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Mini-review

Reactive oxygen species and cancer: A complex interaction

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ABSTRACT

Elevated levels of Reactive Oxygen Species (ROS), increased antioxidant ability and the maintenance of redox homeostasis can cumulatively contribute to tumor progression and metastasis. The sources and the role of ROS in a heterogeneous tumor microenvironment can vary at different stages of tumor: initiation, development, and progression, thus making it a complex subject. In this review, we have summarized the sources of ROS generation in cancer cells, its role in the tumor microenvironment, the possible functions of ROS and its important scavenger systems in tumor progression with special emphasis on solid tumors.

1. Introduction

Cancer continues to be the biggest challenge for mankind, with an estimated 1,735,350 new cases of cancer and 609,640 cancer related deaths for 2018 in the United States alone, and an estimated 8 million cancer related deaths worldwide in 2012 with projected 23 million new cases annually by 2030 [1,2]. Understanding the mechanisms of tumor development and progression is necessary for decoding the complex biology of cancer. Many aspects of tumor microenvironment including reactive oxygen species (ROS) contribute to the progression of a solid tumor. Increased ROS levels along with deregulated redox homeostasis and increased antioxidant ability constitute one of the many hallmarks of a cancer cell [3]. Understanding and elucidating the role of ROS in the tumor microenvironment is critical for developing new approaches to combat this disorder.

Superoxide anion ($\bullet O_2^-$), hydrogen peroxide (H_2O_2) and hydroxyl radicals ($\bullet OH$), belonging to a group of highly reactive and heterogeneous molecules derived from oxygen (O_2) collectively are the major forms of ROS in biological systems. ROS are generated endogenously through multiple mechanisms and the major sources are the mitochondria, NADPH oxidase (NOX) complexes in the cell membrane, peroxisomes and endoplasmic reticulum [4]. Increased ROS generation often has been linked to tissue injury or DNA damage associated with infection, aging, ionizing radiation, mitochondrial DNA mutations, and cellular proliferation. However, there has been increasingly new and significant information pointing to an essential role for increased ROS generation in several cellular processes associated with neoplastic transformation, aberrant growth, proliferation, and apoptosis. These cellular processes may be a result of the activation of signaling pathways in response to intracellular changes in ROS levels. It is well established that ROS levels are persistent and elevated in almost all cancers and their role in cancer initiation has also been well

Abbreviations: ADT, Androgen deprivation therapy; ALS, Amyotrophic lateral sclerosis; APE1, apurinic/apyrimidinic endonuclease1/redox factor-1; ARE, Antioxidant response element; ATM, Ataxia telangiectasia mutated; ATP, Adenosine Triphosphate; AR, Androgen receptor; CDKN1A, Cyclin dependent kinase inhibitor 1A; CRPC, Castration Resistant Prostate Cancer; CSC, Cancer stem cell; CXCL12, C-X-C Motif Chemokine Ligand 12; DHT, Dihydro testosterone; EGFR, Epidermal growth factor receptor; EMT, Epithelial-mesenchymal transition; ERK, Extracellular signal-regulated kinase; FoxO, Forkhead homeobox type O family; GATOR1, Gap Activity TOward Rags 1; GC, Gastric Cancer; GSH, HIF1α-Hypoxia inducible factor 1α; PTEN, Phosphatase and tensin homolog; RTK, Receptor tyrosine Kinase; IGF1, Insulin-like growth factor 1; JAK2, Janus Kinase 2; MAPK, Mitogen-activated protein kinase; mROS, Mitochondrial ROS; NOX, NADPH oxidase; Nrf2, Nuclear factor erythroid-2-related factor 2; PCa, Prostate Cancer; PDAC, Pancreatic ductal adenocarcinoma; ROS, Reactive Oxygen Species; SIRT3, Mitochondrial sirtuin; STAT, Signal transducer and activator of transcription; TEC, tumor endothelial cell; TFAM, Mitochondrial transcription factor A; TGFβ, Transforming growth factor beta; TRX1, Thioredoxin-1; VEGF, Vascular endothelial growth factor

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documented. Mounting evidence from recent studies points to a role of ROS associated signaling in proliferation, survival and other phenotypic behavior of cancer cells, alteration of DNA methylation in tumor suppressor genes and responsiveness to therapeutic interventions [5]. Our pioneering studies in prostate cancer (PCa), demonstrated the essential role of ROS production by the extra-mitochondrial source NOX in tumor progression and metastasis [6]. In the case of advanced PCa, androgen deprivation therapy (ADT) induced oxidative stress can contribute to the development of castration-resistant prostate cancer (CRPC) through AR signaling [7]. We also observed, ROS signaling was critical for the aggressive phenotype of androgen-independent PCa cells [8] and changes in the balance between ROS and antioxidants might result in increased ROS in the tumor microenvironment.

Tumor microenvironment plays a key role in developing and establishing the morphology, growth, and invasiveness of a malignancy. Association between oxidative stress and PCa risk has been well recognized, and many recent studies point to a role for oxidative stress in the development and progression of this disease. The average age of diagnosis of PCa is about 66 years [1] and, hence, the changes in cellular metabolism occurring over the years may play a significant role in the development and progression of this disease. The progression of a tumor is generally associated with the selection of cells harboring mutations supporting cancer cell proliferation and surveillance [9], which could be a result of increased ROS [9]. Another study reported high ROS in the metastatic cell lines of PCa along with increased antioxidant status and resistance to H_2O_2 [10].

Use of antioxidants to prevent cancer has caught the interest of many researchers since studies have proven that ROS mediated oxidative stress can initiate cancer and drive cancer progression. However, such attempts have met with limited success [11]. This highlights the need for a much deeper understanding of the varied roles of ROS and redox balance within a tumor microenvironment, which can help us evolve newer strategic targeting of oxidant and antioxidant systems to combat cancer cells. We have previously reviewed the role of oxidative stress in PCa [8] and this review article is an attempt to evaluate the role of ROS in cancer progression, and metastasis with special reference to solid tumors. In this article, we have discussed the sources of ROS, and antioxidant mechanisms and analyzed the advancements in understanding the role of ROS in hypoxia re-oxygenation, tumor microenvironment and immunity, cancer stem cells (CSCs) and cell signaling pathways related to tumor maintenance, progression, and metastasis. Moreover, recent studies on the ROS levels in aging and cancer development has also been discussed briefly, as age is one of the most studied risk factors for cancer [12].

