Chapter 7

Reactive Oxygen Species, Cellular Redox Homeostasis and Cancer

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Additional information is available at the end of the chapter

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Abstract

Redox homeostasis is attained by the cautious regulation of both reactive oxygen species (ROS) formation and removal from the body system. A shift in ROS balance promotes oxidative injury and tumour development by inflicting damage to DNA and inducing inconsistencies in the genome. The sources of endogenous ROS in a cell include mETC, NOX, LOX, cytochrome P450 and XO. The exogenous risk factors of ROS are pollutants, chemicals/drugs, radiation and heavy metals. Oxidative phosphorylation in the mitochondria produces ROS with unpaired electrons. Superoxide anion is the major ROS produced in the human mitochondria. Bulk of the ROS generation in the mitochondria occurs at the electron transport chain as derivatives of respiration. Cancer cells sustain ROS production by suppressing the antioxidant-generation system. Balance between ROS production and subsequent detoxification is regulated by scavenging enzymes and antioxidant agents. Failure in sirtuin-3 (SIRT3), ATM and p53 activities elevates the intracellular levels of ROS. PKCα induces the expression of NOX (DUOX) during cancer development and the consequent increase in ROS production. The PI3K/AKT signalling pathway activates NOX with consequent ROS production and subsequent induction of instability in the genome, leading to cancer. In conclusion, the interruption of the redox pathways that regulate ROS and its redox signalling activities affects cell physiology and can ultimately result in abnormal signalling, uncontrolled oxidative impairment and tumorigenesis.

Keywords: homeostasis, cancer, reactive oxygen species, mitochondrial electron transport chain (ETC), NOX, GSH, glutathione oxidase (GPX), superoxide dismutase (SOD), thioredoxin (TRX), sirtuins

1. Introduction

Reactive oxygen species (ROS) are known as oxygen free radicals, which greatly contribute in complex cellular pathways, such as metabolism, immune system regulation, proliferation, differentiation and vascular transformations [1, 2]. ROS have a short life span and possess unpaired electrons [3]. Oxidative stress, DNA damage and cancer occur as a result of ROS imbalance due to dysregulated generation of free radicals (ROS) from oxygen and inability to neutralise and detoxify the harmful effects caused by the free radicals in the body through counteracting their oxidative effect by antioxidants [4–6]. Under normal and healthy circumstances, ROS production and removal are strictly regulated and controlled by very effective defensive machinery that blocks excessive ROS production. Some ROS, such as superoxide anion radical (O_2^-) and hydrogen peroxide (H_2O_2), are necessary life functions because they play a vital role in the regulation of cell defence mechanisms necessary for signalling, steroid synthesis, G-protein-coupled-receptor activation, gene expression and transcription factor regulation [7, 8]. Therefore, ROS can act both as good and bad molecules because of their dual nature and can either induce regulation of cellular physiology or promote the induction of cytotoxicity depending on generation levels, site of generation and magnitude of generation [9]. However, high ROS levels make cells vulnerable to damage. The derivatives from oxygen contain free radicals, such as superoxide anion (O_2^-) and hydroxyl radical (OH^-) plus non-radical molecules, such as hypochlorous acid and H_2O_2 [3], which have been linked to oxidative injury due to their high reactivity potential against proteins, lipids and DNA [10].

The generation of ROS can be activated by either various endogenous or exogenous factors. The major source of endogenous ROS in cells of mammals is the mitochondrial electron transport chain (ETC). Other endogenous ROS sources are from the activities of NADPH oxidases (NOX), lipoxygenases (LOX), cytochrome P450 and xanthine oxidase (XO) [11]. Exogenous factors that contribute to ROS production are pollutants, chemicals/drugs, radiation and heavy metals [12]. Redox homeostasis is attained by cautious regulation of both ROS formation and removal from the body system [10]. Maintenance of homeostasis and signalling event of redox require the significant regulation of synthesis and detoxification. An interruption to the redox route that regulates ROS and its redox signalling activities affects cell physiology and can ultimately result in abnormal signalling, uncontrolled toxic by-product accumulation, oxidative impairment and cytotoxicity [2]. High oxidative stress levels are normally linked to abnormalities, which characterise tumour-specific modification that exposes the cancer cells to additional raise of ROS depending on the strength of their antioxidant defence system [13].

