Exploiting Reactive Oxygen Species in Cancer Therapy: Opportunities and Challenges

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Abstract

Reactive oxygen species (ROS) are highly reactive compounds produced by the electron transport chain in mitochondria and various enzymes like NADPH oxidase. While balanced ROS are crucial for cell survival and function, an imbalance can lead to cellular damage, particularly affecting DNA, which may induce mutations linked to cancer. Interestingly, elevated ROS levels can trigger apoptosis in cancer cells, presenting a therapeutic opportunity to enhance treatment responses in therapies such as chemotherapy and radiation. This review discusses the dual role of ROS in healthy versus cancerous cells and highlights current drugs like IACS-010,759, VLX600, and GBS-01 developed for ROS-based treatment strategies. It emphasizes the need for more targeted approaches to maximize therapeutic efficacy while minimizing harm to healthy cells.

Introduction

Reactive oxygen species are compounds containing oxygen atoms with an unpaired electron, making them highly reactive. These substances are generated during the electron transport chain as a byproduct within the mitochondria, along with other cellular processes that involve proteins like NADPH oxidase. In the mitochondria, the electron transport chain is used to produce ATP through Complexes I-IV and the ATP synthase. About 0.2%-2% of electrons in the electron transport chain leak out and interact with oxygen, producing ROS.[1] Most ROS produced in the electron transport chain are produced at Complex I, and Complexes II-IV produces negligible amounts compared to those at Complex I.[1] It is crucial ROS are produced in proper concentrations at these complexes for cell survival because they serve as messengers within the cell and help manage various cellular functions, such as gene expression, cell division, cell differentiation, and the response to stress.[2] They can influence pathways like growth-factor signaling pathways and mitogenic pathways, and both help stimulate cell division, growth differentiation, and survival.[3,4] As a redox signaling messenger, ROS can cause reversible modifications to biomolecules in the cell but become dangerous when they bind to the cell's macromolecules, DNA, lipids, and proteins, and lead to the formation of cancer.

Dangers of ROS

ROS act as messengers, making them vital to cell survival but only in balanced amounts. Disrupting this equilibrium, either a lack of ROS or excess ROS, may disrupt cell processes and harm the cell. ROS equilibrium is the balance between ROS production and removal. ROS can build up due to overproduction or failure of the antioxidant system. ROS can be overproduced when there are hypoxic conditions in the cell. The mitochondria prioritizes generating ROS over ATP, the cell's main source of energy.[5] This leads to an excess of ROS in the cell, disrupting the balance.

Excess ROS can damage DNA, proteins, and lipids by modifying them in such a way that theycan no longer function properly. This is especially important if ROS modifies DNA because it can lead to mutations that promote cancer cell growth and proliferation.[2,6] ROS can modify DNA by binding to the backbone or base of the DNA strand. Because of the double helix shape making the backbone the most exposed region of DNA, ROS reacts to the backbone and

changes its structure. In response to this change, the base is oxidized and deprotonated.[7] This results in different properties of the base and could lead to a mutation that causes cancer. With these new properties, the base pairing or "code" of the gene in the strand is changed, and genes can become turned on or off. If a DNA mutation turns on an oncogene, a mutated gene that has the potential to cause cancer, the cell can grow into a cancer cell.

Once a cancer cell forms, it can proliferate rapidly and become a tumor in the body. This becomes dangerous because cancer cells have an environment full of oxidative stress, where the body can no longer regulate ROS levels, and this can quickly spread to healthy cells. Not only can tumors spread this environment of oxidative stress to surrounding healthy cells, but they can also deprive healthy cells of necessary nutrients because the proliferation of cancer cells consumes many resources. This lack of resources weakens normally-functioning cells. Cancer cells can become even more dangerous via metastasis by breaking off from the main tumor and moving through the bloodstream to other organs, leading to the cancer spreading throughout the body.[8]