2. Sources of ROS and their role in tumor progression

2.1. Role of mitochondrial ROS generation in tumorigenesis and tumor progression

ROS is produced in many cellular compartments including mitochondria which is the major source of ROS (mROS) [13]. The mitochondrial electron transport chain is a well characterized source through which mROS is produced in the superoxide form which can be further converted into H_2O_2 [3]. Through mROS, ATP and other metabolites, ROS plays an important role in the progression of cancer [14]. mROS can be utilized by cancer cells to aberrantly activate growth factors signaling cascade and promote angiogenesis under hypoxic conditions [15]. It has been reported that mitochondrial sirtuin, SirT3 can function as a tumor suppressor by suppressing mROS and regulating hypoxia inducible factor 1α (HIF-1α) [16] (Fig. 1).

Mutations in mitochondrial DNA (mtDNA), can result in increased mROS production [15]. Mutations of mtDNA have often been linked to aberrations in the oxidative phosphorylation (OXPHOS) activity and the effects of a high rate of aerobic glycolysis, *aka* the Warburg effect, and these, in turn, have been linked to tumorigenesis, and tumor progression [17,18]. ROS along with the mitochondrial membrane potential and normal OXPHOS activity plays a key role in the regulation of mitochondria mediated apoptosis induction [19,20]. Notch and β-catenin signal, essential for cellular differentiation, were lost due to a failure to generate mitochondria derived ROS in mitochondrial transcription factor A (TFAM) deficient keratinocytes of mice [21]. In a mouse model of K-Ras driven lung cancer, complete loss of TFAM which is required for mitochondrial DNA stability resulted in tumor growth inhibition, indicating that a critical level of mROS is necessary for tumor progression [22] (Fig. 1). Moreover, a recent study reported that highly metastatic tumor cells of B16F10 melanoma and super-invasive human cervix cancer are distinguished from poorly metastatic ones by enhanced production of mitochondrial superoxide [23].

With special reference to PCa, the link between metabolic alteration and mtDNA mutation are reported [24–26]. Deletions of mtDNA were observed to be higher in malignant prostates of older patients compared to that of younger, suggesting that increased oxidative stress with time caused an accumulation of mutations in mtDNA [25]. Studies have also reported that point mutations and mtDNA instability occurred at a high frequency in PCa, mediated by cellular oxidative stress [27,28]. Thus, the malignant transformation of the prostate gland could be initiated by ROS mediated mtDNA mutations, resulting in genetic or epigenetic alterations [8]. These mutations further affect regulatory pathways which may cause the metabolic switch [29]. Increased ROS production in PCa cells itself could be a consequence of mtDNA mutation which could lead to impairment of the electron transport chain, resulting in decreased citrate production, generating more ROS. These studies reveal the critical role of mROS in tumor progression and metastasis.

2.2. Role of NOX4 in NADPH oxidase mediated tumor progression

Enzymatic generation of superoxide anion ($\bullet O_2^-$) and subsequently hydrogen peroxide (H_2O_2) by NOX is brought about by transfer of electrons from NADPH across the membrane and coupling them to molecular oxygen. Along with the phagocyte NADPH oxidase (NOX2/gp91^{phox}), six other homologs of the phagocyte NADPH oxidase have been identified thus far, namely NOX1, NOX3, NOX4, NOX5, DUOX1, and DUOX2 [30]. The isoforms NOX4, NOX2, and NOX5 which are absent in normal prostate cell lines have been reported in PCa cell lines in our studies [8]. NOX4 can be induced under hypoxia in different tissues [31], and previous studies have reported that the ectopic expression of NOX1 in PCa cells can enhance growth, tumorigenicity, and angiogenesis [32]. Also, downregulation of NOX5 can result in growth arrest and apoptosis [33]. Expression of NOX including NOX1, NOX2, and NOX4 was elevated manifold in rat prostate following castration [34]. These studies and our earlier report on ROS generation resulting from increased NOX expression in PCa [6] have been further validated by more recent reports showing high levels of NOX4 expression in PCa tissues (7/19 patients) [35]. NOX5 expression was not only observed distinctly in human PCa tissue microarray, but it was also consistently expressed compared to other NOX isoforms in both benign and malignant prostate epithelial cell lines [36]. Also, it has been reported [37] that NOX expression is directly associated with PCa progression in TRAMP mice and NOX inhibition was associated with a reduction in the proliferative and clonogenic potential of PCa cells. The expression of p^{22phox}, the transmembrane subunit of the NOX isoform which forms a stabilizing complex, was increased in PCa along with increased ROS levels. It was also observed to positively regulate AKT/ERK/HIF-1/VEGF pathway *via* ROS and was associated with regulating cell proliferation, transformation, and tumorigenesis [38]. NOX5 silencing impaired the proliferation of NOX5-expressing PCa cells (PC-3, LNCaP) [36]. Although other NOX isoforms play a critical role in tumor progression, several reports point towards the important role of NOX4 in tumor maintenance, progression, and metastasis.

Activation and upregulation of NOX4 expression: Hypoxia through the binding of HIF-1α activates the NOX4 gene and in turn,

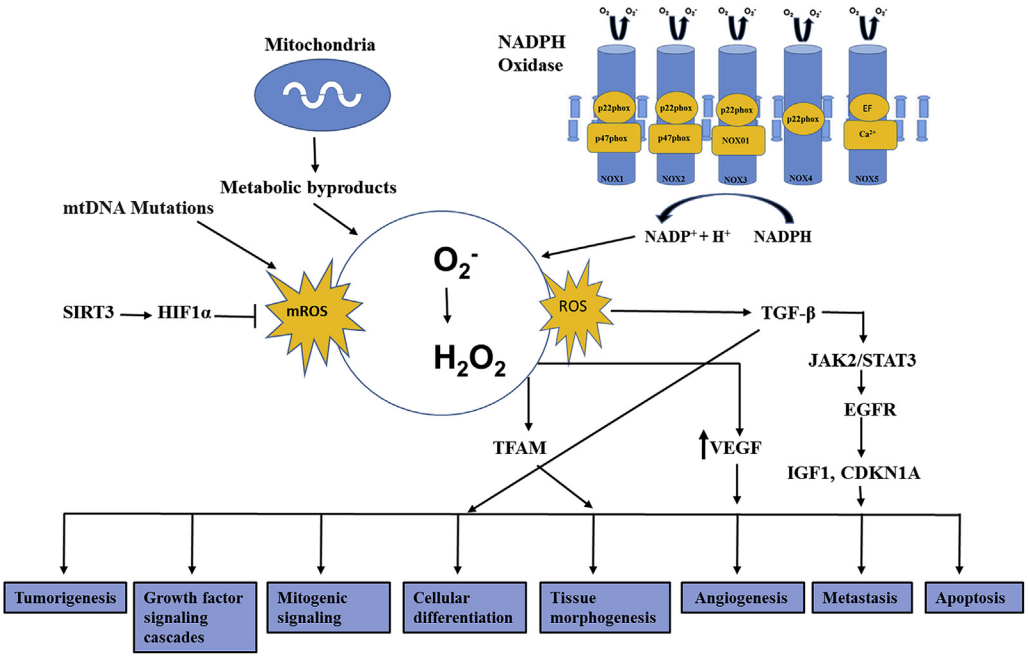

Fig. 1. Mitochondrial and NADPH Oxidase ROS mediated Biological effects on tumor cells extends from tumorigenesis to metastasis. The figure represents the sources of ROS and its biological effects on tumor progression. ROS can be generated in mitochondria as a byproduct of the electron transport chain or can be generated through activation of NADPH oxidases (NOX). ROS derived from both mitochondria or NOX can contribute towards tumor progression at every step from tumorigenesis to metastasis. mROS: Mitochondrial ROS; TFAM: Mitochondrial transcription factor A; SIRT3; Mitochondrial sirtuin; VEGF-Vascular endothelial growth factor.

