# Chapter 2
# Impact of Exercise, Reactive Oxygen and Reactive Nitrogen Species on Tumor Growth

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**Abstract** Physical activity results in numerous health benefits. Specifically, regular exercise reduces the risk of developing cardiovascular disease, metabolic syndrome, and cancer. The exercise-induced health benefits are attributed to alterations in hormone levels, growth factors, decreased obesity, and/or decrease in pro-inflammatory mediators. In addition to these factors, exercise-induced reactive oxygen species (ROS) and reactive nitrogen species (RNS) production has drawn a lot of attention in recent years. In this regard, during exercise the production of ROS and RNS increases in the body. It is now well accepted that physiological levels of ROS/RNS produced during exercise play an important role in cells including the control of gene expression and regulation of cell signaling pathways. However, high levels of ROS/RNS can damage cellular components. For example, excessive ROS and RNS can directly damage DNA by causing DNA base modifications leading to carcinogenesis. Although the production of ROS/RNS increases during muscular contractions, exercise also promotes the upregulation of several antioxidant enzymes that can counteract the increased production of these oxidants. Therefore, exercise can have differential effects on carcinogenesis. For example, moderate physical activity increases the expression of endogenous antioxidants that may protect against a carcinogenic event. In contrast, regular bouts of exhaustive exercise have been shown to impair the immune system and could reduce immune-surveillance and increase the risk of some cancers. Therefore, identifying the optimal amount of physical activity that can lead to cancer-preventive effects is of paramount importance.

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## 2.1 Introduction

A plethora of research articles suggest that regular exercise decreases the risk of developing different types of cancers (e.g., colon, breast, prostate, endometrial, and lung). Despite the large number of studies suggesting a positive correlation between physical activity and cancer prevention, other investigators report that this correlation may not be always true [16, 55, 64, 67]. These disparate results may be attributed to several factors. For example, physical activity can have different influences on carcinogenesis, depending on energy supply and the intensity and frequency of exercise. In general, moderate intensity exercise has cancer-preventive potential and a myriad of other health benefits. However, a single exhaustive bout of exercise may increase the risk for cancer development [11, 44].

The molecular mechanisms underlying the cancer preventive or cancer promoting effects of exercise have not yet been fully investigated. One of the reasons for such controversy may be attributed to the levels of exercise-induced reactive oxygen species (ROS) and reactive nitrogen species (RNS) production that can differentially affect health. High levels of ROS/RNS can damage cellular components, but physiological levels of ROS/RNS play an important role in cells including the control of gene expression and regulation of cell signaling pathways [13, 49, 52, 53, 59]. This chapter will discuss the role that exercise-induced free radical generation plays in tumor growth. We will begin this chapter with an overview of the different species of ROS and RNS and this section will be followed by a discussion of the sources of ROS and RNS. We will then summarize the major cellular antioxidant systems and discuss how exercise can affect these systems. We will conclude with a discussion of the effect of exercise-induced ROS/RNS on cancer development and progression.

## 2.2 Reactive Oxygen Species and Reactive Nitrogen Species

We will begin this chapter by discussing the major species of ROS and RNS. In the context of reactive species, a free radical is any atom/molecule that contains one or more unpaired electrons [21]. This unpaired electron makes radicals unstable and reactive. In this regard, free radicals can be formed by either losing or gaining an electron. The name ROS includes oxygen centered radicals and non-radicals, and reactive derivatives of oxygen (e.g., hydrogen peroxide). Similarly, the term RNS refers to both nitrogen radicals along with other reactive molecules where the reactive center is nitrogen. The following section will summarize the chemical composition and properties of the main ROS and RNS.

Superoxide is generated as an intermediate in several biochemical reactions including the incomplete reduction of oxygen to water during oxidative phosphorylation. Also, many inflammatory cells can produce significant amounts of superoxide in an effort to protect against invading organisms [17]. The dismutation of superoxide produces hydrogen peroxide. Hydrogen peroxide is a more stable ROS and it is permeable to cellular membranes. Despite that hydrogen peroxide is a relatively

weak oxidizing agent; at high levels it is cytotoxic, mainly because it can generate hydroxyl radicals through the Fenton reaction. Hydroxyl radicals possess a strong oxidizing potential and are highly reactive and potentially are the most damaging ROS present in biological materials.

