Reactive Oxygen Species (ROS), Cancer

https://pubmed.ncbi.nlm.nih.gov/15158766/
ROS stress in cancer cells and therapeutic implications 2004
The escalated ROS generation in cancer cells serves as an endogenous source of DNA-damaging agents that promote genetic instability and development of drug resistance. Malfunction of mitochondria also alters cellular apoptotic response to anticancer agents. Despite the negative impacts of increased ROS in cancer cells, it is possible to exploit this biochemical feature and develop novel therapeutic strategies to preferentially kill cancer cells through ROS-mediated mechanisms.

https://pubmed.ncbi.nlm.nih.gov/18172854/
Reactive oxygen species: current knowledge and applications in cancer research and therapeutic 2008
Reactive oxygen species (ROS) are natural products inevitably generated along cellular metabolism. Due to their highly reactive nature, which can damage DNA, proteins and lipids, cells utilize antioxidative or defense systems to balance these toxic products to keep the cells in a state of redox homeostasis. However, under the situation of imbalance in redox status, depending on the magnitude of ROS encountered, high levels of ROS can induce apoptosis, whereas chronic low levels of ROS promote vascular diseases such as arteriosclerosis. Although ROS seem to be catastrophic to life, accumulating evidence points to the beneficial roles of ROS by virtue of the ability as chemotherapeutic agents to cure human diseases. Many anti-cancer drugs have been developed in this way which can generate ROS and cause oxidative stress-induced apoptosis in cancer cells. The effects of ROS are paradoxical because they can act as both disease culprits and chemotherapeutic agents.

https://pubmed.ncbi.nlm.nih.gov/20818163/
A matter of balance between life and death: targeting reactive oxygen species (ROS)-induced autophagy for cancer therapy 2010
Reactive oxygen species (ROS) have been implicated in many biological functions and diseases. Often their role is counterintuitive, where ROS can either promote cell survival or cell death depending on the cellular context.
In cancer treatment, therapeutic drugs that increase ROS and autophagy have been implicated in their mechanism for cell death, such as 2-methoxyestrodial (2-ME) and arsenic trioxide (As(2)O(3)), whereas other therapeutic drugs that induce ROS and autophagy seem to have a protective effect. This has led to different approaches to treat cancer patients where autophagy is either activated or inhibited. Both views of ROS and autophagy are valid and reflect the balance within a cell to either survive or die. Understanding this balancing act within a cell is essential to determine whether to block or activate ROS-controlled autophagy for cancer therapy.

https://pubmed.ncbi.nlm.nih.gov/19249331/
Therapeutic strategies by modulating oxygen stress in cancer and inflammation 2009
On the contrary, because of its highly cytotoxic nature, ROS can also be used to kill cancer cells if one can modulate its generation selectively in cancer. To achieve this goal, a unique therapeutic strategy was developed named as "oxidation therapy", by delivering cytotoxic ROS directly to the solid tumor, or alternatively inhibiting the antioxidative enzyme system, such as HO-1 in tumor.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3880197/
Reactive oxygen species in cancer 2010
Elevated rates of reactive oxygen species (ROS) have been detected in almost all cancers, where they promote many aspects of tumor development and progression. However, tumor cells also express increased levels of antioxidant proteins to detoxify from ROS, suggesting that a delicate balance of intracellular ROS levels is required for cancer cell function.

https://pubmed.ncbi.nlm.nih.gov/15769673/
Reactive oxygen species in tumor progression 2005
However, it is also known that ROS can induce cellular senescence and cell death and can therefore function as anti-tumorigenic agents. Therefore, the mechanisms by which cells respond to reactive oxygen species depends on the molecular background of cell and tissues, the location of ROS production and the concentration of individual ROS species. Carcinoma cells produce ROS at elevated rates in vitro, and in vivo many tumors appear persistent to oxidative stress.

https://www.nature.com/articles/s12276-020-0384-2
ROS in cancer therapy: the bright side of the moon 2020
Reactive oxygen species (ROS) constitute a group of highly reactive molecules that have evolved as regulators of important signaling pathways. It is now well accepted that moderate levels of ROS are required for several cellular functions, including gene expression. The production of ROS is elevated in tumor cells as a consequence of increased metabolic rate, gene mutation and relative hypoxia, and excess ROS are quenched by increased antioxidant enzymatic and nonenzymatic pathways in the same cells. Moderate increases of ROS contribute to several pathologic conditions, among which are tumor promotion and progression, as they are involved in different signaling pathways and induce DNA mutation. However, ROS are also able to trigger programmed cell death (PCD).
Reactive oxygen species (ROS) produced in eukaryotic cells through aerobic metabolism have evolved as regulators of important signaling pathways. ROS, previously considered mere byproducts of cellular respiration, are oxygen-containing molecules with high reactivity. They include hydroxyl (HO^{*}) and superoxide (O_2^{*}) free radicals and nonradical molecules, such as hydrogen peroxide (H_2O_2), which is less reactive than the majority of ROS but is able to reach any cellular compartment prior to being converted by peroxiredoxins and glutathione peroxidases into water and oxygen. In fact, H_2O_2 plays the role of a second messenger in some pathways that involve the transduction of extracellular signals and the control of gene expression, contributing to what is currently defined as redox signaling[1].
Tight regulation of ROS levels is crucial for cellular life; in fact, moderate ROS contribute to the control of cell proliferation and differentiation. Therefore, eukaryotic cells benefit from a complex scavenging system based on superoxide dismutases (SODs), located in the cytoplasm, mitochondria and the extracellular matrix; glutathione peroxidase (GPX); glutathione reductase (GR); peroxiredoxin; thioredoxin; and catalase, which convert superoxide anions into water and recycle the antioxidants in the reduced state.
It has been determined that each cell is exposed to ~1.5×10^5 oxidative hits per day. If, for any reason, ROS production increases or the number of scavenged ROS decreases, then cells experience a condition known as oxidative stress.
ROS as double-edged swords in cancer
ROS and apoptosis (type I programmed cell death)
The most common method by which ROS kill transformed cells is the activation of PCD, which is completed within less than 60 min by a family of cysteine-dependent aspartate-directed proteases known as caspases. Triggered by an extrinsic or an intrinsic pathway, caspase-induced PCD culminates with the