NOX4 stabilizes HIF-1α [37,39]. In a recent study, Hanley et al. (2018) [40] have reported that TGF-β dependent trans-differentiation or activation of fibroblasts to cancer associated fibroblasts (CAFs) or myofibroblasts depends on ROS produced by NOX4, which was shut down through NOX4 inhibition highlighting NOX4 as a therapeutic target. An earlier report alluding to this study in human prostatic stromal cells treated with TGFβ1 to induce fibroblast to myofibroblast differentiation revealed up-regulation of ROS producing NOX4. This study also demonstrated that NOX4 derived ROS is required for TGFβ1-mediated phosphorylation of c-jun N terminal kinase, which is essential for the cytoskeletal remodeling of prostatic stromal cells [41]. Through gene expression profiling studies in pancreatic ductal adenocarcinoma patients (PDAC), NOX4 was found to be upregulated when p16 is inactivated. The elevated NOX4 also supported increased glycolysis and promoted PDAC growth through ROS mediated oxidation of NADH [42].

Role in Metastasis: There is mounting evidence suggesting the role of NOX4 towards the development of metastasis. NADPH oxidase inhibition protected against metastasis of human lung cancer cells by decreasing miR-21 expression [43], whereas overexpression of NOX4 in lung cancer cell lines showed increased metastasis in nude mice than control cells [44]. Anoikis resistance, a critical step towards metastasis, was conferred by NOX4 upregulation in lung cancer cells through activation of EGFR and Src [45]. NOX4 expression was significantly upregulated and associated with poor overall survival in gastric cancer (GC) patients. This study also revealed that NOX4 expression was associated with cell migration, epithelial-mesenchymal transition (EMT) in GC cell lines and these functions of NOX4 may be through JAK2/STAT3 pathway [46] (Fig. 1). Helfinger et al. (2016) [47], demonstrated a significant reduction (38%) in tumor vascularization in methylcholanthrene-induced fibrosarcomas of NOX4−/− mice, and thus promotion of tumor angiogenesis by NOX4 through HIF-1α stabilization and subsequently inducing VEGF expression. An earlier study by Jajoo S et al. (2009) [48] observed that activation of the purine nucleoside receptor, adenosine A(3) receptor (A(3)AR) in PCa cells reduced protein kinase A mediated stimulation of ERK1/2, leading to reduced NADPH oxidase activity and cancer cell invasiveness thus suppressing PCa metastasis.

Genomics of NOX4 in clinical PCa: NOX4 is overexpressed in several solid malignancies including prostate [35]. Decoding NOX4 genomics in prostate clinical specimens also revealed that the NOX4 gene is amplified in cancer compared to normal prostate [49–53]. Data analysis [49] suggested high NOX4 expression in primary as well as metastasized (castrate) PCa when compared to normal samples. This study also highlights that clinically high NOX4 is associated with biochemical recurrence of PCa. Further, amplification of NOX4 gene (19%) in both CRPC-Adenocarcinoma (n = 13/107) and CRPC-Neuroendocrine (n = 7/107), suggested that amplified NOX4 gene expression may be critical for driving PCa towards androgen independence and aggressiveness through unknown mechanisms [53]. Mutation in NOX4 gene could be a possible mechanism for amplification in PCa patients since missense mutation (Q505L, A296S, H480Y), splicing (G117G, X183_splice, G117 =), non-sense mutation (R84*, G254*) and frameshift mutation (I395Nfs*8) have been reported the most in a few studies [53–56]. Further analysis of CRPC-neuroendocrine data [53] to explore NOX4 role in metastasis, revealed co-occurrence of NOX4 and metastasis associated genes in PCa (IGF2R [Insulin-like growth factor 2 receptor], IGF1[Insulin like growth factor 1], CXCL12 [C-X-C Motif Chemokine Ligand 12], and CDKN1A [Cyclin dependent kinase inhibitor 1A]) [57]. All metastasis associated genes were amplified in CRPC-neuroendocrine (9–22%), while significant co-occurrences of NOX4 were observed with IGF1 ($p < 0.001$) and CDKN1A ($p < 0.001$) genes. These observations highlight that amplified NOX4 in aggressive PCa can influence metastasis through direct or indirect interaction with genes associated with metastasis of PCa. Further evidence is needed based on genomics profile and function to establish NOX4 as a key component of PCa and its microenvironment which ultimately drives primary PCa to CRPC.

3. Antioxidant response to ROS

3.1. Role of redox balance in tumor progression

Cancer cells generate high levels of ROS to maintain neoplastic state, however, they also increased levels of antioxidant proteins to survive under these harsh conditions [58] (Fig. 2). Antioxidant enzyme systems in a cancer cell are regulated by the redox regulators including nuclear factor erythroid-2-related factor 2 (Nrf2), forkhead homeobox type O family (FoxOs), ataxia telangiectasia mutated (ATM) and apurinic/apyrimidinic (AP) endonuclease1/redox factor-1 (APE1/Ref-