Another ROS found in cells is hyperchlorite that can be formed by the action of myeloperoxidase utilizing hydrogen peroxide. Hyperchlorite is also produced by neutrophils and can oxidize biomolecules. Further, when in the acid form (i.e., hypochlorous acid), this oxidant can cross cell membranes and promote fragmentation and aggregation of proteins [21].

Nitric oxide is the main RNS and it is synthesized in many cell types from the amino acid L-arginine. The synthesis of nitric oxide occurs through three nitric oxide synthases (NOS): (1) neuronal NOS; (2) endothelial NOS; and (3) inducible NOS. Each of these nitric oxide synthases convert L-arginine into nitric oxide and L-citrulline by utilizing NADPH. Nitric oxide is a weak reducing agent, but it can react with oxygen to form nitric dioxide or with superoxide to produce peroxynitrite [20]. Peroxynitrite is a strong oxidizing agent that can lead to depletion of thiol groups, DNA damage, and nitration of proteins.

## 2.3 Sources of ROS and RNS During Exercise

It is now well accepted that whole body exercise results in increased production of ROS and RNS that can cause lipid, DNA, and protein oxidation in the blood and other cells. The generation of ROS and RNS by skeletal muscle increases during exercise, but other potential sites of ROS and RNS exist. Surprisingly, few studies have investigated the predominant tissues responsible for exercise-induced oxidant production. This is probably due to limited access to other tissues (other than skeletal muscle) in humans and the fact that several organ systems are linked via the increased metabolic requirement of contracting skeletal muscles. However, it is feasible that other tissues such as the heart, lungs or white blood cells may contribute significantly to the total body generation of ROS and RNS during exercise [50]. In this regard, investigators proposed that common metabolic changes that occur during exercise (e.g., increased release of catecholamines) may play a role in the increased ROS generation [9]. Further, in situations that exercise results in significant muscle damage, inflammatory processes may play an important role in radical production. The following paragraphs discuss the main sites of ROS and RNS generation by focusing in skeletal muscle.

Mitochondria have been considered the main source of intracellular ROS in muscle fibers and early reports suggested that 2–5 % of the total oxygen consumed by mitochondria may undergo one electron reduction to produce superoxide [6]. However, recent evidence suggests that only about 0.15 % of mitochondrial oxygen utilized is converted to superoxide [60]. Further, mitochondria produce more ROS in the basal state of respiration (state 4) compared to the active state of respiration (state 3) [2, 49, 50]. Therefore, it appears that mitochondria are not the primary source of free radical production in contracting skeletal muscles.

In addition to mitochondria production of ROS, muscle cells contain numerous sites that are capable of producing ROS. For example, NAD(P)H oxidase enzymes associated with the sarcoplasmic reticulum which also release superoxide to the intracellular space. Further, reports indicate that NAD(P)H oxidase complex is also expressed in the sarcolemma and thus it can also release superoxide into the extracellular space [29]. In addition to NAD(P)H oxidases, there are other plasma membrane redox systems that are capable of transferring electrons from intracellular reductants to extracellular electron acceptors [56]. For example, external NADH oxidase proteins can reduce protein thiols and oxygen in vivo [10].

Phospholipase $A_2$ is another enzyme that produces ROS. Specifically, phospholipase $A_2$ cleaves membrane phospholipids to release arachidonic acid which is a substrate for ROS-generating enzyme systems such as the lipoxygenases [70]. Also, activation of phospholipase $A_2$ can stimulate NAD(P)H oxidases and increased phospholipase $A_2$ activity has been reported to stimulate ROS generation in muscle mitochondria and cytosol [19].