Cancer is one of the leading causes of death globally. Recent evidence suggests altered redox stability and dysregulated redox signalling as the two frequent hallmarks of cancers, which are implicated in the progression of malignancy and treatment resistance [13]. Cancer cells have been postulated to persistently exhibit high levels of reactive oxygen species (ROS) as a result of alterations in microenvironment, genetic mutations and dysregulation of metabolic processes [13]. This shift in pro-oxidant balance promotes tumour development by inflicting damage to DNA and causing inconsistency in the genome [1]. The DNA damage and instability induced to the genome activate an inflammatory reaction leading to stability of hypoxia

inducible factor-1 and subsequent metabolic reprogramming [13, 14]. The ROS detoxification mechanism has provided selective advantage for its survival during pro-oxidation situations. Balance between ROS production and its quick detoxification are regulated by scavenging enzymes and antioxidant agents that limit the accumulation of ROS in the body.

2. Roles of mitochondria in ROS formation

Mitochondria generates 90% of the energy required for cells and tissues to function effectively and serves as the core site for energy metabolism in the cells, since it is involved in the generation of ATP via oxidative phosphorylation (OXPHOS) [15]. This process liberates electron from reducing substrates and delivers the electron to O_2 leading to the establishment of electrochemical gradient which triggers the ATP synthesis. Oxidative phosphorylation in the mitochondria produces ROS with unpaired electrons due to electron reduction from the oxygen [16–18]. Superoxide anion (O_2^-•) is the major ROS produced in the human mitochondria which is formed due to monoelectronic O_2 reduction. Most ROS originate from the superoxide anion which also mediates oxidative chain reactions.

In vivo production of O_2^-• could either be synthesised enzymatically by cyP450-dependent oxygenases, NADPH oxidase and xanthine oxidase or non-enzymatically by transferring an electron directly to O_2 [18]. O_2^-• is capable of reacting with free radicals such as nitric oxide (NO•) to produce reactive nitrogen species (RNS) [19]. O_2^-• dismutation can occur spontaneously or through superoxide dismutases (SODs) catalysed reaction to generate hydrogen peroxide (H_2O_2) [20–22]. The mitochondrial generated H_2O_2 has numerous probable fates. H_2O_2 is fairly stable and permeable to the membrane, and therefore, it can diffuse inside the cell and get eliminated by mitochondrial or cytosolic antioxidant systems, which are catalase, thioredoxin-peroxidase and glutathione-peroxidase [23]. Mitochondrially produced H_2O_2, also function as a cytosolic signalling molecule, thereby, affecting the networks that control energy metabolism, stress response, redox balance and cell cycle [24–26]. None metabolised H_2O_2 in the mitochondria undergoes Fenton reaction and then transformed subsequently into hydroxyl radical (•OH) which is naturally a very strong oxidant with high damaging impact on molecules due to its high reactive nature [27]. The above reason has made researchers to believe that mitochondria have developed competent systems for H_2O_2 removal and also mechanisms for metal chelating (chaperone proteins) which prevents the formation of radical. Bulk of the ROS generation in the mitochondria occurs at the electron transport chain (ETC) as derivatives of respiration [17, 18, 28]. The ETC terminal component known as cytochrome c oxidase (Complex IV) acquires four (4) electrons from cytochrome c and then reduces one molecule of O_2 to form two H_2O. All the intermediates that is partially reduced are retained until reduction is fully achieved [16].

2.1. ROS and mitochondrial activation of apoptosis

High exposure of the mitochondria to ROS results to injurious consequences such as inflicting oxidative mitochondrial DNA damage. It has also been suggested that ROS is deeply involved