formation of apoptotic bodies that are eliminated by adjacent phagocytes74.
As noted above, chemotherapy and radiotherapy cause an increase in intracellular ROS that can lead to apoptosis[92,93] *via* extrinsic or intrinsic pathways[94,95].
Many drugs used in anticancer therapy induce oxidative stress.
Furthermore, platinum-based drugs elevate ROS levels that promote PCD .....
ROS and autophagy (type II programmed cell death)
Recently, an important therapeutic approach to kill cancer cells has been presented by ROS-induced autophagy114. Specifically, it has been reported that H2O2-dependent inactivation of autophagy-related gene-4 (ATG4) increases LC3-associated autophagosomes and that ATM-mediated oxidation of AMP-activated protein kinase (AMPK) inhibits mammalian target of rapamycin 1 (TORC1), a pivotal negative regulator of autophagy115,116,117 (Fig. 2). Indeed, autophagy, also known as type II programmed cell death, is now considered not only as a cell survival mechanism but also a tumor suppressor mechanism that induces the death of transformed cells118. In this regard, it has been reported that H2O2 induces autophagic cell death in glioma cells after treatment with the polycyclic ammonium ion sanguinarine, which increases electron leakage from mitochondria and induces NOXs119.
ROS and necroptosis (type III programmed cell death)
ROS are also able to induce necrosis, which was originally considered an unregulated form of cell death but is now recognized as type III programmed cell death (necroptosis)121,122. ROS generated after the formation of ceramide or after an increase in energy metabolism induced by several receptor-interacting protein kinases (RIPs), either in the mitochondrial ETC and/or by NOXs, have been reported to enhance necroptosis
ROS and multidrug resistance
Increased ROS levels are thought to impair the multidrug resistance of cancer cells, which causes cancer development and metastasis during or after chemotherapy

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8380163/
Reactive Oxygen Species (ROS) Regulates Different Types of Cell Death by Acting as a Rheostat 2021
Reactive oxygen species (ROS) are essential for cellular signaling and response to stress. The level of ROS and the type of ROS determine the ability of cells to undergo cell death. Furthermore, dysregulation of the antioxidant pathways is associated with many diseases. It has become apparent that cell death can occur through different mechanisms leading to the classifications of different types of cell death such as apoptosis, ferroptosis, and necroptosis. ROS play essential roles in all forms of cell death, but it is only now coming into focus that ROS control and determine the type of cell death that occurs in any given cell.
Cellular reactive oxygen species (ROS) are tightly controlled to dictate different cell fates, such as differentiation or cell survival. When ROS are produced in excess, such as in cells under metabolic stress, this leads to cell death. This suggests that a “ROS rheostat” exists in cells controlling cellular survival. This rheostat controls ROS levels in the context of cellular microenvironmental signals ensuring that appropriate cellular functions are conducted. This is accomplished by ROS participating in cell signaling pathways, for example, during cell adhesion, host defense, or gene expression. When in excess, ROS may have deleterious effects on signaling and cellular damage leading to cell death.
The different types of cell death induce specific cell signaling pathways. Nevertheless, there are common features among these cell death pathways. One predominant feature is the reliance on ROS signaling and control. ROS produced by cells under stress, or cells with reduced antioxidant capacity, can determine whether the cell survives or dies, and the type of cell death mechanism engaged. This ability of ROS to act as a rheostat determining not only cell death but the type of cell death is only now coming into focus under pathological or physiological conditions.
Reactive oxygen species (ROS) is a type of unstable molecule that contains oxygen and easily reacts with other molecules in a cell [7]. ROS include reactive molecule derivatives of oxygen (nonradicals) and also oxygen-centered radicals (free radicals). Free radicals and nonradicals can react with each other to produce more free radicals and nonradicals; for instance, two superoxide anions ($O_2^{\bullet-}$) can react to form hydrogen peroxide (H_2O_2), a nonradical ($2O_2^{\bullet-} + 2H_2 \longrightarrow H_2O_2 + O_2$). In turn, hydrogen peroxide can break down in the presence of transition metal ions to produce hydroxyl radical HO^-, the most reactive and damaging of all oxygen free radicals [4, 8, 9]. Other oxygen-derived free radicals are peroxide ion ($O_2^{\bullet 2-}$), perhydroxyl radical ($HO_2^{\bullet}$), alkoxyl radical ($RO^{\bullet}$), and peroxyl radical ($ROO^{\bullet}$). Singlet oxygen ($^1O_2$) and hypochlorous acid (HOCL) are other nonradical derivatives of oxygen [10, 11].
Under physiological conditions, ROS are generated by numerous sources including mitochondria respiratory chain (the major source), NADPH oxidases, xanthine oxidases, lipoxygenases, nitric oxide synthases, and cyclooxygenases (Figure 1). Ninety percent of ROS are generated when electrons escape from the mitochondrial electron transport chain (ETC).
The electrons in the ETC leak out and interact with oxygen to produce superoxide or hydrogen peroxide.
Antioxidants are responsible for ROS elimination or prevention of ROS formation to avoid damaging oxidative stress. The antioxidant systems can be divided as enzymatic and nonenzymatic (Table 1). The first one consists mainly in superoxide dismutases, catalase, glutathione peroxidases, peroxiredoxins, and thioredoxins. Nonenzymatic antioxidants are molecules that act by directly quenching free radicals or by radical scavenging; this include but are not limited to vitamins E, C, and A; glutathione; and uric acid [8, 10, 25].

