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THE SWORD OF ROS IN CANCER

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ABSTRACT

Cancer is a disease involving abnormal cell growth with the potential to invade or spread to other parts of the body. This disease is a complex heterogeneous disease with high mortality and absence of procedures for early detection. The most common factors to cause cancer include aging, tobacco, sun exposure, radiation exposure, chemicals and other substances, some viruses and bacteria, certain hormones, inheritance of cancer, alcohol, poor diet, lack of physical activity, or being overweight. Genetic mutations lead to cancer by accelerating cell division rates or inhibiting normal control over the mechanism, such as cell cycle arrest or programmed cell death or necrosis. As a mass of cancerous cells grows enormously and develop into a tumor. The prime important molecule in cancer is Reactive Oxygen Species, which play a dual role. These molecules constantly generated and eliminated in the biological system and are required to drive regulatory pathways. Under normal physiological conditions, cells control ROS levels by balancing the generation of ROS with their elimination by scavenging systems. But under oxidative stress conditions, excessive ROS molecules which can damage cellular proteins, lipids and DNA, leading to cause fatal lesions in the cell that contribute to carcinogenesis. Uneven rise in intracellular ROS moiety result in cancer cell cycle arrest, senescence and apoptosis leading to cancer. This can be prevented with cancer chemotherapy, depletion of cells from antioxidant proteins or generation of ROS by immune cells. (Geou-Yarh Liou and Peter Storz 2010). Cancer cells have greater ROS stress than normal cells due to oncogenic stimulation, increased metabolic activity and mitochondrial malfunction.

Reactive Oxygen Species Types

Reactive oxygen species (ROS) are chemically reactive species containing oxygen. For example it includes peroxides, superoxide, hydroxyl radical, **singlet oxygen**, and alpha-oxygen.

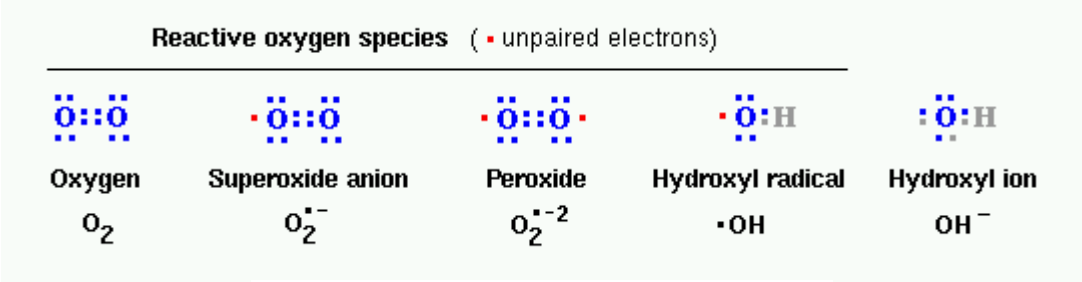


Fig. 1: Reactive oxygen species (vivo.colostate.edu).

ROS can be divided into two groups: free oxygen radicals and non-radical ROS. Free oxygen radicals consists of superoxide (O2•−), hydroxyl radical (•OH), nitric oxide (NO•), organic radicals (R•), peroxyl radicals (ROO•), alkoxyl radicals (RO•), thiyl radicals (RS•), sulfonyl radicals (ROS•), thiyl peroxyl radicals (RSOO•), and disulfides (RSSR). Non-radical ROS include hydrogen peroxide (H2O2), singlet oxygen (1O2), ozone/trioxygen (O3), organic hydroperoxides (ROOH), hypochloride (HOCl), peroxynitrite (ONO−), nitrosoperoxycarbonate anion (O=NOOCO2 −), nitrocarbonate anion (O2NOCO2 −), dinitrogen dioxide (N2O2), nitronium (NO2 +), and highly reactive lipid-or carbohydrate derived carbonyl compounds. Among

them, superoxide, hydrogen peroxide and hydroxyl radicals are the most well studied ROS in cancer. (Geou-Yarh Liou and Peter Storz 2010).

FREE OXYGEN RADICALS	NON-RADICAL ROS
Superoxide (O2•−),	Hydrogen Peroxide (H2O2),
Hydroxyl Radical (•OH),	Singlet Oxygen (1O2)
Nitric Oxide (NO•)	Ozone/Trioxygen (O3)
Organic Radicals (R•)	Organic Hydroperoxides (ROOH)
Peroxyl Radicals (ROO•)	Hypochloride (Hocl)
Alkoxyl Radicals (RO•),	Peroxynitrite (ONO−)
Thiyl Radicals (RS•)	Nitrosoperoxy carbonate Anion (O=NOOCO2 −)
Sulfonyl Radicals (ROS•)	Dinitrogen Dioxide (N2O2)
Thiyl Peroxyl Radicals (RSOO•),	Nitronium (NO2 +)
Disulphides(RSSR•)	

Generation of Reactive Oxygen Species

The generation of reactive oxygen species occurs by two ways, one is mitochondrial oxidation pathways along with NADPH Oxidases (NOX) and another is cellular response to other factors such as cytokines, bacterial invasion, xenobitics etc. Among these all reactive oxygen species, superoxide, hydrogen peroxide and hydroxyl radicals are the most well studied ROS in cancer. . In mitochondrial oxidation pathways that is in electron transport chain the five enzyme complexes ,Superoxide radicals generated at complexes I and III are released into the intermembrane space which comprises 80% of superoxide radicals generated in the mitochondria and remaining 20% are made by mitochondrial matrix. The mitochondrial permeability transition pore in the outer membrane of the mitochondrion allows the passage of superoxide radicals into the cytoplasm where it is dismutated to hydrogen peroxide, a highly diffusible secondary messenger.