in the extrinsic pathway of apoptosis. Extrinsic receptor-mediated pathway for cell death requires active engagement of the death receptors on the cell membrane surface with their corresponding ligands [29]. Receptor-mediated apoptotic pathway comprises of death receptors such as CD95 (Fas), TNF-related apoptosis-inducing ligand (TRAIL) receptors and TNF. Activation of Fas as well as TNFR1 generate ROS due to superoxide ($O_2\bullet-$) production and formation of NADPH oxidase daises derived from lipid raft. Induction of apoptosis or necrosis is linked with lipid raft-mediated downstream ROS generation [30, 31]. Downregulation of FLIP (FLICE inhibitory protein), a strong inhibitor of apoptosis is mediated by ROS via ubiquitination and consequent proteasome degradation or by scavenging of nitric oxide (NO) to prevent FLIP S-nitrosation and cytoprotection [32]. ROS sensitises cancer cells to apoptosis induced by TRAIL [33]. CD95 and TRAIL death receptors have been observed to be highly upregulated in reaction in the presence of hydrogen peroxide via NF-kappa B activation [34]. ROS promote apoptosis via JNK activation, inducing either intrinsic or extrinsic apoptotic signalling [35]. TNFα induced ROS perpetrates oxidation of JNK, thereby, inactivating-phosphatases via catalytic transformation of their cysteine into sulfenic acid resulting to prolonged activation of JNK which is necessary for the release of cytochrome c and cleavage of caspase 3 as well as cell death [36]. TNFα activates MAPK cascade. ASK1, a redox-sensitive MAPK kinase, is located at the JNK upstream. Reduced thioredoxin1 (Trx1) binds to ASK1 during non-oxidising circumstances to form a complex known as ASK1 signalosome (Trx1/ASK1 complex) which perform redox switch functions. Persistent cellular ROS causes detachment of the oxidised Trx1 from the Trx1/ASK1 complex leading to full ASK1 activation through TRAF2/6 recruitment [37]. ASK2 a member of ASK family attaches to ASK1 and stabilises it in mitochondria, nucleus and cytosol. Saxena et al. have revealed that redox protein known as thioredoxin interacting protein (TXNIP) with apoptosis promoting potential under oxidative stress, shuttles from the nucleus to the mitochondria leading to the removal of TXNIP from ASK1 and formation of a compound with mitochondrial Trx2. This suppression of the inhibition is mediated by Trx2 results in ASK1phosphorylation and induction of the mitochondrial pathway for apoptosis with caspase-3 cleavage and cytochrome c release [38]. The major target for ROS inside the mitochondria is the permeability transition pore (mPTP) in which the oxidative modification of its proteins has significant influence on the anion fluxes within the mitochondria [39]. This could cause overload of Ca^{2+} and ROS in reaction to pro-apoptotic stimuli causing mPTP to assume a very high state of conductance allowing unrestrained entry of solutes along the electrochemical gradient into the matrix of the mitochondria. The above phenomenon is termed mitochondrial permeability transition (MPT), which results in mitochondrial membrane potential dissipation and consequent osmotic swelling of the matrix of the mitochondria due to fluid influx [40]. The early phase of the mitochondrial swelling involves water movement from inter-cristae spaces into the mitochondrial matrix. Persistent movement of this water exacts pressure on the outer membrane due to increased volume of the matrix leading to mPTP opening and/or rupturing of the outer membrane of the mitochondria allowing the matrix to expand further [41]. This causes cytochrome c to be released with consequent activation of the downstream effector caspases by Apaf-1-pro-caspase 9-apoptosome complex.

3. Antioxidant system responsible for the redox homeostasis

The antioxidant systems are either enzymatic or non-enzymatic. The enzymatic antioxidant system consists of peroxiredoxin (Prx) system, catalase, SOD and the glutathione peroxidase (GPx) system, while the non-enzymatic antioxidant systems consist of α-tocopherol, lipoic acid and ascorbic acid [42–45].

3.1. Superoxide dismutases (SOD)

Intracellular ROS levels are regulated by the balance between ROS generating enzymes and antioxidant enzymes, which include superoxide dismutases (SOD), catalase, thioredoxin and glutathione peroxidase (GPX) [42]. SOD functions to convert O_2^- into H_2O_2, which is later converted into water by glutathione peroxidase or catalase. Human cells express three types of SOD: MnSOD (manganese SOD) expressed by the mitochondria, CuZnSOD (copper-zinc SOD) expressed by the cytoplasm and third is the extracellular SOD. A study has demonstrated that lack of MnSOD in mice generated excessive oxidative stress causing their mortality [46]. Another study also revealed that mice with a deficiency of CuZnSOD developed hepatocellular carcinoma due to sustained oxidative damage [47]. Lack of MnSOD has also been linked to elevated risk of lung cancer, prostate cancer, non-Hodgkin's lymphoma and ovarian cancer [48–51].