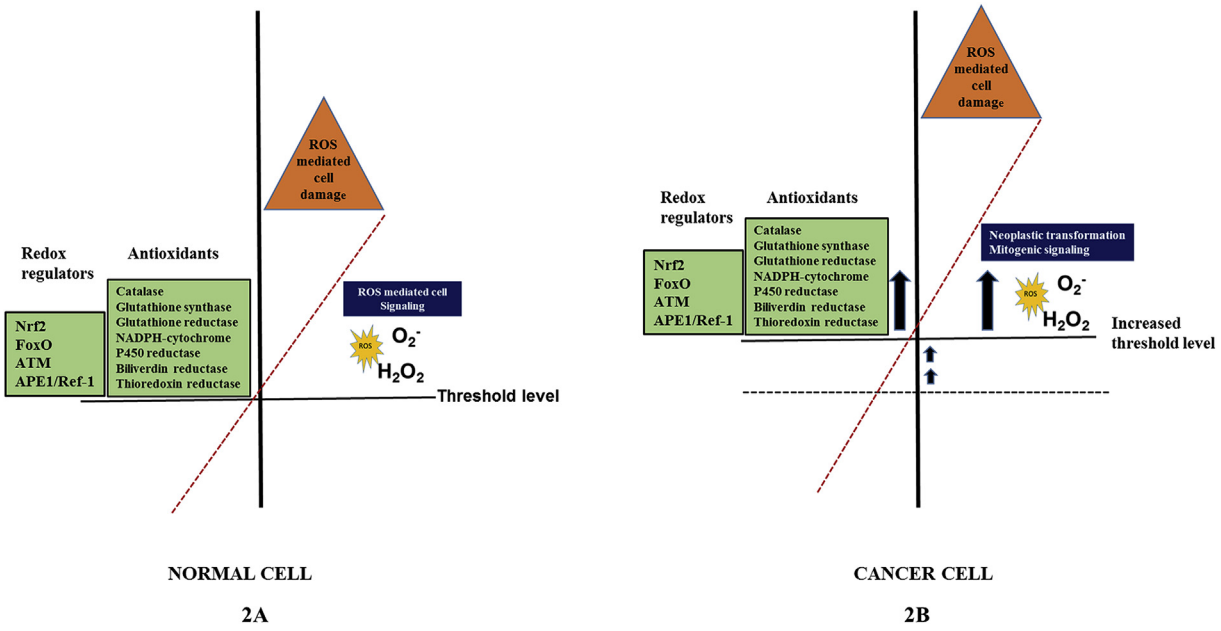

Fig. 2. Redox balance in tumor progression. A. Increased ROS generation in normal cells can lead to oxidative stress and ROS mediated cell damage (Dotted Red line). B. Cancer cells have increased threshold for oxidative stress (Solid black line) and high ROS levels are required for neoplastic transformation and mitogenesis. Increased antioxidant levels are also observed in cancer cells to prevent ROS mediated cell damage. . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

1) (Fig. 2). Cells which can successfully undergo metastasis have been reported to have reversible metabolic changes through GSH regeneration in order to withstand increased oxidative stress [59]. Increase in antioxidants like thioredoxin-1 (TRX1) has been reported in CRPC and has been associated with the progression of the disease [60]. The study also reported that TRX1 inhibition lead to an increase in p53 levels and cell death in CRPC cells deprived of androgen due to increased ROS levels. Endostatin, an antiangiogenic agent, was found to inhibit CRPC growth through upregulation of ROS scavenging antioxidants like catalase, glutathione synthase, glutathione reductase, NADPH cytochrome P450 reductase, biliverdin reductase, and thioredoxin reductase [61].

3.2. Nrf2 mediated ROS balance required for tumor progression

Nrf2 is an oxidative stress sensitive transcription factor encoded in humans by the *NFE2L2* gene. In the absence of stress, Nrf2 binds to Keap1 (Kelch ECH associating protein 1) which results in its ubiquitination. Under oxidative stress, the conformation of cysteine rich Keap1 can be altered by ROS, leading to inactivation of Keap1-Nrf2 binding. This results in the translocation of Nrf2 to the nucleus and binding to the Antioxidant Response Element (ARE) to regulate the expression of antioxidant proteins. The activation of Nrf2 mediated defense against ROS creates an optimal environment for cell growth in both normal and cancer cells [62]. The role of Nrf2 mediated antioxidant response in the tumor microenvironment with high ROS and its contribution towards tumor progression has been a subject of many important studies. Although many studies have highlighted that activation of the Nrf2 pathway decreases the sensitivity of cells to carcinogens, it has been well established that cancer cell survival and growth in oxidizing tumor environment can be enhanced through aberrant activation of Nrf2 [63]. Nrf2 in A549 lung cancer cells have been observed to promote cancer cell proliferation possibly through maintenance of the redox balance [64]. Similarly, Nrf2 was also implicated in the maintenance of pancreatic cancer cell proliferation by regulating mRNA translation [65]. In NOX4 overexpressed A549 tumors, Nrf2 inhibition led to cell growth inhibition, reversing the enhancement effect of NOX4 on cell growth and also apoptosis resistance [66]. Oncogenes are also known to directly affect ROS levels through Nrf2 as it has been observed, transcription of Nrf2 and its target gene expression are elevated upon oncogenic activation of KRAS ($KRAS^{G12D}$), c-MYC ($c\text{-}MYC^{ERT12}$), and BRAF ($BRAF^{V619E}$) [67]. High levels of ROS and increased survival in mutant p53 cancer cells can be attributed to the attenuation of Nrf2 activity and function [68]. Oxidative stress in the aggressive phenotypes of PCa [6] and the subsequent activation of Nrf2 can promote their survival and development of chemoresistance [69]. Frohlich et al. (2008) [70] reported the initiation of cellular transformation in the prostate tissues as a result of the disruption of Nrf2 mediated response. This study also revealed upon analysis of human PCa microarray datasets that the expression of Nrf2 and members of the antioxidant glutathione-S-transferase (GST) family were extensively decreased. Enhanced AR activity during ADT in PCa cells may be through the induction of oxidative stress. Recent studies have indicated that dihydrotestosterone stimulation suppressed total Nrf2 levels in androgen independent C4-2B cells but elevated total Nrf2 levels in androgen dependent LNCaP cells [71]. Increased sensitivity of PCa cells to radiation as a result of decreased ROS levels through upregulation of Nrf2 *in vitro* and *in vivo* has also been reported [72]. As recent studies have shown, ROS accumulated in tumor blood vessels can enhance tumor endothelial cell (TEC) migration through the upregulation of angiogenesis related genes by altered regulation of Nrf2. ROS inhibits Nrf2 expression in TECs leading to SMAD2/3 mediated transcription of *Biglycan* (BGN), a proteoglycan required for the TEC motility stimulated by ROS [73]. Although our knowledge of Nrf2 and redox balance within a tumor microenvironment has expanded, it is our observation that Nrf2 plays a definite yet complex role within different sub-populations of a solid tumor microenvironment.