Table 1

Antioxidants and their targets.

Enzymatic antioxidants		
Antioxidant	**ROS**	**Reaction**
Superoxide dismutases	Superoxide	$O_2^{\bullet-} + e^- + 2H^+ \longrightarrow H_2O_2$
Catalase	Hydrogen peroxide	$2H_2O_2 \longrightarrow 2H_2O + O_2$
Glutathione peroxidase	Hydrogen peroxide	$H_2O_2 + 2GSH \longrightarrow 2H_2O + GSSG$
Thioredoxins	Oxidized proteins	$R\text{-}S_2 + Trx\text{-}(SH)_2 \longrightarrow R\text{-}(SH)_2 + Trx\text{-}S_2$
Peroxiredoxin	Hydrogen peroxide	$H_2O_2 + Prx\text{-}S^{\bullet} \longrightarrow H_2O + Prx\text{-}SOH$ $H_2O_2 + Prx\text{-}SOH \longrightarrow H_2O + Prx\text{-}SO_2H$
Nonenzymatic antioxidants		
Antioxidant	ROS	Reaction
GSH	Hydrogen peroxide Oxygen radicals	$2GSH + H_2O_2 \longrightarrow GSSG + 2H_2O$ $GSSG + NADPH + H^{\bullet} \longrightarrow 2GSH + NADP^+$
$\alpha^{\bullet}$-Tocopherol (vitamin E)	Lipid peroxyl radicals	$\alpha\text{-}TOH + LOO^{\bullet} \longrightarrow \alpha\text{-}TO^{\bullet} + LOOH$ $\alpha\text{-}TO^{\bullet} + AscH^{-\bullet} \longrightarrow \alpha\text{-}TOH + Asc^{\bullet-}$
Ascorbic acid (vitamin C)	Free radicals, iron, and copper	$AscH^{-\bullet} \rightarrow Asc^{\bullet-} + 2H^+ + 2e$

The balance between prooxidant and antioxidant regulatory mechanisms within a cell determines whether it survive or dies. Under physiological conditions, the

production of reactive oxygen species (ROS) is counterbalanced by their elimination and/or prevention of formation to maintain a steady-state (stationary) ROS level. This maintains cellular homeostasis, allowing ROS to act as signaling molecules to accomplish physiological functions. When this balance is lost, favouring enhanced ROS levels (through increased ROS production or decreased antioxidants), oxidative damage can occur on proteins, lipids, DNA, nucleic acids, and other macromolecules, leading to functional disturbances and eventually to cell death

https://www.sciencedirect.com/science/article/abs/pii/S1040842824001045
The involvement of ROS-regulated programmed cell death in hepatocellular carcinoma 2024
We discussed ROS as a “Double-edged sword” intumorigenesis.
We summarized the mechanism of ROS regulating hepatocellular carcinoma through programmed cell death. ·We disscused the potential therapies targeting ROS-regulated cell death.
Reactive oxidative species (ROS) is a crucial factor in the regulation of cellular biological activity and function, and aberrant levels of ROS can contribute to the development of a variety of diseases, particularly cancer. Numerous discoveries have affirmed that this process is strongly associated with "programmed cell death (PCD)," which refers to the suicide protection mechanism initiated by cells in response to external stimuli, such as apoptosis, autophagy, ferroptosis, etc. Research has demonstrated that ROS-induced PCD is crucial for the development of hepatocellular carcinoma (HCC). These activities serve a dual function in both facilitating and inhibiting cancer, suggesting the existence of a delicate balance within healthy cells that can be disrupted by the abnormal generation of reactive oxygen species (ROS), thereby influencing the eventual advancement or regression of a tumor. In this review, we summarize how ROS regulates PCD to influence the tumorigenesis and progression of HCC. Studying how ROS-induced PCD affects the progression of HCC at a molecular level can help develop better prevention and treatment methods and facilitate the design of more effective preventative and therapeutic strategies.
Tumor cells typically produce more ROS due to their rapid growth and metabolic abnormalities, leading to persistent oxidative stress. To adapt to this high-level oxidative stress environment, tumor cells enhance their antioxidant capacity, such as increasing the level of GSH and NADPH to protect cells from impairment. Generally speaking, the level of ROS in the tumor microenvironment is elevated compared to that in normal cells, which is attributed to the rapid proliferation rate, high metabolic activity, increased ability to invade the periphery, and resistance to chemotherapeutic agents. Simultaneously, tumor cells adapt to such high pressure and cultivate a matching antioxidant system, so that the ROS in the tumor microenvironment is regulated to a level compatible with the active cell biological function of the tumor but still higher than that of normal cells. On one hand, moderate levels of ROS in tumors can stimulate tumor cell proliferation, metastasis, and drug resistance by modulating some signaling pathways, such as PI3K/AKT, MAPK, NF-κB, and so on. On the other hand, excessive levels of ROS in turn can suppress tumor cell growth and survival, by triggering programmed cell death, such as apoptosis, necrosis, autophagy, and ferroptosis(Porporato et al., 2018). Therefore, ROS have a double-edged sword role in cancer, and their effects depend on the type, level, source, and duration of ROS exposure(Luo et al., 2016).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8049370/
Advances in Imaging Reactive Oxygen Species 2021
Reactive oxygen species (ROS) play a pivotal role in many cellular processes and can be either beneficial or harmful. The design of ROS-sensitive fluorophores has allowed for imaging of specific activity and has helped elucidate mechanisms of action for ROS. Understanding the oxidative role of ROS in the many roles it plays allows us to understand the human body. This review provides a concise overview of modern advances in the field of ROS imaging.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7978298/
The double-edged roles of ROS in cancer prevention and therapy 2021
These double-edged roles in cancer progression include the ROS-dependent malignant transformation and the oxidative stress-induced cell death.
Ultraviolet radiation (UVR) increases oxidative stress not only by upregulating nitric oxide synthase (NOS) synthesis but also by impeding catalase (CAT) to scavenge hydrogen peroxide, thus leading to increased risk of sunburn, photoaging and skin cancer [16].
Ionizing radiation (IR) stimulates ROS generation by immediately inducing extracellular water radiolysis or causing intracellular mitochondrial metabolic disorder, thereby destroying cancer cells or, conversely, facilitating their survival and metastasis [17]. Besides, many carcinogens in the environment play oncogenic roles by inducing ROS accumulation.
The two major sources of endogenous ROS are the **mitochondrial respiratory chain**, which generates ROS as a byproduct [18, 19], and active **NADPH oxidases (NOXs)**, whose primary function is ROS production. In addition, peroxisomes and endoplasmic reticulum membranes have also been identified as cellular sites of ROS generation [20, 21]. Here, we mainly discuss research status on ROS production in mitochondria and by NOXs (Figure (Figure11).
Mitochondria-derived ROS
In mammalian cells, the mitochondrial electron transport chain (ETC) is the main source of ATP 22. However, during oxidative phosphorylation and energy transduction, approximately 1% of molecular oxygen gains electrons leaked from the ETC, yielding superoxide 23. Some superoxide is released into the cytoplasm through the mitochondrial permeability transition pore (MPTP) located in the outer mitochondrial membrane (OMM) 24. However, most superoxide is dismutated to H2O2 by superoxide dismutases (SODs) in the mitochondrial matrix or intermembrane space (IMS) 25. H2O2 is highly diffusible and specifically carried into the cytoplasm by aquaporins (aquaporins 3 and 8) as a second messenger to regulate multiple signaling pathways 26, 27.
Antioxidant defense mechanisms
Antioxidant defense systems sustain the balance between the generation and neutralization of ROS to maintain redox equilibrium and protect macromolecules from indiscriminate destruction inflicted by oxidative stress (Figure (Figure11).