There is an another major site for the generation of ROS termed as peroxisomes where superoxide and H2O2 are generated through xanthine oxidase in the peroxisomal matrix and membranes. Other sources of ROS include endogenous metabolites such as fatty acids, prostaglandins, and exogenous components including drugs, flavorings, coloring agents, antioxidants, etc. These substances are modified in the smooth endoplasmic reticulum and transformed into free radicals, especially ·OH. The NOX-mediated mechanism involves various stages such as activation of NOX genes and transmembrane proteins for the transport of electrons across biological membranes where there is a reduction of molecular oxygen into superoxide by NOX as a part of redox signaling. (Burdon RH.1995)

Oxidative Stress–Induced ROS Generation

Free radicals' contribution is versatile in carcinogenesis and the malignant progression of tumor cells, which may be considered as a unique characteristic of cancer. In general, low concentration of ROS acts as the mitogens and promotes cell proliferation and survival, whereas intermediate concentration leads to a transient or permanent cell cycle arrest and induces cell differentiation. At high concentration, ROS may induce oxidative damage, especially in the DNA, causing mutations which eventually lead to cancer. (Goustin AS, et al. 1986)

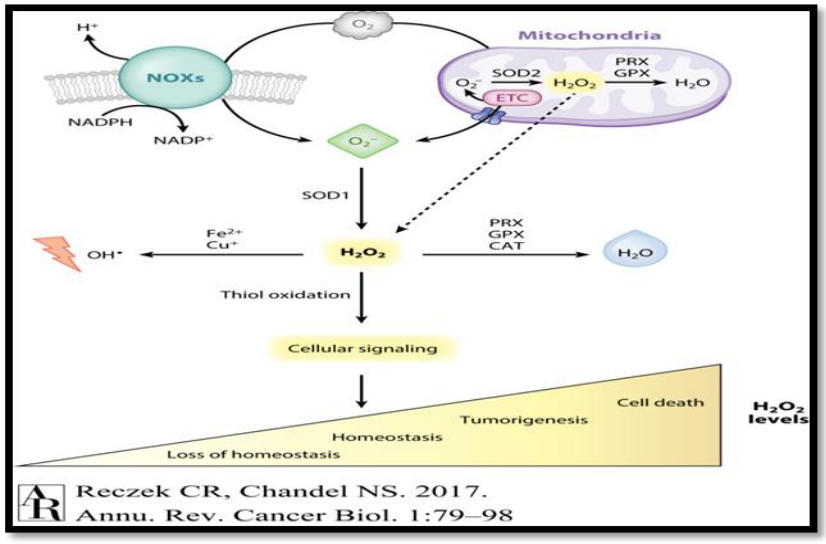
ROS in Genomic Instability and Cancer Development

Cancer cells show metabolic oxidative stress compared with normal cells, which is mainly due to inherent mitochondrial dysfunction and NOX activation. As a part of metabolic reactions, high levels of ROS are generated and unregulated levels can lead to oxidative damage such as DNA mutation–causing initiation and slow progression of cancer. These oxidative damages comprise a mixture of DNA lesions including base damage, DNA single-strand breaks, and DNA double strand breaks, rearrangement of DNA sequence, base modification, DNA miscoding lesions, gene amplification, and oncogenes activation.