4. Hypoxia Re-oxygenation and cancer: ROS, tumor microenvironment and immunity

The tumor microenvironment is characterized by regions of hypoxia, nutrient deprivation and low extracellular pH arising from unorganized and hemorrhagic vasculature [74]. Deregulated angiogenesis is also a feature of the tumor microenvironment, developing blood vessels with structural and functional abnormalities (Fig. 3) [75]. Also, there is blood vessel compression by growing tumor cells impairing the

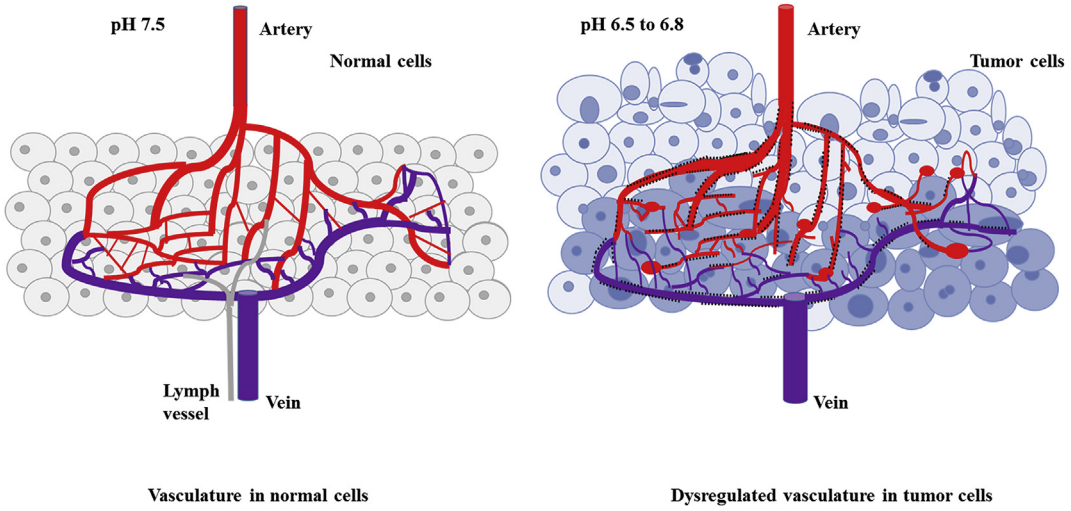

Fig. 3. Vascularization in normal and solid tumor. A. Normal tissue showing smooth vascularization with arterial (red) and venous blood vessels (blue) and presence of lymphatic vessels (grey). B. Solid tumor tissue showing irregular vascularization. Blood vessels show intermittent dilations, irregular branching, and leaky endothelial cell walls, resulting in regions of hypoxia (purple) within solid tumor. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

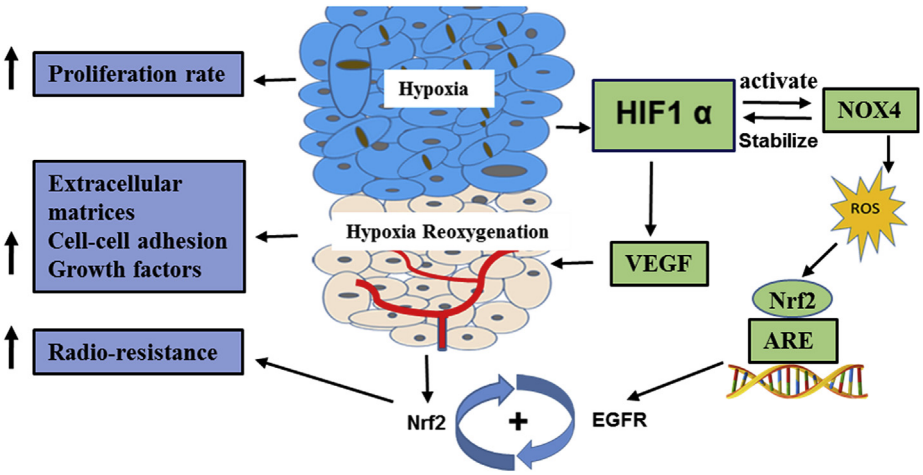

Fig. 4. Biological effects of hypoxia re-oxygenation. Intra-tumor heterogeneity with regions of hypoxia and re-oxygenation and their biological effects. Recurrent cycles of Hypoxia re-oxygenation also leads to ROS generation and increase in antioxidant enzymes. HIF1α is stabilized under hypoxia leading to VEGFA expression, angiogenesis and reoxygenation. TGF-β and hypoxia re-oxygenation can promote tumor progression through ROS-mediated activation of Nrf2 and EGFR.

blood supply to areas of the solid tumor. These features can lead to cycles of acute hypoxia followed by re-oxygenation [76,77]. Both acute and chronic hypoxia can co-exist within a tumor leading to intra-tumor heterogeneity [74,76]. Tumor hypoxia is a major contributing factor to the failure of many anticancer therapies [78]. A recent study through *In Silico* analysis of genome scale transcriptomic data collected on tissue samples of breast carcinoma, colon, and lung adenocarcinoma, revealed hypoxia and the re-oxygenation sub-populations of cancer cells within each tissue with distinct genomic and transcriptomic characteristics contributing to cancer development in a complementary manner. It was observed that the hypoxia sub-population had higher proliferation and apoptosis rates than the re-oxygenation one resulting in an acidic environment. The re-oxygenation sub-population can also contribute by generating new extracellular matrices, strengthening cell-cell adhesion and being the major source of growth factors required for tissue growth [79] (Fig. 4). Thus, hypoxia and consecutive cycles of hypoxia re-oxygenation exert multiple influences on tumor cell biology contributing to tumor progression and hence, tissue hypoxia is considered a central factor for tumor aggressiveness and metastasis [80]. Moreover, Le et al. (2014) [81] reported four distinct hypoxic cell populations in a HEK293T cell model with sustained oxidative metabolism, which was tumorigenic and expressed the genes associated with mitochondrial function. Recurrent cycles of hypoxia followed by re-oxygenation and cell proliferation can lead to ROS generation [82]. Superoxide is produced under hypoxic conditions by mitochondrial leakage and repeated cycles of hypoxia re-oxygenation can lead to peroxide production [83–85]. Antioxidant enzymes against superoxide's and peroxides XDH, SOD2, IDO1 and GPX2, GPX3, GPX5 are also up-regulated in the respective hypoxia and re-oxygenation sub-population [79]. Tissue hypoxia results in the activation of HIF-1α and can subsequently promote cell proliferation by activating downstream targets responsible for angiogenesis and increased survival of cancer cells. Even in non-hypoxic conditions, HIF-1α has been found to be overexpressed in PCa tumors [86]. Increased ROS has been implicated in the stabilization of HIF-1α [87] and stress induced MAPKs like p38MAPK and JNK have also been reported to play a part in the expression of HIF-1α in tumors [88]. Moreover, inhibition of ROS and STAT3 pharmacologically resulted in a significant reduction of EGF induced HIF-1α expression in PCa cells, thus affecting PCa cell progression through ROS/STAT3/HIF-1α/TWIST1/N-cadherin signaling [89]. HIF-1α expression is also known to be induced by CCAAT/enhancer binding protein delta (C/EBPδ) [90] which can reduce tumor incidence but are known to promote tumor metastasis [91].

