes, like c-Myc and BRCA1, produce ROS in their respective reaction pathways. The high respiratory activity of cancerous tissue is another factor that imbalances the internal redox environment (Yang et al., 2018).

Hydroxyl radicals and peroxynitrite oxidise DNA, causing lesions that are both cytotoxic and mutagenic, like the overexpression of proto-oncogenes. ROS can also damage many negative feedback loop controllers and transcription factors, expediting tumour formation and proliferation. Some transcription factors, like those belonging to the Forkhead box class-O (FoxO) subgroup, are sensitive to redox levels in the cell. FoxO can instigate tumour formation by entering the nucleus and stimulating the expression of cancer-promoting proteins. High ROS levels increase cell proliferation by activating mitosis-initiating proteins, such as MAPK 1/2 (Mitogen Activated Protein Kinase 1/2). Most tumour suppressors have antioxidant properties, but these genes are often mutated or deactivated in cancerous tissue. Phosphatase and Tensin Homolog (PTEN), a cell cycle regulator and tumour suppressor, is inactivated by H_2O_2 in various cancers. Another example is the p53 gene, which regulates various aspects of the antioxidant defence system and is mutated in most cancer cells, resulting in ROS buildup (Arfin et al., 2021).

While these findings implicate ROS for their role in cancer progression, they also have anti-tumorigenic roles. They activate the antioxidant defence system to maintain redox homeostasis and to ensure ROS levels do not become cytotoxic, which is a notable mechanism of immune evasion used by cancer cells. Detachment of cancer cells from the basement membrane during metastasis increases ROS levels within the cell, thus pushing it towards apoptosis.

ROS in Therapeutics

Many conventional chemotherapies target mitochondria and induce oxidative stress, causing cell death. One of the most efficacious cancer therapies, cisplatin, owes its high efficiency to an ROS-caused cytotoxic effect. This is hypothesised to be caused by genomic instability due to increased ROS levels, leading to apoptosis. Radiolysis of water during radiotherapy also causes a surge in intracellular ROS levels.

The function of ROS in a cell depends on their concentration. This implies that changing their concentration will affect the progression of cellular reactions. One proposed therapy for cancer is induced cell death via an increase in ROS levels above threshold, either by increasing oxidative stress or by reducing ROS scavenging. Since cancer cells have a more active redox environment than normal cells, this method can target cancerous tissue while leaving healthy cells intact.

Additionally, cancer stem cells (CSCs), which are a subpopulation of cancerous tissue that are known to be key drivers of malignancy, metastasis, and recurrence, have lower concentrations of ROS. The reason for this remains unknown but makes CSCs immune to most conventional radiotherapies and chemotherapies (Reczek and Chandel, "The Two Faces of Reactive Oxygen Species in Cancer"). According to Shi et al., it may be caused by the expression of ROS scavenger proteins, which can be a mechanism to ensure a tumour's longevity. This suggests that a targeted increase in ROS concentration in CSCs may kill them or hinder their function. This is significant because CSCs contribute greatly to cancer recurrence after remission and have proven difficult to eliminate. Thus, targeted

therapy is a viable treatment option, but it still requires deeper research due to the complex roles of ROS in cancer signalling.

Another proposed preventative treatment is antioxidant therapy. A comprehensive Chinese study (with a sample size of 132,837) conducted in 2012 by Zhang et al. (2012) showed that vitamin E intake can reduce the risk of liver cancer in participants with no reported family history of liver cancer. Yet, the study also found that for people with a family history of liver cancer, an increased risk of incidence was associated with vitamin E and multivitamin use. This shows the complex interplay between antioxidants and ROS in maintaining the cellular redox environment and preventing tumorigenesis. Another placebo-controlled study conducted in England found that treatment with beta-carotene and vitamin E had either adverse effects or offered no benefits, also exemplifying the intricacy of redox homeostasis (Omenn et al., 1996). Additionally, depending on the mode of administration, uneven distribution of antioxidants within the body and dosage may prove to be issues (Luo et al., 2022). In light of this information, further research is needed to shed light on the viability of antioxidant treatments for cancer.

Exciting research into mitochondria-targeted antioxidants showed that they can inhibit cancer signalling pathways. MitoTEMPO, a superoxide scavenger, successfully killed cancerous melanoma cells in vivo by reducing ROS levels while leaving normal cells unharmed (Nazarewicz et al., 2013). However, a study conducted in 2021 by Gal et al. found that mitoTEMPO does not influence melanoma and lung tumour metastasis and proliferation rates, indicating that this is another area that needs further research.

CONCLUSION

Reactive oxygen species are a consequence of aerobic life, and the human body has evolved to use these molecules efficiently. Owing to their high oxidising power, ROS can be harmful to cells when they are above basal levels and can cause oncogenesis. While it is indisputable that high ROS levels promote cancer development and progression, they are also indispensable to cancer therapy. An ever-growing body of evidence shows that reactive oxygen species are crucial to understanding cancer and may be pivotal in finding treatments. So far, mitochondria-targeted antioxidant therapy, like mitoTEMPO, and induced oxidative stress in cancer cells seem to be promising treatments. However, many essential pathways and mechanisms are still poorly understood and require further research to be elucidated. Cancer being the largest cause of death in the world makes this a significant issue and an area of interest for academicians and laypeople. Further understanding of these key ROS mechanisms and pathways will allow us to create new therapies and provide an optimistic outlook on the future of cancer therapeutics.

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