Furthermore, numerous studies suggest xanthine oxidase can also promote superoxide generation in skeletal muscle [18]. Although rat skeletal muscles contain significant levels of xanthine oxidase [32], human skeletal muscle cells *per se* appear to possess low amounts of xanthine dehydrogenase or oxidase [22]. Clearly, additional research is required to determine the role that xanthine oxidase plays in exercise-induced ROS production in humans.

The main oxidant that falls under the RNS category is nitric oxide produced by NOS. Skeletal muscle normally expresses neuronal NOS and endothelial NOS. Neuronal NOS is strongly expressed in fast-twitch muscle fibers. In contrast, endothelial NOS is localized to muscle mitochondria [35]. Inducible NOS is also expressed in skeletal muscle in some inflammatory conditions, but it does not play a significant role in normal muscle [61]. In this regard, nitric oxide is generated continuously by skeletal muscles and this production is increased by contractions. Importantly, data show that neuronal NOS is the prime source of the nitric oxide released from skeletal muscle during muscular contractions [25].

In summary, ROS and RNS production increases during exercise and these damaging molecules can be generated at various compartments within cells and by numerous organelles and enzymes (Fig. 2.1). Thus, given the importance of maintaining redox homeostasis in cells, it is not surprising that cells contain a network of antioxidant defense mechanisms to reduce the potential for oxidative damage during periods of increased ROS/RNS. The following section discusses the major antioxidants found in cells.

## 2.4 Cellular Antioxidant Defense Systems

To prevent oxidative damage to cells, a well-organized system of antioxidants act in a synchronized fashion. Cells contain both enzymatic and non-enzymatic antioxidants that are strategically located throughout cellular compartments and work

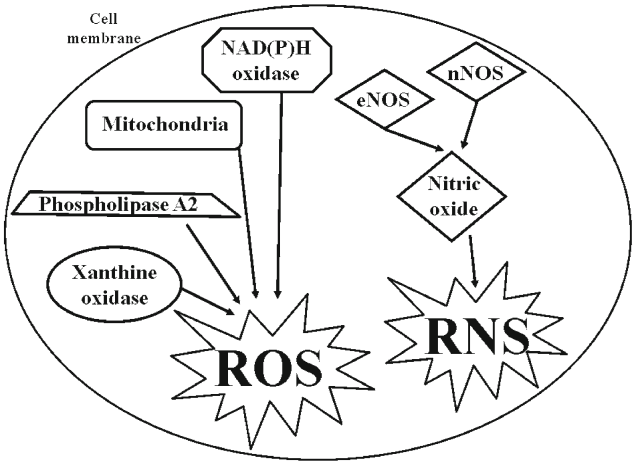


**Fig. 2.1** Diagram showing the main enzymes involved in the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in the cell. *eNOS* endothelial nitric oxide synthase, *nNOS* neuronal nitric oxide synthase

together to regulate ROS and RNS. The primary antioxidant enzymes in cells include superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT). Other antioxidant enzymes such as thioredoxin (TRX), glutaredoxin (GRX), and peroxiredoxin (PRX) also contribute to cellular protection against oxidation. The location and function of these key enzymes is discussed in the following sections.

Three isoforms of SOD (SOD1, SOD2, SOD3) exist in cells and each incorporates a transition metal in the active site to accomplish the catalytic breakdown of the superoxide anion. SOD1 is located in the cytosol and the mitochondrial intermembrane space and requires copper-zinc as a co-factor. SOD2 uses manganese as a cofactor and is located in the mitochondrial matrix, whereas SOD3 incorporates copper-zinc as a cofactor and is found in the extracellular space. All three isoforms of SOD dismutate superoxide radicals to form hydrogen peroxide and oxygen. However, as noted previously, hydrogen peroxide is still considered a ROS and cells detoxify hydrogen peroxide by using the enzymes GPX and CAT.