Role of ROS as an anticancer agent

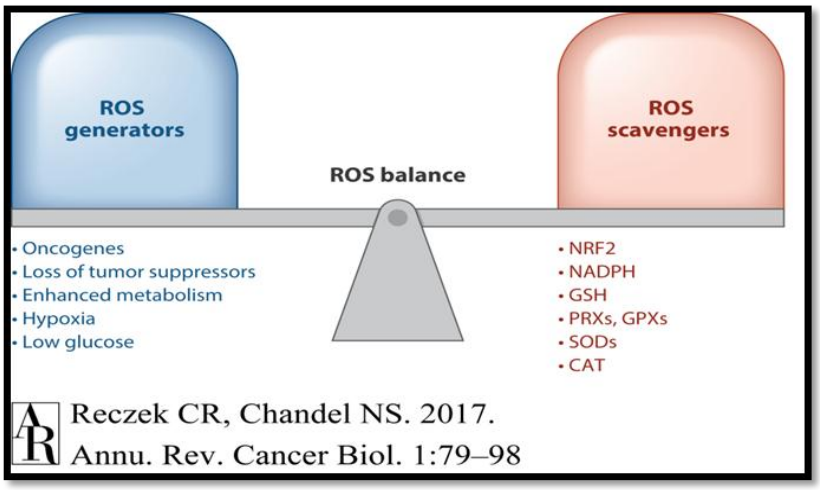
ROS have important role in tumor suppression and tumor promotion depending on their concentrations. Moreover, most cancer cells have higher levels of ROS than normal cells, which is beneficial for their survival and development. Higher the level of ROS, the antioxidant capacity of cancer cells is regulated to maintain redox balance and prevent ROS levels from excessive increase to induce cell death (M. Schieber and N. S. Chandel 2014) (C. Gorrini, I. S. Harris, and T. W. Mak, 2013). However, this effect is very limited in tumor cells. Therefore, either increasing or reducing ROS can be an effective strategy in cancer therapy by disrupting redox balance in tumor cells (S. Galadari, A. Rahman, 2014).

ROS Regulation



ROS Homeostasis

Normal cell survival and proper cell signaling are two important facors in ROS homeostasis. Low levels of ROS can activate signaling pathways to regulate metabolic adaptation, differentiation, and cellular proliferation in a controlled manner (Sena & Chandel 2012). Compared with normal cells, cancer cells have an higher production of spatially localized ROS that hyperactivates the cell signaling pathways necessary for cellular transformation and tumorigenesis (Sabharwal & Schumacker 2014).



Balance of reactive oxygen species (ROS) in cancer cells. Cancer cells increase the rate of localized ROS production to hyperactivate cell signaling pathways necessary for tumorigenesis. ROS accumulation can occur as a result of oncogene activation, tumor suppressor loss, increased metabolic activity, nutrient deprivation (e.g., low glucose), or limited oxygen (i.e., hypoxia). Because excessive ROS levels can induce oxidative damage and cell death, cancer cells regulate ROS accumulation by increasing their antioxidant capacity. Cancer cells activate the transcription factor NRF2 (nuclear factor erythroid 2–related factor 2) to increase the expression of antioxidants, such as superoxide dismutases (SODs), peroxiredoxins (PRXs), glutathione peroxidases (GPXs), and catalase (CAT); genes involved in NADPH production; glutathione (GSH) synthesis and utilization genes; and detoxification enzymes. This delicate balance between ROS production and ROS elimination maintains an optimal ROS level for protumorigenic signaling.

HERBAL NANOPARTICLES AND ROS

It is well established that in addition, ROS are involved in the antitumor activity of many chemotherapeutic agents, small molecular targeted drugs, and radiation therapy, as well as their side effects (Orsini F, Migliaccio E, Moroni M, 2004). Nanoparticles play an important role in increasing drug concentration in cancer cells by enhancing drug accumulation by passive and active targeting mechanisms as well as by decreasing drug efflux from cancer cells. The antioxidant effects of Herbal nanoparticles can relieve the toxic side effects of

chemo- and radiotherapy on normal cells by eliminating excessive ROS. Sulforaphane is a component of cruciferous vegetables and some medicinal plants (H. R. Teppo, Y. Soini 2017). Herbal medicines derived bioactive ingredients or nanoparticles have been shown to suppress chronic inflammation of tissues and prevent carcinogenesis. These effects are the facts such as herbal medicines are homologous to food and are rich in antioxidants such as saponins, flavonoids, and polyphenols, which can reduce the oxidative damage caused by excess ROS in normal cells Quercetin can protect human normal lung epithelial cells (BEAS-2B) from Cr(VI)-mediated carcinogenesis by targeting miR-21 and PDCD4 signaling, reducing ROS production. Purslane polysaccharides (PPs), a principal bioactive constituent of the Portulaca oleracea L. possess a wide range of antioxidant, immunomodulatory, and antitumor activities. Compounds such as curcumin and triptolide can simultaneously induce ROS generation and inhibit antioxidant defense, causing cancer cell death and enhancing the efficacy of chemotherapy (M. López-Lázaro 2008). This pleiotropic effect may be beneficial in overcoming the resistance of cancer cells to conventional single-target (Martin-Cordero, A. Jose Leon-Gonzalez (2012). However, due to the bimodal nature of ROS and CHM, identifying the specific types of ROS and antioxidant molecules that are uniquely required for anticancer as well as antitumour activities.

CONCLUSIONS

There has been a change in understanding concept of ROS in cancer, from toxic chemical species that promote genomic instability and tumorogenesis to critical signaling molecules that can participate in pro- and antitumorogenic signaling events. Given the causal role of ROS in promoting tumorogenesis and the widely held belief that antioxidants are tumor suppressors, ROS-manipulation strategies have previously focused on antioxidant therapy. ROS not only are damaging molecules but also function as specific secondary messengers, involved in various physiological and pathological responses. This is the current focus on the debate in the field of redox biology and accounts for inconsistency with clinical and experimental studies on ROS.

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