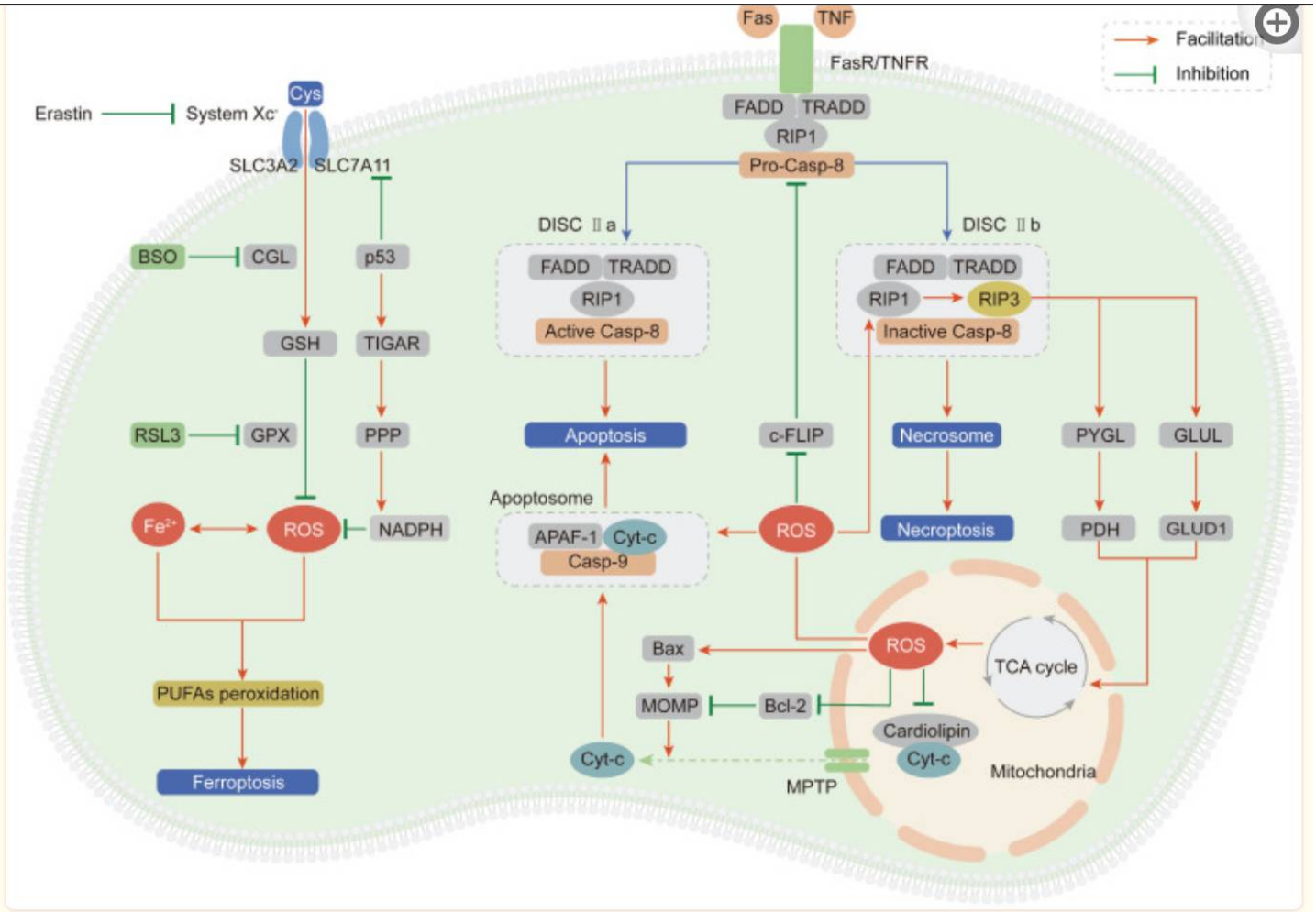


Figure 3

ROS induce cell death, mainly including apoptosis, necroptosis and ferroptosis. (I) Exceeding ROS promote both the extrinsic and intrinsic apoptosis pathway: ROS activate extrinsic apoptosis pathway by accelerating the ubiquitin degradation of c-FLIP, then enhancing the binding between the adaptor protein and pro-caspase-8; ROS induce intrinsic apoptosis by facilitating the release of Cyt-c from mitochondria to cytoplasm to form apoptosome with casp-9 and APAF-1. (II) ROS and necroptosis form a positive feedback loop: ROS stabilize RIP3 protein to lead to the formation of DISC IIb (necrosome); in turn, RIP3 can facilitate the TCA cycle and aerobic respiration in mitochondria to induce ROS generation. (III) Ferroptosis is a ROS-dependent form of RCD: the basic of ferroptosis is GSH anabolism disorder leads