3.2. Glutathione oxidase (GPX)

GPX is a selenium-dependent antioxidant enzyme, which regulates hydrogen and lipid peroxide levels. Lack of GPX in the body increases tissue damage by ROS [43] and low GPX levels, which results in increased LDL oxidation [44]. GPX catalyses the reduction of hydrogen peroxide to form glutathione disulphide (GSSG) with glutathione (GSH) functioning as the substrate. An increased risk of bladder cancer, lung cancer and breast cancer has been associated with the substitution of proline-leucine at codon 198 in human GPX [52–55].

3.3. Thioredoxins (Trx)

The protective function of thioredoxins (Trxs) in cells against oxidative stress is via the reaction between their active site known as 2-cysteine and ROS resulting in reduction of oxidised proteins. Trxs also function as hydrogen donors to thioredoxin-dependent peroxide reductases. Trx possesses a Cys-Gly-Pro-Cys active site, which is essential for redox regulatory functions of Trx. Trx, when combined with Trx reductase and NADPH, forms a redox-sensitive machinery, which controls the levels of oxidised cysteine on proteins. The antioxidant properties of Trx can be attributed to the reduction of the oxidised form of Trx peroxidase by Trx, while the reduced peroxidase scavenges H_2O_2 [45]. The two isoforms of Trx are Trx1 (expressed in the cytoplasm and the nucleus) and Trx2 (expressed in the mitochondria), which are very crucial for cell survival [56]. Trx1 is a redox-sensitive binding protein that controls the

activity of NF-κB through the reduction of cys62 on the p50 of NF-κB [57]. Trx1 has been linked to breast tumours, colon cancer, cervical cancer, gastric cancer, lung cancer, liver cancer and melanoma and carcinomas of the pancreas [58–62].

3.4. GSH

GSH is a thiol protein consisting of cysteine, glutamine and glycine, which functions as an important antioxidant in detoxification of metabolic processes [63]. Elevated levels of GSH in the cancerous patient tissue are reinforced by improved accessibility to the biosynthetic