ROS and reactive nitrogen species, which are considered the key messengers in the regulation of p38 MAPK mediated apoptosis pathway, can be involved in regulating activities in the cell such as

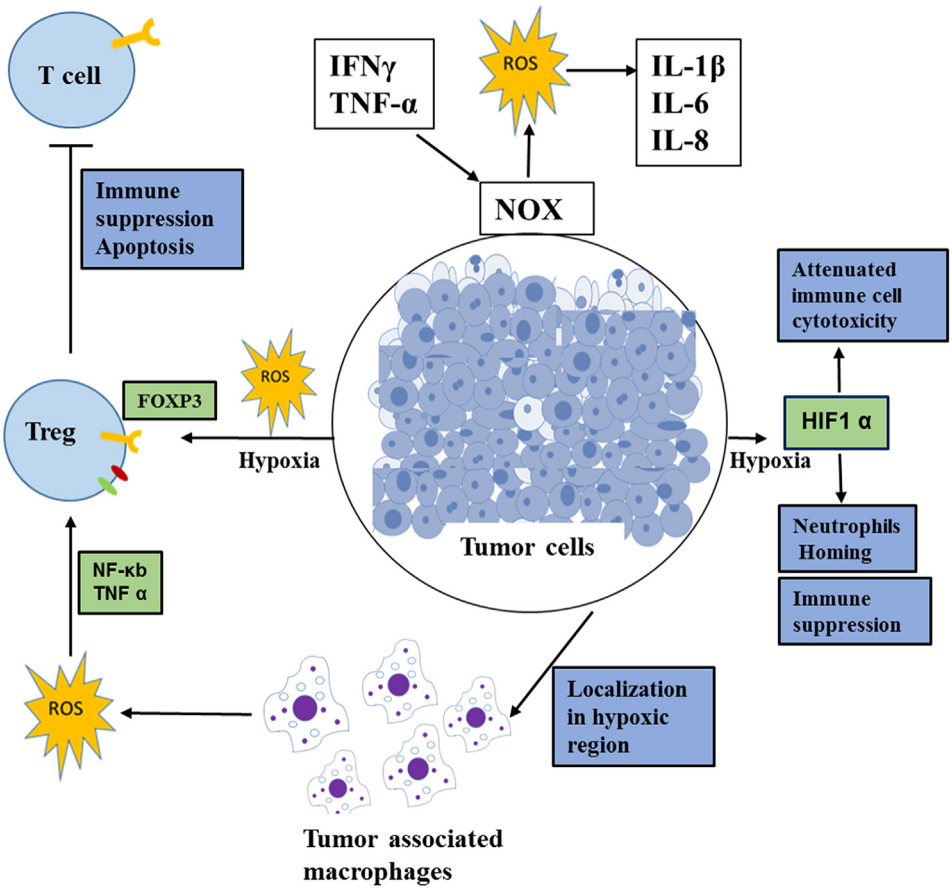

Fig. 5. Effects of hypoxia/reoxygenation on tumor immunity, the hypoxic tumor microenvironment helps in tumor promoting inflammation and avoiding immune destruction.

differentiation, survival, and apoptosis [92]. We observed this critical role of hypoxia in activating p38 MAPK and androgen independent AR stabilization and activity leading to increased aggressiveness of LNCaP PCa cells [93]. ROS/hypoxia caused the upregulation of αB-crystallin in HNSCC (Head and neck squamous cell carcinoma) which led to prolonged survival of these cells under hypoxic conditions. The heat shock protein αB-crystallin can confer stress resistance to cells by inhibiting the processing of caspase-3 and its expression is associated with several types of cancer including metastasis formation in HNSCC and breast carcinomas [94]. Studies in A549 lung carcinoma cell line have shown that combined treatment of TGF-β and hypoxia re-oxygenation can confer radio-resistance and promote tumor progression through ROS mediated activation of Nrf2 and EGFR [73] (Fig. 4).

The hypoxic tumor microenvironment is also involved in modulating immune surveillance and tumor promoting inflammation (Fig. 5). Studies have shown that hypoxic tumor microenvironment can create an immune-suppressive network supporting tumor growth [95–97]. Hypoxia driven reprogramming of tumor microenvironment impaired the migration of immune effector cells into the tumor, and also affected multiple elements of immune cell differentiation. Also, hypoxia mediated activation of HIF-1 and VEGF pathways attenuate the cytotoxic function of immune cells and support the immune tolerance of tumors. Similarly, hypoxia, ROS, and inflammation are associated in an interactive manner in tumors, primarily through HIF-1 and induced by various cytokines such as TNF-α, interleukins (IL-1β, IL-6, IL-8), and transcription factors such as NF-κB. Reprogramming of tumor metabolism, caused by hypoxia promotes the progression of cancer by producing growth factors and producing immunosuppressive cytokines. Hypoxia recruits neutrophils to hypoxic sites of inflammation in tumors and delays their apoptosis via HIF-1α dependent NF-κB activity thus, promoting sustained inflammation [87,98]. HIF's also suppress both innate and adaptive immune mechanisms through the regulation of differentiation of myeloid-derived suppressor cells [99]. A study by Hasmim et al. (2015) [100] suggests HIF, regulated TAM (tumor associated macrophage) localization to hypoxic regions in a tumor, and TAM, through ROS and its effects on Treg cells can inhibit T cell mediated killing of cancer cells. Moreover, HIF-1α is associated with the recruitment of Treg cells to the site of the tumor [101]. ROS can also cause SUMO-specific protease 3 accumulation which is involved in Treg cell-mediated suppression of T cell response against tumor [102]. Thus, controlling ROS effects under hypoxic conditions in a tumor microenvironment might be crucial for developing successful immunotherapy strategies.

Apart from HIF-1α, hypoxia could also result in activation of other pathways like phosphatidylinositol 3-kinases (PI3K)/Akt pathway, NADPH oxidase (NOX) mediated pathways, and Wnt/β-catenin pathway, thus contributing to the HIF-1α dependent and independent effects of hypoxia in cancer cells [103]. A recent study reported that human PCa cells and their extracellular vesicles (EVs) are significantly enriched in triglycerides under hypoxic conditions. This is linked to survival response following hypoxic stress as accumulated lipids could support growth following re-oxygenation [104]. Hypoxia treatment of PC3 cells led to changes associated with EMT such as decreased expression of E-cadherin, increased vimentin, snail, and also increased cell invasion and metastasis properties [105].

5. ROS mediated cell signaling pathways

ROS, at moderately elevated levels, may act as a secondary messenger and control various signaling pathways. ROS can also activate

Table 1
Different transcription factors/genes regulated by ROS in different cancers.