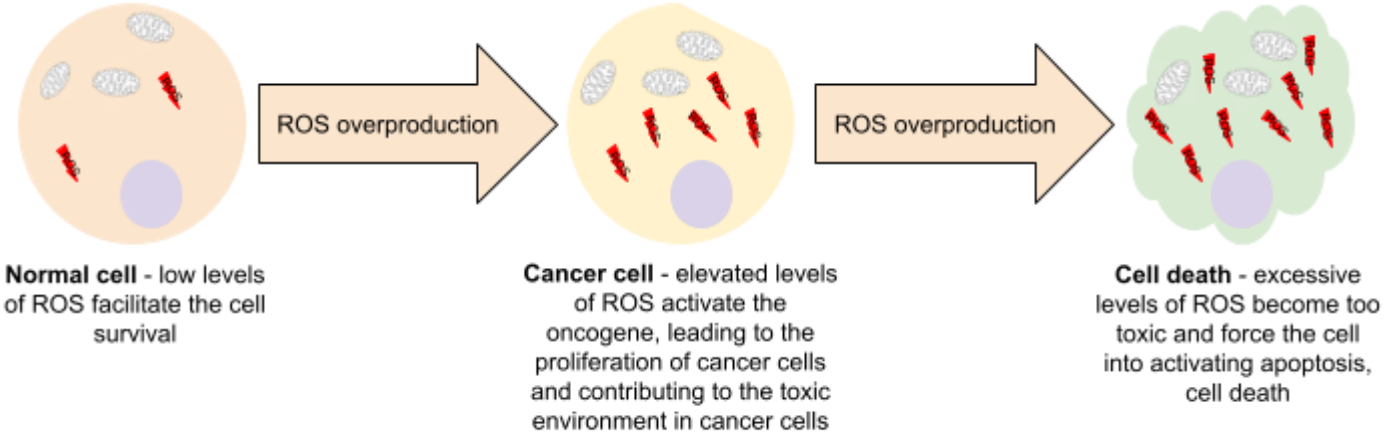

Fig 1. Concentrated ROS can lead to cell death

On the other hand, higher levels of ROS can kill cancer cells by activating a process called apoptosis, which is a form of programmed cell death. Through the electron transport chain at mitochondrial complex I, enough ROS can be produced to start a signaling cascade that damages the cell enough to lead to programmed cell death. This may help in treating cancer more effectively, as it has also been found that ROS can be used to make other types of cancer treatments more effective. Cancer cells can be exposed to more ROS, and this makes them more susceptible to chemotherapy or radiation.[2] Thus, ROS can both be produced by cancer cells as well as lead to their apoptosis if ROS are in high enough concentrations within the cancer cells. The possibility of improving cancer treatment by weakening the tumor cells with ROS should be studied further to develop the field of cancer research and improve the chances of saving patients.

Treatments

Researchers have begun studying the effect of ROS on cancer cells and the benefits of harnessing ROS to treat cancer. A few drugs targeting cancer cells through ROS have been

researched and developed. These drugs inhibit proteins in the electron transport chain to produce ROS and weaken the cancer cell.

IACS-010,759, which has passed clinical trials, inhibits the standard and chemotherapy-induced oxygen consumption rates by targeting oxidative phosphorylation (the OXPHOS process), a metabolic process crucial to cell survival as the primary source of ATP. In the OXPHOS process, NADH and FADH2 donate electrons at complex I that go through the electron transport chain to create ATP.[9] Targeting the OXPHOS process inhibits parts of the electron transport chain, and this disrupts the production of ATP in the cell. Since ATP is vital to the survival and proliferation of all cells, including cancer cells, decreased ATP levels can weaken the cancer cell, making it more susceptible to other cancer treatments. IACS-010,759 has been shown to effectively kill leukemia stem cells and residual cancer cells, both individually and with chemotherapy.[10] Although it is successful in reducing cancer cells, it may lead to adverse effects such as fatigue and nausea.[10]

Two other drugs targeting ROS effects are VLX600 and GBS-01. VLX600, whose clinical trial was ended early, triggers cell death by inhibiting mitochondrial activity and respiration. Preventing the intake of glucose further improves the performance of VLX600 in inducing cell death. VLX600 also successfully depletes cells of nutrients and energy, increases glycolysis, and inhibits the proliferation of the cancer cells. However, this drug can also lead to irritation in the skin, eyes, or respiratory system.[11,12] GBS-01, on the other hand, has undergone clinical trials in Japan, and has been shown to weaken the cancer cells ability to withstand glucose and nutrient deprivation. GBS-01 also inhibits mitochondrial complex I, generating ROS as a result. By generating more ROS, the cancer cell becomes weaker due to the volatile nature of ROS. The benefits of a drug cocktail like GBS-01 are a high ratio of a compound called arctigenin that aids in the prevention of cancer cell metastasis and can induce apoptosis.[13] However, GBS-01 can also lead to liver damage, elevated blood pressure, and excessive breaking down of red blood cells.[14]

Conclusions

ROS are compounds important to the survival of cells and the body. However, they become dangerous when they are overproduced, like at Complex I in the electron transport chain. If ROS are overproduced in cells, they can bind to DNA easier and cause mutations that lead to cancer. At a certain point, ROS can be overproduced so much in the cancer cell that it becomes weaker. Drugs have been developed to take advantage of this and overproduce ROS through Complex I to make them more sensitive to therapies. Although drugs weakening cancer cells through the overproduction of ROS in the electron transport chain have been developed, they have shown negative effects on the bodies of patients. Researchers should continue to look into ways to improve the efficacy of drugs and minimize the side effects on the body.

Drugs targeting increased ROS production have been shown to have negative effects on the whole body, such as irritation, nausea, infection, and damage to organs. These drugs cause these side effects and help treat cancer through processes that create ROS, but their focus is not necessarily to produce ROS in order to weaken cancer cells. ROS overproduction could be one of the ways that these drugs weaken cancer cells and inhibit cancer progression, but not the primary method. To further the research in this field, researchers should research ways to make the drugs more targeted to limit their side effects on the rest of the body. They should also work on understanding the delicate balance of natural ROS production from the electron transport chain and pharmacologically increased ROS concentration to weaken cancer cells..

Future research should consider approaches to optimizing I increased ROS production in cancer cells while mediating the therapeutic ROS concentration to minimize off-target effects on healthy cells and organs.. ROS have always viewed as a destructive force in cells, but their role in cell survival as messengers and their ability to increase cancer cell susceptibility to chemotherapy treatments make them important compounds in cells.

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