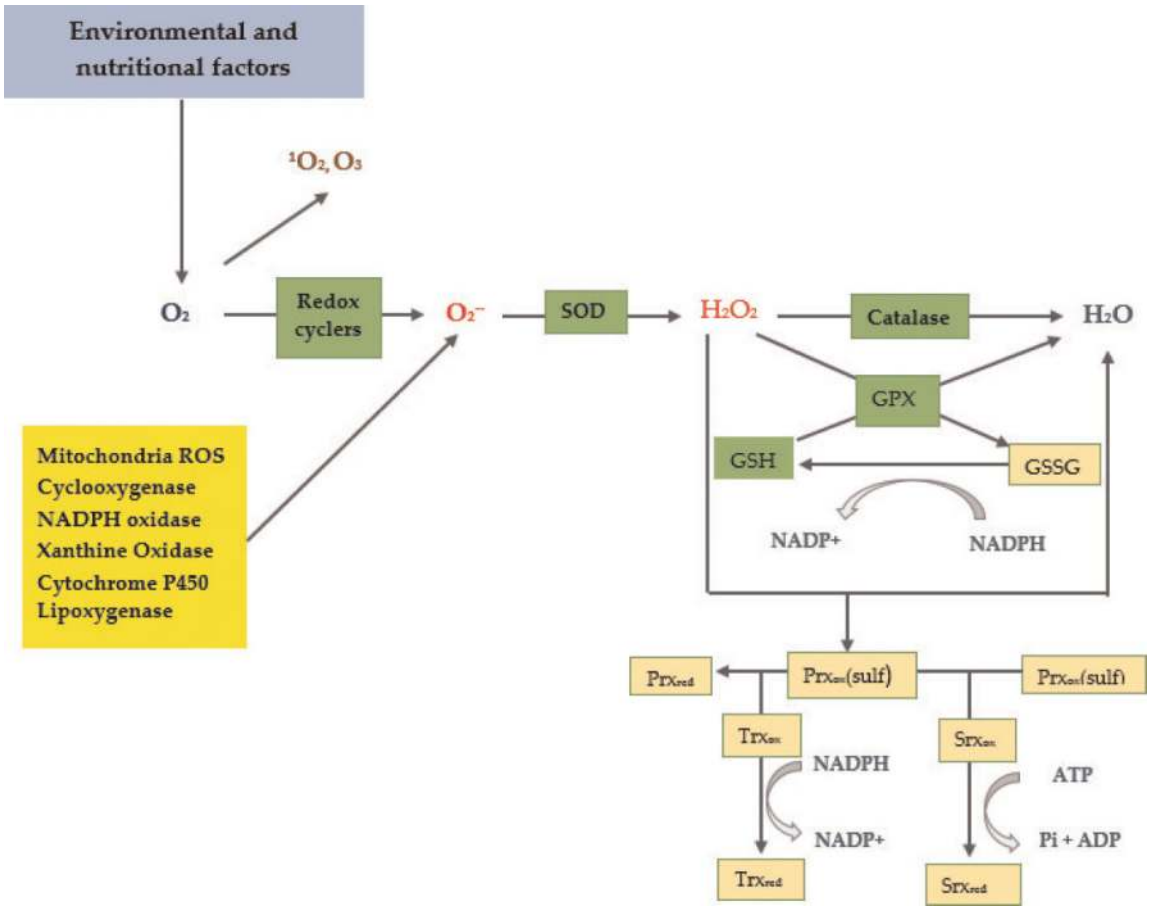

Figure 1. Mechanism of ROS formation and disposal. Enzymatically or non-enzymatically generated superoxide reacts with other radicals. The generated superoxide and H_2O_2 form hydroxyl radicals and singlet oxygen. SODs catalyse the dismutation of the superoxide, while H_2O_2 decomposition to water is catalysed by catalases in conjunction with glutathione peroxidase/GPx and Prxs. Thiol, a component of cysteine found in Prx, is oxidatively converted into Cys-sulfenic acid by (Prx_{ox}) and subsequently reduced by thioredoxin (Trx_{red}). H_2O_2 further oxidises Cys-sulfenic acid (Prx_{ox}) into Cys-sulfinic acid and reduced subsequently back by ATP and reduced sulfiredoxin (Srx_{red}) to Cys-sulfenic acid (Cys-SOH). Cys-SOH formed functions to regulate protein activities by absorbing the oxidative insults leading to the deflection of injurious oxidative impairment [24]. Cys-SOH can be converted into oxidative post-translational modification (Ox-PTM) in redox environment. This modification reacts with tripeptide glutathione (Glu-Cys-Gly) to form S-glutathionylated Cys (GSSG) or react with thiol to form disulphide bond. Formation of GSSG protects the Cys of the host from further oxidative reactions.

elements of GSH, such as glutamate, cysteine and glycine [64, 65]. The negative regulator of cysteine/glutamate known as SLC7A11 is always upregulated in human tumours [66]. Glutamate cysteine ligase modifier subunit (GCLM) is also upregulated in many types of human cancer but also requisite for effective GSH synthesis [67]. The cellular levels of GSH and its regeneration are modulated by NADPH and GR catalysing the reduction of oxidised GSSG back to GSH, in a process facilitated by the upregulation of NADPH production by cancer cells (**Figure 1**). Maintenance and elevation of GSH levels in cells are critical for the initiation and proliferation of tumours [67, 68]. Loss of GSH, or decrease in the ratio of glutathione to glutathione disulphide (GSH:GSSG), results in increased oxidative stress susceptibility and cancer development. Also, elevated levels of GSH increase antioxidant activities against numerous cancer cells, thereby enhancing the resistance of the cancer cells against oxidative stress [69].

3.5. Peroxiredoxins (Prxs)

Prxs are made up of six isoenzyme families capable of reducing H_2O_2 and alkyl hydroperoxides to their resultant H_2O or alcohol. Prxs are essential antioxidants that mediate the balancing mechanism of cellular H_2O_2 production, which is necessary for signalling and cell metabolism [70]. Nrf2 upregulates Prxs in oxidative stress circumstances [71]. PRDX1 plays the role of tumour suppressor in the development of breast cancer by interacting with oncogene (c-Myc) suppressing its transcriptional action [72, 73]. Contrarily, PRDX1 has promotional activities on pancreatic carcinoma, hepatocellular cancer, oesophageal cancer, oral cancer and lung cancer via upregulation of heme-oxygenase 1 and NF-κB pathway activation [74–77]. PRDX2 stimulates colorectal carcinoma by upregulating Wnt/β catenin levels, while it stimulates prostate cancer by upregulating the receptive activities of androgen [78, 79].