to the lethal accumulation of PUFAs peroxidation; p53 plays opposite roles on ROS and ferroptosis by inhibiting SLC7A11 expression or increasing NADPH production.

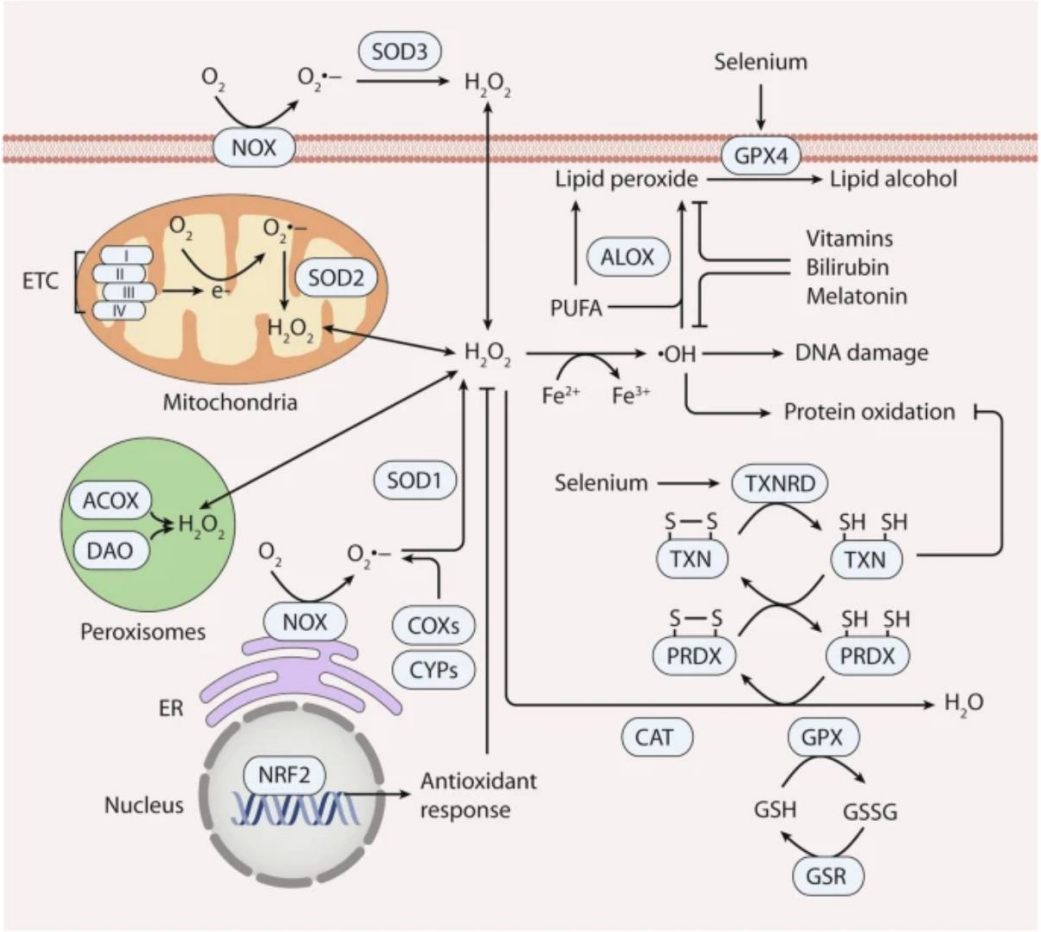
https://pubmed.ncbi.nlm.nih.gov/29124687/
Ultraviolet Light Induced Generation of Reactive Oxygen Species 2017
More specifically UV light can induce ROS by affecting the enzyme catalase and up-regulating nitric oxide synthase (NOS) synthesis. It may also cause a decrease in protein kinase C (PKC) expression leading to increased ROS production. UVR is capable of modifying DNA and other chromophores resulting in elevated ROS levels. The effects of raised ROS levels can vary based on the intracellular oxidant status of the cell.

https://www.nature.com/articles/s41419-024-06939-5
Oxidative cell death in cancer: mechanisms and therapeutic opportunities 2024