Transcription Factors/ Genes	Regulation	Cancer Type	References
HIF-1α	Activation	Prostate cancer	[8,131]
Snail	Activation	Breast cancer	[8,132]
Ets	Activation	Ovarian cancer; Prostate cancer	[8,133]
JNK/AP-1	Activation	Myelodysplastic syndrome	[134]
CXC4	Activation	Prostate cancer	[113]
NF-κB	Activation	Breast cancer	[135]
PTEN	Inhibition	Hepatocellular carcinoma	[136]
PI3K	Activation	Breast cancer	[106]
MAPK	Activation	Neuroblastoma; Transformed cells	[137,138]
AKT	Activation	Breast cancer	[135]
STAT3	Activation	Cervical cancer	[139]
CXCL14	Activation	Breast cancer	[140]
NRF2	Activation	Breast, Lung, and Pancreatic cancer.	[64,65,141]

many transcription factors like HIF-1α, snail, Ets etc. essential for the maintenance of oncogenic phenotype [8] (Table 1). Besides playing a critical role in tumorigenesis, ROS can also be integral to the regulation of signaling networks associated with proliferation, tumor cell survival and cancer progression [13] (Fig. 6).

5.1. ROS mediated cell signaling is integral for tumor cell survival and growth regulation

Elevated ROS levels can affect signaling cascades which are pro-proliferative like activation of PI3K/AKT signaling, through hyper-phosphorylation of PI3K and activation of AKT, thus upregulating cell cycle promoting genes [106]. Activation of the PI3K/AKT pathway also downregulates detoxification of ROS by transcription factors of the class O forkhead box (FOXO) family [107]. Besides, it has been reported in colorectal carcinoma cells that, apoptosis induced by FOXO due to increased ROS levels can be suppressed by ERK mediated inhibition of FOXO3a [107,108]. We have earlier reported that the extra-mitochondrial ROS plays an important role in modulating the activities of the growth regulatory proteins ERK1/2 and p38 MAPK in prostate cancer cells [6], besides implicating p38 MAPK as an early factor in the hypoxic response of androgen dependent PCa cells [93]. Peroxiredoxin (PRX) the antioxidant protein with diverse functions in tumors, may be required for the activation of p38 MAPK by H_2O_2 through PRX1 expression [109]. PRX3, which regulates the apoptosis signaling by scavenging mitochondrial H_2O_2 was observed to be upregulated at the protein level in LNCaP cells [110], thus increasing tumor cell survival. SENP3, a redox sensitive molecule which increases under oxidative stress, can reverse SUMO2/3 modification, leading to enhanced cell proliferation, tumorigenesis, and angiogenesis in cancer cells. SENP3 can also de-SUMOylate Forkhead box protein C2 (FOXC2) an EMT inducing transcription factor thus mediating the EMT inducing effects of ROS [111]. A recent study has reported the link between p38 MAPK and FOXC2 and the reversal of EMT transition upon inhibition of p38 MAPK [112]. Overall, ROS mediated cell signaling is critical for tumor cell survival, growth, and proliferation.

5.2. ROS mediated cell signaling is associated with tumor progression and metastasis

Studies have shown that the upregulation of the chemokine (CXC) receptor 4 (CXCR4) has been associated with PCa progression and metastasis, and also PTEN (Phosphatase and tensin homolog) inactivation permits CXCR4 mediated functions. Chetram et al. (2011) [113] have demonstrated that oxidation of the active site of PTEN by ROS can lead to PTEN catalytic inactivation in PCa cells (Fig. 6). Their study also demonstrated that ROS increased pAKT and CXCR4 expression. Thus, ROS mediated PTEN inactivation and enhanced cell migration and invasion in a CXCR4 dependent manner. EMT plays an integral role in cancer metastasis and Transforming growth factor β (TGF-β), which is a prominent EMT-inducer in the cancer microenvironment. TGF-β induced NOX4 expression and ROS generation is responsible for the activation of a number of EMT related signaling pathways in normal and metastatic human breast epithelial cells [114] and ROS is increased in significant amounts upon stimulation of TGF-β. In hepatocellular carcinoma, however, NOX4 inhibits epithelial to amoeboid transition through suppression of Rho and Cdc42 GTPase expression and also by suppressing the contractility of actomyosin [115]. Thus, ROS plays an important role in EMT and metastasis.

5.3. Cell signaling and regulation of ROS levels in tumor

Studies pertinent to upstream regulators of NADPH oxidase mediated high ROS generation in solid tumors have been limited. However,

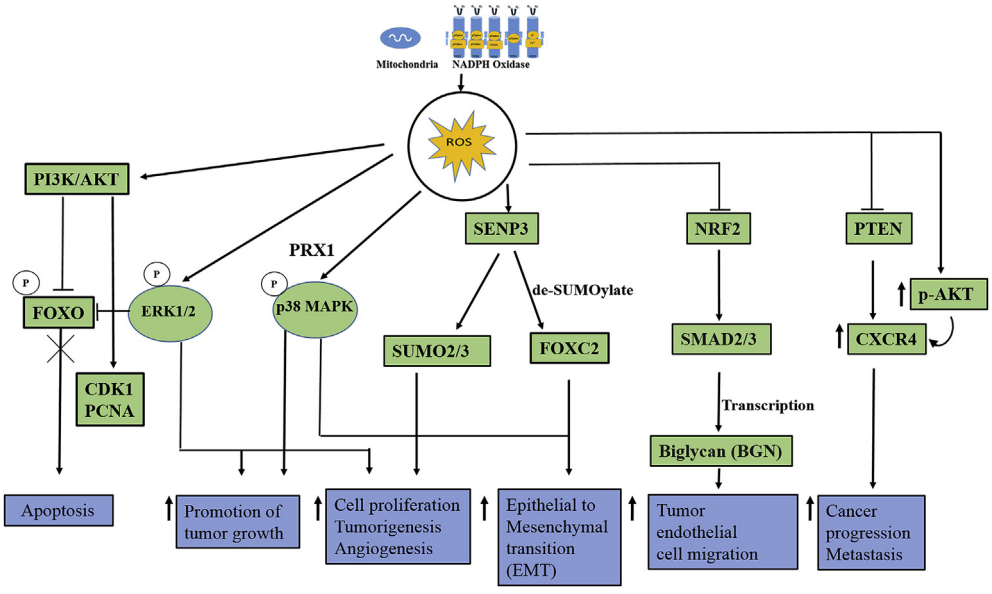

Fig. 6. Schematic representing ROS mediated cell signaling pathways and their biological effects.

Table 2
Genes regulating ROS levels in different cancers.

Genes	Effect on ROS levels	Cancer Type	References
SirT3	Decreased	Prostate cancer	[16]
FOXO	Decreased	Gastric cancer	[46]
Snail	Increased	Prostate cancer	[142]
IGF-1	Increased	Ovarian cancer	[143]
AKT	Increased	Glioblastoma, Ovarian	[144,145]

a recent study implicates mTORC1/S6 kinase signaling in the translational regulation of NOX4 mRNA [116]. NPRL2 tumor suppressor gene belonging to the GATOR1 complex and an inhibitor of mTORC1 can also induce production of ROS through NOX2 [94]. Similarly, the oncogene c-Myc increases ROS tolerance by activating transcription of GSH biosynthesis genes in response to H_2O_2. ROS mediates growth factor signaling cascades such as Angiotensin II (Ang II) and T cell receptor signaling through HIF-1α under hypoxic conditions by inhibition of protein tyrosine phosphatases [15]. Intestinal stromal PPARβ/δ has also been shown to modulate oxidative stress in human intestinal cancer cell lines [117]. We have summarized the genes regulating ROS levels in different cancers in Table 2.