Five different isoforms of GPX have been reported in mammals (GPX1-GPX5) [12]. Each of these GPX enzymes catalyze the reduction of hydrogen peroxide or organic hydroperoxide to water and alcohol, respectively, using reduced glutathione (GSH). To function, GPX requires a supply of GSH to provide electrons and since GSH is oxidized by GPX to form oxidized glutathione (GSSG), cells must possess a path capable of regenerating GSH. The reduction of GSSG back to GSH is achieved by glutathione reductase, a flavin containing enzyme whereby NADPH provides the reducing power [43]. CAT also catalyzes the breakdown of hydrogen peroxide into water and oxygen. Although CAT and GPX share common substrates, compared to GPX, CAT has been reported to have a lower affinity for hydrogen peroxide at low concentrations [58].

Along with the previously discussed primary antioxidant enzymes, cells also contain additional enzymes that participate in the maintenance of redox balance (e.g., TRX, GRX, PRX). Cells have two TRX isoforms; TRX1 is found in the cytosol and TRX2 is found in the mitochondrial compartment [5]. TRX participates in maintaining proteins in their reduced state, and once oxidized, TRX is then reduced by electrons from NADPH using the enzyme thioredoxin reductase [27].

The antioxidant enzyme GRX participates in the protection and repair of protein and non-protein thiols during oxidative stress [5, 26]. Specifically, GRX protects thiols by the transfer of electrons from NADPH to disulfide substrates and this cycle is connected with glutathione and glutathione reductase [5]. While both TRX and GRX control the redox state of thiol groups, their concurrent presence in cells suggests different functions for each protein [41].

The last enzymatic antioxidant to be discussed is PRX that reduces both hydroperoxides and peroxynitrate using electrons provided by physiological thiols. In mammals, cells express six isoforms of PRX (PRX I-VI) that are located throughout the cell. Specifically, PRX I, II, and VI are found in the cytosol, PRX III is located in the mitochondrion, PRXIV is located in the extracellular space, and PRX V is located within both mitochondria and peroxisomes [54].

In addition to enzymatic antioxidants, several other nonenzymatic antioxidants are found in cells (e.g., GSH, uric acid, bilirubin). GSH is the most abundant non-protein thiol in cells and as an antioxidant, GSH serves a variety of roles. First, GSH can directly react with several ROS by donating a hydrogen atom [68]. Further, GSH acts as a substrate for GPX to eliminate hydrogen peroxide and organic hydroperoxides [43]. Furthermore, GSH can reduce vitamin E radicals that are formed in chain-breaking reactions with lipid peroxyl radicals and GSH can reduce the vitamin C radical derived from the recycling of vitamin E.

Uric acid is another important non-enzymatic antioxidant that is produced as a by-product of purine metabolism. Data show that uric acid is a useful scavenger of peroxyl radicals, hydroxyl radicals, and singlet oxygen [1]. In this regard, urate can protect against oxidative damage by acting as an electron donor. Also, urate can chelate iron and copper ions and prevent them from producing hydroxyl radicals via the Fenton reaction [21].

Two additional non-enzymatic antioxidants are α-lipoic acid and bilirubin. α-lipoic acid is a naturally occurring compound found in a variety of foods. Functionally, α-lipoic acid can provide antioxidant effects by recycling vitamin C [8]. Further, bilirubin is produced as a byproduct of heme metabolism and bilirubin possesses antioxidant potential against peroxyl radicals and can also protect cells from hydrogen peroxide [4, 62, 63].

In summary, cells contain several antioxidant systems (both enzymatic and non-enzymatic). These systems are found in select locations in the cell to counteract ROS and RNS production. Also, these systems are interconnected to maximize ROS/RNS detoxification. Figure 2.2 shows the distribution of the main antioxidants between blood, cytoplasm, and mitochondria.