Reactive oxygen species (ROS) are highly reactive oxygen-containing molecules generated as natural byproducts during cellular processes, including metabolism. Under normal conditions, ROS play crucial roles in diverse cellular functions, including cell signaling and immune responses. However, a disturbance in the balance between ROS production and cellular antioxidant defenses can lead to an excessive ROS buildup, causing oxidative stress. This stress damages essential cellular components, including lipids, proteins, and DNA, potentially culminating in oxidative cell death. This form of cell death can take various forms, such as ferroptosis, apoptosis, necroptosis, pyroptosis, paraptosis, parthanatos, and oxeiptosis, each displaying distinct genetic, biochemical, and signaling characteristics. The investigation of oxidative cell death holds promise for the development of pharmacological agents that are used to prevent tumorigenesis or treat established cancer. Specifically, targeting key antioxidant proteins, such as SLC7A11, GCLC, GPX4, TXN, and TXNRD, represents an emerging approach for inducing oxidative cell death in cancer cells. This review provides a comprehensive summary of recent progress, opportunities, and challenges in targeting oxidative cell death for cancer therapy.

While moderate ROS levels are involved in a spectrum of signaling pathways that are vital for cell growth, differentiation, and progression, elevated ROS levels are potent triggers of cell death [7]. In cancer cells, heightened oxidative stress results from increased ROS production and/or compromised ROS-scavenging capacity [8]. Even a slight elevation in ROS levels within cancer cells relative to that in normal cells can surpass a critical threshold, inducing cancer cell death and suppressing tumor development [9]. Thus, agents that induce ROS generation hold the potential to be used in targeted strategies for eradicating malignancies.

Fig. 1: Overview of ROS generation and elimination.



Reactive oxygen species (ROS) are labile oxygen-containing molecules primarily generated by the mitochondrial electron transport chain (ETC), peroxisomes, NADPH oxidase (NOX), lipoxygenase (ALOX), cyclooxygenases (COXs), and cytochrome P450s (CYPs). ROS elimination is facilitated by antioxidant systems, encompassing enzymatic antioxidants (e.g., SOD, CAT, GPX, and the thioredoxin [TXN]-thioredoxin reductase [TXNRD] system) and non-enzymatic antioxidants (e.g., glutathione [GSH], vitamins or analogs, selenium, and metabolites such as bilirubin and melatonin). Superoxide dismutase (SOD) transforms $O_2^{\bullet-}$ into H_2O_2, subsequently reduced to H_2O by catalase (CAT), glutathione peroxidase (GPX), or peroxiredoxins (PRDX). Among these, ALOX significantly contributes to lipid peroxidation, while GPX4, a selenocysteine-containing enzyme, quenches lipid peroxides. Central to the antioxidant network, TXNRD—a pivotal selenoprotein antioxidant—donates electrons to the TXN–PRDX axis. Moreover, the transcription factor NRF2 prominently regulates the antioxidant system, orchestrating the expression of genes crucial to antioxidant defense mechanisms.

https://www.sciencedirect.com/science/article/pii/S0160412024001211

Current insights and future perspectives of ultraviolet radiation (UV) exposure: Friends and foes to the skin and beyond the skin 2024

6. UV light as a treatment

UV light is a double-edged sword for health. Although UV light can damage the body's health, it can also be involved in the synthesis of some beneficial substances and can be used as a means of treating some diseases (Table 1). UV involved in the synthesis of vitamin D in the human body, which is not deficient in the right amount of sunlight exposure (Knuschke, 2021). UVB radiation induces the synthesis of pro-vitamin D3 in the skin, and 7-dehydrocholesterol or vitamin D3 precursors undergo photochemical reactions in the epidermal layer of spiny cells and basal cell layer to form vitamin D3, which then goes to the liver and kidneys for a series of transformations to eventually form vitamin D (Mohania et al., 2017).

UV radiation may be associated with reduced cancer risks. Vitamin D synthesis is largely determined by UV exposure, from which 70 % of vitamin D is derived. In an animal study, Fabpl-Cre; Apc15flox/+ mice that developed intestinal tumors were used, and UVB irradiation were applied. The UV-irradiated group exhibited reduced progression to malignancy in comparison to the control group (Rebel et al., 2015).

Phototherapy is extensively employed in the treatment of bone cancer, which is clinically accepted, minimally invasive and highly targeted. When subjected to irradiation at specific wavelengths, the photosensitizer in PDT can **elevate intracellular ROS levels**, while the photothermal agent in PTT can induce photothermal conversion, effectively eliminating tumor cells (Sun et al., 2021).

https://pubmed.ncbi.nlm.nih.gov/32331350/
Low-Frequency Magnetic Fields (LF-MFs) Inhibit Proliferation by Triggering Apoptosis and Altering Cell Cycle Distribution in Breast Cancer Cells 2020
Magnetic fields, as a non-invasive therapy, have shown anti-tumor effects in vitro and in vivo; however, the detailed mechanisms involved are still not clear. In this study, we found that in exposure to low-frequency magnetic fields (LF-MFs) with an intensity of 1 mT and frequencies of 50, 125, 200, and 275 Hz, separately, the proliferation of breast cancer cells was inhibited and LF-MF with 200 Hz reached the optimum inhibition effect, on exposure time-dependently. Notably, we found that exposure to LF-MF led to MCF-7 and ZR-75-1 cell apoptosis and cell cycle arrest. Moreover, we also discovered that LF-MF effectively increased the level of reactive oxygen species (ROS), suppressed the PI3K/AKT signaling pathway, and activated glycogen synthase kinase-3β (GSK-3β). We demonstrated that the GSK3β activity contributed to LF-MF-induced cell proliferation inhibition and apoptosis, while the underlying mechanism was associated with the inhibition of PI3K/AKT through increasing the intracellular ROS accumulation. These results indicate that LF-MF with a specific frequency may be an attractive therapy to treat breast cancers.