6. ROS levels are critical in cancer stem cells (CSCs)

Sub-populations of cells within a tumor exhibiting characteristics of a stem cell and capable of cancer initiation are known as CSCs. ROS are maintained at low levels in CSCs like normal stem cells and have enhanced defense against ROS than that of non-tumorigenic cells [118]. A characteristic feature of stem cells is their ability to maintain the stem cell pool and this is facilitated by redox homeostasis through an intricate network involving scavenger antioxidant enzyme systems, crucial redox regulators and ROS sensitive molecules, such as HIF, p38 MAPK and p53 [119]. Recent studies implicate activation of Nrf2 signaling and maintenance of low ROS levels in the growth and survival of CSCs. A sub-population of head and neck cancer cells which produced low ROS when compared to a sub-population of cells with higher ROS production have demonstrated increased chemoresistance and tumorigenicity [120]. CSCs specific cell surface markers, CD44 and CD13, were found to be associated with ROS regulation [63]. Increased ROS and p38 MAPK activation, were observed in CD44 knockdown mice along with cellular senescence. Expression of CD13, a surface marker for liver CSCs, reduced TGFβ mediated ROS production which promoted the survival of liver CSCs [63,121]. Nrf2 plays a key role in the maintenance of CSCs similar to its effects in normal stem cells and Nrf2 signaling has been observed in many CSC models. In a recent study, Nrf2 levels and the levels of its target genes such as NQO1 and GCLM were observed to be elevated in MCF7 and MDA-MB231 breast cancer cell lines derived mammospheres, whereas the ROS levels were low compared to their monolayer counterparts [122]. CSCs also display an EMT phenotype such as loss of E-cadherin, and this phenotype in CSCs of basal-like breast cancer is promoted by decreased ROS levels due to a metabolic switch to glucose metabolism [123]. Studies on CSCs in PCa have been limited, and factors like CSC markers, the cell of origin and their location within the organ are poorly understood [124]. However, a study on the mechanism of radio-resistance in PCa revealed, higher expression of DNA repair proteins after ionizing radiation in CD^{133+} prostaspheres, with low ROS [125].

7. ROS levels in aging and cancer

The association between aging, ROS, and cancer has been researched for long and yet the underlying mechanisms are not clear. Kudryavtseva et al. (2016) [126] observed similarities in mitochondrial dysfunction, increasing ROS levels and products of the oxidative stress between aging and cancer. Moreover, with aging, increasing ROS levels can cause cell cycle arrest, which can lead to cell senescence [127]. The senescent cells can become hyperfunctional and secrete growth factors and enzymes like matrix metalloproteinases which can convert their microenvironment a fertile place for the development of pre-cancerous cells, thus promoting the development of cancer [128]. Although ROS is known to regulate major epigenetic processes, the role of ROS in DNA methylation during aging processes is not well understood. It has been observed that aging can not only stimulate global hypomethylation but also, hypermethylation of specific gene promoters in cancer patients [129]. ROS mediated DNA methylation in cancer cells can lead to the silencing of tumor suppressor and antioxidant genes [130].

8. Summary

The link between mutations in mitochondrial DNA, mROS and their role in tumorigenesis has been well documented in the past. Recent studies highlight that a critical level of mROS is necessary for tumor progression and mitogenic signaling besides its role in aberrantly activating growth factor signaling cascades, promoting angiogenesis under hypoxic conditions, and their role in metastasis and invasiveness. There is also mounting evidence on the role of NOX mediated ROS in cancer cell proliferation, tumor progression, and metastasis. Recent reports highlight the important role of the isoform NOX4 including high levels of NOX4 expression in cancer tissues of PCa. Also, tissue hypoxia is a key factor for tumor aggressiveness and metastasis, and ROS generation during hypoxia re-oxygenation plays an important role in this phenotype. The existence of distinct hypoxia and re-oxygenation sub-populations within a tumor microenvironment and their respective levels of ROS with distinct effects towards tumor progression, metastasis, and resistance to therapy, highlights the need to rethink the strategy on the target and use of antioxidant therapy. Our review also highlights the critical role played by the Nrf2 mediated antioxidant mechanism in the maintenance of low ROS in CSCs. The potential of Nrf2 as a target in an early tumor to sensitize the tumor cells to radiotherapy remains to be explored. The role of other antioxidant genes in the maintenance of the ROS within elevated threshold levels in cancer cells, along with its role in the activation of transcription factors, essential for the maintenance of oncogenic phenotype has also been discussed. Besides, ROS is a key component of tumor defense against immunity. Studies have documented that P38 MAPK contributes to ROS mediated PCa progression by promoting tumor growth, and metastasis. Our review discusses the link between P38 MAPK, FOXC2 and EMT transition. PCa cells are under inherent oxidative stress, a feature observed through many studies over the years and these observations also highlight the very important role played by ROS not only in malignant transformation but also towards the progression and development of aggressive phenotype of PCa. Thus, the review summarizes the key role of ROS and ROS mediated signaling in hypoxia re-oxygenation conditions and CSCs towards the progression of the solid tumor with emphasis on the role played by NOX4 and Nrf2.

9. Conclusion

The role of ROS in the development and progression of tumors has been well documented and identified as a therapeutic target for a long time, albeit with limited success. There are multiple reasons for therapeutic failure that could involve ROS, which necessitates the need for better understanding of “biology of ROS in tumor and its microenvironment.” ROS constitutes different chemicals with distinct properties. Since their sources and levels can differ at different stages of cancer progression, it can have different effects at different stages of the disease. Adding to this complexity and heterogeneity is the difference in “threshold levels of ROS” in different sub-populations of the tumor microenvironment including the CSCs and sub-populations of hypoxia re-oxygenation along with altered cell metabolism an area which requires more understanding. As such, strategies designed to target ROS-

mediated signaling events may offer promise in the prevention and potential treatment of cancer. However, there is a need to re-strategize and choose targets taking into account the different threshold levels of ROS and ROS-signaling networks to identify potential targets for intervention in solid tumors.

Conflicts of interest

None.

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CRediT authorship contribution statement

Sankaralingam Saikolappan: Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Binod Kumar:** Formal analysis, Writing - review & editing. **Gauri Shishodia:** Writing - review & editing. **Sweaty Koul:** Formal analysis, Writing - review & editing. **Hari K. Koul:** Conceptualization, Supervision, Writing - review & editing.

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