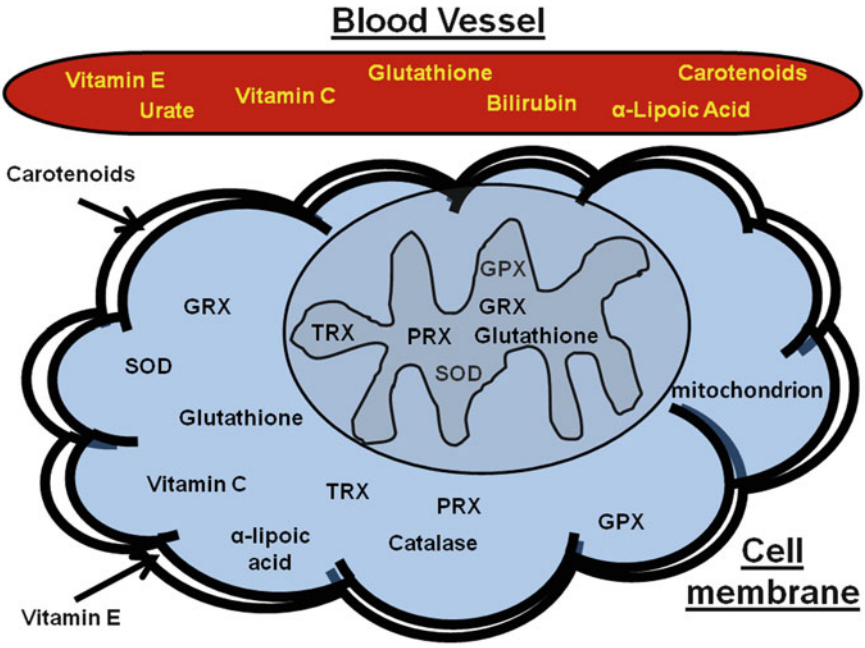


**Fig. 2.2** Illustration showing the distribution of the main antioxidants between blood, cytoplasm, and mitochondria. *GPX* glutathione peroxidase, *SOD* superoxide dismutase 1, *TRX* thioredoxin, *PRX* peroxiredoxin, *GRX* glutaredoxin

## 2.5 Exercise-Induced Changes in Antioxidant Systems

Numerous investigators have studied the effects of exercise on antioxidant systems. Despite the plethora of information available, a consensus answer or whether exercise increases antioxidant capacity has not been reached. For example, some reports indicate that chronic endurance exercise training does not increase SOD activity in muscle, but most studies show that regular bouts of endurance exercise increases the activity of SOD (for a review see [50]). Methodological differences in the assay of SOD activity and variations in the intensity and duration of exercise training could contribute to the differences reported in the literature. For example, a ten-fold difference exists in the relative sensitivity between common methods used to assay SOD activity [46]. It follows that SOD assay techniques with low sensitivity would fail to detect small group differences in SOD activity and could explain the failure to observe exercise-induced increases in muscle SOD activity in some studies.

GPX is also inducible in skeletal muscles and it is noteworthy that endurance exercise increases both cytosolic and mitochondrial GPX activity [31]. Identical to SOD, the magnitude of the exercise-induced increase in GPX in skeletal muscle is

a function of both the exercise intensity and exercise duration. Indeed, compared to low intensity exercise, high intensity exercise produces a greater increase in muscle GPX activity [48].

Whether or not CAT expression in skeletal muscle increases in response to chronic exercise is controversial with studies reporting an increase [51, 66], decrease [36, 37, 48], or no change [48] following exercise training. The ambiguity of these findings may be due to a variety of factors including issues associated with assaying CAT activity.

Finally, at present, the effects of regular exercise on the TRX, GRX, and PRX systems in muscles are not well known. Nevertheless, it is conceivable that exercise-induced upregulation of these antioxidant systems occur as an aid in ROS detoxification.

In regards to the effects of exercise on nonenzymatic antioxidants, numerous investigations demonstrate that skeletal muscle fibers adapt to high intensity endurance exercise by increasing the cellular levels of GSH [37, 38, 40, 45, 57]. This exercise-induced increase in GSH within muscle fibers is likely due to increased activity of a key enzyme (i.e., γ-glutamylcysteine synthase) involved in GSH synthesis [30].