https://pubmed.ncbi.nlm.nih.gov/20610864/
Effects of extremely low frequency magnetic field on the parameters of oxidative stress in heart 2010
Exposure to ELF-MF (40 Hz, 7 mT, 30 min/day for 2 weeks) did not significantly alter tissue TBARS, H(2)O(2), total free -SH groups, reduced glutathione (GSH) and total antioxidant capacity of plasma. By contrast, ELF-MF with the same frequency and induction but used for 60 min/day for 14 days caused significant increase in TBARS and H(2)O(2) concentration ($P<0.01$) and decrease in the concentration of GSH ($P<0.05$) and total free -SH groups in heart homogenates. Moreover, exposure of rats to ELF-MF (40 Hz, 7 mT, 60 min/day for 2 weeks) resulted in the decrease of plasma antioxidant capacity. Our results indicate that effects of ELF-MF on ROS generation in the heart tissue and antioxidant capacity of plasma depend on its working time.

https://pubmed.ncbi.nlm.nih.gov/22314568/
Effects of extremely low frequency magnetic field on oxidative balance in brain of rats 2011
The animals were divided into 3 groups: I - control (shame) group; II - exposed to the following parameters of the magnetic field: 7 mT, 40 Hz, 30 min/day, 10 days; III - exposed to the ELF-MF parameters of 7 mT, 40 Hz, 60 min/day, 10 days.
The study has shown that ELF-MF applied for 30 min/day for 10 days can affect free radical generation in the brain. Prolongation of the exposure to ELF-MF (60/min/day) caused adaptation to this field. The effect of ELF-MF irradiation on oxidative stress parameters depends on the time of animal exposure to magnetic field.

https://pubmed.ncbi.nlm.nih.gov/35746959/
Bidirectional Effect of Repeated Exposure to Extremely Low-Frequency Electromagnetic Field (50 Hz) of 1 and 7 mT on Oxidative/Antioxidative Status in Rat's Brain: The Prediction for the Vulnerability to Diseases 2022
Results showed that repeated exposure changed the oxidative/antioxidative status depending on the intensity of the EMF and the number of exposures. 1 mT EMF created weak changes in the oxidative status in the brain; however, 7 mT EMF moved the balance to a clearly higher level. The changes in the oxidative status after 1 mT EMF were enough to reduce, and after 7 mT EMF to intensify oxidative processes in response to the next stress.

https://pubmed.ncbi.nlm.nih.gov/24334533/
Extremely low frequency magnetic fields induce oxidative stress in rat brain 2013
The continuous exposure to ELF-MF caused OS (oxidative stress) in all the examined regions of brain more significantly at 100 μT than at 50 μT.

https://pubmed.ncbi.nlm.nih.gov/27399314/
Magnetic fields, radicals and cellular activity 2016
Some effects of low-intensity magnetic fields on the concentration of radicals and their influence on cellular functions are reviewed. These fields have been implicated as a potential modulator of radical recombination rates. Experimental evidence has revealed a tight coupling between cellular function and radical pair chemistry from signaling pathways to damaging oxidative processes. The effects of externally applied magnetic fields on biological systems have been extensively studied, and the observed effects lack sufficient mechanistic understanding. Radical pair chemistry offers a reasonable explanation for some of the molecular effects of low-intensity magnetic fields, and changes in radical concentrations have been observed to modulate specific cellular functions. Applied external magnetic fields have been shown to induce observable cellular changes such as both inhibiting and accelerating cell growth. These and other mechanisms, such as cell membrane potential modulation, are of great interest in cancer research due to the variations between healthy and deleterious cells. Radical concentrations demonstrate similar variations and are indicative of a possible causal relationship. Radicals, therefore, present a possible mechanism for the modulation of cellular functions such as growth or regression by means of applied external magnetic fields.

https://pubs.aip.org/aip/apl/article-abstract/125/10/103701/3311147/Radical-pair-mechanism-and-the-role-of-chirality?redirectedFrom=fulltext
Radical pair mechanism and the role of chirality-induced spin selectivity during planaria regeneration 2024
Planaria serve as an intriguing model system wherein the effects of electric and magnetic fields on various biochemical pathways during cell morphogenesis can be studied. Recent experimental observations have demonstrated the non-trivial modulation of reactive oxygen species (ROS) levels by a weak magnetic field (WMF) during planaria regeneration. However, the underlying biophysical mechanism behind this remains elusive. In this work, we investigate the role of the radical pair mechanism (RPM) and attempt to explain the experimental results of the effect of WMFs on ROS modulation during planaria regeneration.

https://royalsocietypublishing.org/doi/full/10.1098/rsif.2022.0325
Magnetic field effects in biology from the perspective of the radical pair mechanism 2022
Hundreds of studies have found that weak magnetic fields can significantly influence various biological systems. However, the underlying mechanisms behind these phenomena remain elusive. Remarkably, the magnetic energies implicated in these effects are much smaller than thermal energies. Here, we review these observations, and we suggest an explanation based on the radical pair mechanism, which involves the quantum dynamics of the electron and nuclear spins of transient radical molecules.
Sensitivity to weak magnetic fields is abundant throughout biology, as discussed in numerous review articles [1–24]. Effects of either static or oscillating weak magnetic fields have been reported on the circadian clock, electron transfer in cryptochrome, stem cells, calcium concentration, the brain's functions such as action potentials, reactive oxygen species (ROS), development, neuronal activities, DNA, memory, anxiety, analgaesia, genetics and many other functions (see §2). Despite the wealth of observations, thus far, there is no clear explanation for the mechanism behind these phenomena. This is mainly due to the fact that the

corresponding energies for such effects are far smaller than thermal energies.
However, there is a promising quantum physics (or spin chemistry) concept that can account for the effects of such weak fields, namely the radical pair mechanism [25,26].