However, data are still lacking on the effects of exercise on the other nonenzymatic antioxidants discussed previously. For example, although an acute bout of exercise may increase α-lipoic acid levels in muscle, chronic exercise training does not appear to change muscle levels of α-lipoic acid [33]. Also, the influence of exercise training on muscle urate levels is unknown, but it is feasible that urate could function as an antioxidant scavenger in muscle fibers during exercise [23, 24]. It is established that prolonged and intense exercise increases blood levels of bilirubin [14, 42]. However, it is unclear if exercise training increases bilirubin content in human skeletal muscle.

## 2.6 Role of Exercise-Induced ROS and RNS on Tumors

Currently, the classic theory of carcinogenesis involves the processes of tumor initiation, tumor promotion, and tumor progression [69]. Tumor initiation begins in cells with DNA alterations induced from a variety of stimuli. The alterations in specific genes modify the cells to replicate at a faster rate compared to normal cells [55]. During the tumor promotion stage there is a fast clonal expansion of the initiated cells. This stage is associated with hyper proliferation, tissue remodeling and inflammation [55]. This stage is followed by the tumor progression stage where preneoplastic cells develop into invasive tumors and this stage is characterized by further clonal expansion [47]. During the tumor promotion stage additional changes in gene expression and DNA damage occur in the tumor cells.

Figure 2.3 summarizes in a simple way the process of how a normal cell can turn to a neoplastic cell by going through the three stages described above (i.e., tumor initiation, tumor promotion, and tumor progression). The carcinogenesis pathway can be interfered with any point during this multistep process. Specifically, the tumor initiation events in carcinogenesis can be inhibited by scavenging ROS and

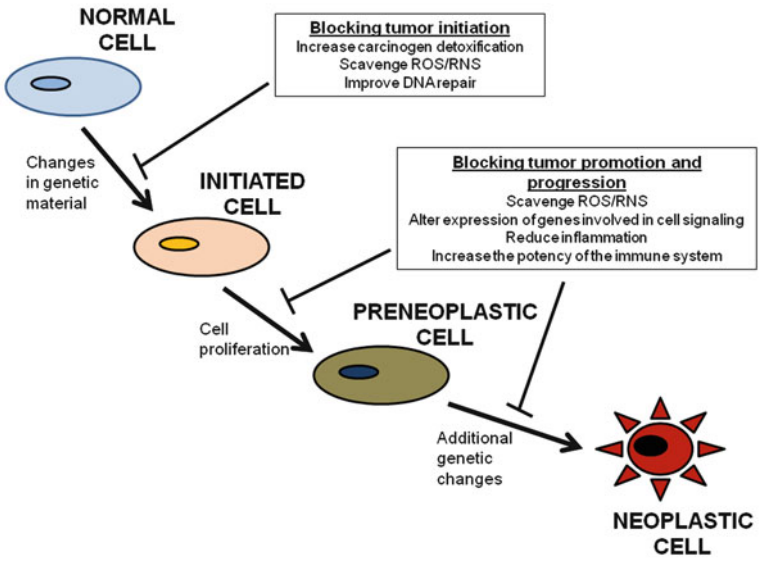


**Fig. 2.3** The three step process in carcinogenesis involves tumor initiation, tumor promotion, and tumor progression. Exercise can have anti-carcinogenic properties and any of these stages and the beneficial effects of exercise are shown in the boxes. *ROS* reactive oxygen species, *RNS* reactive nitrogen species (Adapted from Ref. [55])

RNS, enhancing carcinogen detoxification, and altering certain DNA repair processes [28]. Some possible ways that can block the promotion and progression stages of carcinogenesis include scavenging ROS and RNS, altering the expression of genes involved in cell signaling, decreasing inflammation, and enhancing immune function [28, 55].

As we briefly discussed in the introduction of this chapter, exercise can have a positive effect on cancer prevention. Some of the mechanisms by which exercise prevents cancer are: enhanced antioxidant defense mechanisms, reduction in bodyweight, decreased reproductive hormone levels, altered growth factor hormones (e.g. insulin-like growth factor-1), and a reduction in chronic inflammation [7].

One common feature of the metabolic activation of all pro carcinogens is that their ultimate DNA reactive carcinogenic species are electrophilic and several oxidants fall in this category. Specifically, ROS and RNS can directly damage DNA that can lead to carcinogenesis by causing DNA base modifications. For example, hydroxyl radical can attack DNA to form 8-hydroxyguanine [15]. That is, hydroxyl radicals can react with pyrimidines, purines, chromatin proteins and can cause base modifications and genomic instability with the ultimate result of altering gene expression. Therefore, exercise-induced increases in ROS and RNS production can aid in the cell's mutation rate and in the development and maintenance of its oncogenic phenotype by acting as a secondary messenger in intracellular signaling cascades [65].

In addition to that, high levels of ROS and RNS have been proposed to be involved in cancer metastasis. For example, ROS/RNS can act as signaling molecules in the mitogen-activated protein kinases (MAPKs) and p21 activated kinase (PAK). These molecules have been shown to be regulated by ROS and to play a critical role in cancer cell metastasis [39]. Therefore, high levels or ROS/RNS not only can promote carcinogenesis, but can also cause metastasis of tumor cells.

Also, exercise-induced ROS/RNS can stimulate several other inflammatory signal transduction pathways via activation of redox-sensitive transcription factors such as NF-κB which functions as a tumor promoter and has been known to be involved in inflammation-associated carcinogenesis. NF-κB is a major transcription factor regulating cyclooxygenase-2 (COX-2), a rate-limiting enzyme in prostaglandin biosynthesis. Abnormal upregulation of COX-2 has been implicated in cancer development [44]. A single bout of maximal exercise can accelerate NF-κB activation and COX-2 expression in human peripheral blood mononuclear cells [34]. Maximal exercises have been shown to induce the phosphorylation of both IKK and IκB which in turn can result in cancer development [44].

Directly scavenging DNA-reactive intermediates with endogenous antioxidants or antioxidant enzymes that can scavenge oxidants can be a likely approach for modulating carcinogenesis. The induction of antioxidants represents an important cellular defense in response to oxidative and electrophilic insults. For example, nuclear transcription factor erythroid 2p45–related factor 2 (Nrf2) regulates the induction of several antioxidant genes. In this regard, exercise has been show to increase the nuclear localization of Nrf2 and subsequent binding to antioxidant response elements [3].

Therefore, when these findings are taken together, it is hypothesized that the levels of ROS/RNS produced during exercise depend on the activity load. This is important since ROS and RNS can differentially regulate redox sensitive transcription factors such as Nrf2 (e.g. anti-cancer growth) or NF-κB (e.g. pro cancer growth). In this regard, current knowledge suggests that moderate exercise results in low levels of ROS/RNS production that induce antioxidant gene expression, which confers tolerance to the oxidative stress induced by a carcinogenic insult. In contrast, supramaximal or prolonged (e.g. hours) exercise to fatigue may impair the immune system and result in an increased risk of cancer. However, it is possible that the high level of oxidative stress associated with supramaximal or prolonged (e.g. hours) exercise to fatigue may lead to induction of greater compensatory systems.

## 2.7 Conclusions

Regular exercise can be beneficial in preventing carcinogenesis. There are many mechanisms that have been proposed to explain this cancer-preventive effect of exercise. Some of these factors include alterations in hormone levels, growth factors, and decreased obesity. Exercise can also reduce pro-inflammatory mediators and reduce chronic inflammation. However, exercise can also cause oxidative stress

since during exercise production of ROS/RNS increases. The increased oxidant production can alter cellular redox status that can affect a myriad of downstream pathways. It is clear that excessive ROS/RNS can cause DNA damage and can induce carcinogenesis. Paradoxically, exercise also enhances carcinogen detoxification by modulating antioxidant expression and promoting DNA repair processes. Although this relationship between exercise, ROS/RNS, and antioxidant expression has been known for many years, the total effect of exercise is not fully known. Importantly, physical activity is one of the few modifiable factors that can prevent the development of various malignancies. Therefore, future research should focus on trying to identify the optimal load of physical activity that can lead to cancer-preventive effects.

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