https://onlinelibrary.wiley.com/doi/full/10.1002/qua.24943
Radical Pair Mechanism 2015
A radical is an atom, molecule or ion that has unpaired valence electrons. Radicals and radical pairs often play a very important role as intermediates in thermal, radiation, and photochemical reactions.1 The presence of unpaired electron spins in these systems allows one to influence and control these reactions using interactions between external magnetic fields and electron spins.2 However, until 1970, most scientists believed that ordinary magnetic fields had no significant effect on chemical or biochemical reactions, as the magnetic energy of typical molecules, under ordinary magnetic fields, is much smaller than the thermal energy at room temperature and is much smaller than the activation energies for those reactions.1, 2 This situation changed significantly in the 1970s after a series of experimental results were reported on magnetic field effects on chemical reactions.3-7 Because of these experimental studies, a number of researchers have made an effort to theoretically explain the magnetic field effects on the chemical reactions.8, 9 Thanks to these and the subsequent efforts, we are now able to explain systematically magnetic field effects in terms of the radical pair mechanism. The radical pair mechanism was then successfully applied to explain the chemically induced nuclear polarization and electron polarization, which were shown to be based on the spin dynamics of radical pairs.2

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6353618/
Weak magnetic fields alter stem cell–mediated growth 2019
Weak magnetic fields affect reactive oxygen species levels, stem cell proliferation/differentiation, and new tissue growth.
While strong magnetic fields are known to change chemical reaction rates and free radical concentrations, the debate remains about whether static weak magnetic fields (WMFs; <1 mT) also produce biological effects. Using the planarian regeneration model, we show that WMFs altered stem cell proliferation and subsequent differentiation via changes in reactive oxygen species (ROS) accumulation and downstream heat shock protein 70 (Hsp70) expression.
WMFs were also found to produce transient induction of the membrane permeability transition and increased cytosolic cytochrome c levels in human amniotic cells via an increase in reactive oxygen species (ROS) (*13*).

https://pubmed.ncbi.nlm.nih.gov/26807660/
Extremely low frequency magnetic fields regulate differentiation of regulatory T cells: Potential role for ROS-mediated inhibition on AKT 2016
Our previous studies showed that extremely low frequency magnetic fields (ELF-MFs) inhibited tumor growth and change proportion of splenic regulatory T cells (Treg cells). Here, we focus on the effect of ELF-MFs on lung metastatic melanoma mouse model and the regulatory mechanism of ELF-MFs on the differentiation of Treg cells. Tumor-bearing mice were exposed to sham ELF-MFs and ELF-MFs (0.4 T, 7.5 Hz) 2 h/day for 27 days. Metastatic tumor burden of lung was significantly decreased after ELF-MF treatment.
Taken together, our data show that ELF-MF exposure promoted the inhibitory effect of ROS on AKT pathway and decreased Foxp3 expression, which provides an explanation for why ELF-MF exposure can inhibit differentiation of Treg cells and enhance antitumor effect in metastatic melanoma mouse model.

https://www.mdpi.com/1422-0067/22/11/5785
Modulation of Cellular Response to Different Parameters of the Rotating Magnetic Field (RMF)—An In Vitro Wound Healing Study 2021
The presented study was conducted to determine whether a low-frequency RMF (rotating magnetic field) with different field parameters could evoke the cellular response in vitro and is possible to modulate the cellular response. The cellular metabolic activity, ROS and Ca^{2+} concentration levels, wound healing assay, and gene expression analyses were conducted to evaluate the effect of RMF. It was shown that different values of magnetic induction (B) and frequency (f) of RMF evoke a different response of cells, e.g., increase in the general metabolic activity may be associated with the increasing of ROS levels. The lower intracellular Ca^{2+} concentration (for 50 Hz) evoked the inability of cells to wound closure. It can be stated that the subtle balance in the ROS level is crucial in the wound for the effective healing process, and it is possible to modulate the cellular response to the RMF in the context of an in vitro wound healing.

https://pubmed.ncbi.nlm.nih.gov/28936716/
Induction of reactive oxygen species: an emerging approach for cancer therapy 2017
Reactive oxygen species (ROS), a group of ions and molecules, include hydroxyl radicals (·OH), alkoxyl radicals, superoxide anion (O_2·-), singlet oxygen ($^1O_2$) and hydrogen peroxide (H_2O_2). Hydroxyl radicals and alkoxyl radicals are extremely and highly reactive species respectively. Endogenous ROS are mainly formed in mitochondrial respiratory chain. Low levels of ROS play important roles in regulating biological functions in mammalian cells. However, excess production of ROS can induce cell death by oxidative damaging effects to intracellular biomacromolecules. Cancer cell death types induced by ROS include apoptotic, autophagic, ferroptotic and necrotic cell death. Since abnormal metabolism in cancer cells, they have higher ROS content compared to normal cells. The higher endogenous ROS levels in cancer cells endow them more susceptible to the ROS-induction treatment. Indeed, some anticancer drugs currently used in clinic, such as molecular targeted drugs and chemotherapeutic agents, effectively kill cancer cells by inducing ROS generation. In addition, photodynamic therapy (PDT) is mainly based on induction of ROS burst to kill cancer cells. The mechanism of cell death induced by radiotherapy using ionizing radiation also refers to ROS production. Moreover, ROS play an important role in tumor immune therapy. Altogether, combining above traditional treatments with ROS-induced agents will be considered as a promising strategy in cancer therapy. In this review, we focus on our current understanding of the anticancer effects of ROS.