4. Enzymes responsible for the redox homeostasis

Some of the enzymes associated with redox homeostasis are NADPH oxidase, ATM kinase and sirtuin-3 among others.

4.1. NADPH oxidase

NADPH oxidase is hetero-proteins, which consist of seven isoforms. ROS production by NADPH oxidase is via the NOX protein. NADPH oxidases are referred collectively as the NOX family. The NOX family is comprised of NOX (NOX1, NOX2, NOX3, NOX4 andNOX5) and dual oxidases (DUOX1 and DUOX2) [80–82]. The isoforms DUOX1 and DUOX2 contain additional peroxidase domains, which exert the catalytic dismutation of superoxide anion to yield H_2O_2 [74]. Cytosolic electron transfer from NADPH across the cell membrane is catalysed by NADPH oxidase, thereby oxidising the molecular oxygen, which is later reduced to generate ROS species called superoxide anion radical (O_2^-). Generation of NADPH in the mitochondria plays a critical role in metastasis. In many tumour cells, reductive carboxylation in the mitochondria to generate NADPH is powered by mitochondrial citrate transporter

(mCTP), cytosolic isocitrate dehydrogenase (IDH1) and mitochondrial isocitrate dehydrogenase (IDH2). This development assists cells to retain redox balance in the mitochondria averting the oxidative trauma received as a result of the detachment from the extracellular matrix [75].

4.2. ATM kinase

ROS production can be inhibited by ATM kinase and the same ATM kinase also serves as the function of redox-regulated DNA damage sensing protein [76]. ATM-regulated tumour suppressor works by interfering with KEAP1-facilitated NRF2 ubiquitination, thereby activating and stabilising the major regulators of antioxidants [77]. ATM facilitates the upregulation of glucose-6-phosphate dehydrogenase in order to promote NADPH production, thereby suppressing ROS levels [83].

4.3. Sirtuin-3

ROS levels are inherently elevated in cancer cells owing to mitochondrial defective oxidative metabolism [84]. Upregulated oxidative signals are implicated in the development and advancement of different cancer types [85]. Raised levels of ROS contribute to the initiation of cancer, transformation to malignancy and therapy resistance. ROS inflicted damage is more frequently seen in mitochondrial DNA than nuclear DNA because of its closeness to the main ROS source of generation and inadequate restoring capacities. For instance, silent information regulators of gene transcription-3 (sirtuin-3) are crucial in ROS regulation and effective flow of electrons via ETC. Failure in sirtuin-3 activities elevates intracellular levels of ROS, thereby inducing instability to the DNA of the mitochondria [86]. Sirtuins are an enzyme family, which is dependent on NAD-class III histone deacetylase. Seven homologues of Sirtuins (SIRT1–7) exist in mammals [87]. SIRT1 deacetylate gene regulates proteins like p53, forkhead proteins and NF-κB, which modulate resistance of cells to stress [36]. The deacetylase function of sirtuin proteins depends on the intracellular or endogenous content of NAD^+ [87]. Sirtuins are involved in the catalysis of exclusive reactions that lead to the formation of deacetylated substrate, acetyl ADP-ribose (AADPR) and nicotinamide [87]. Also, SIRT1 interrupts apoptosis, rescuing vulnerable cells after repetitive oxidative stress exposure [60]. SIRT2 deacetylate cytoskeletal proteins, such as forkhead proteins, histones, etc. SIRT3 reacts to redox status changes in the mitochondria by influencing the enzyme activities of manganese superoxide dismutase (MnSOD), which in turn scavenges ROS in the mitochondria and thus modulating the levels of ROS and metabolic homeostatic reliability [87].

5. Pathways implicated in redox homeostasis

Dysregulations associated with various tumour proliferations, autophagy and apoptosis depend on the activation of targets sensitive to redox reactions, such as PKC, Akt, PTEN, p53, etc. [88].

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5.1. PKC pathways

PKC has isoenzymes, such as PKCα, PKCβ and PKCδ, with conflicting actions in different cancers [89]. PKCβ is the isoenzyme of PKC responsible for the stimulation and phosphorylation of p66/shc, which binds to cytochrome c in order to activate ROS generation [90]. Recent studies demonstrated that PKCα induces the expression of DUOX (a member of NOX family) during cancer development and subsequent ROS production [91, 92]. PKCδ has been demonstrated to be involved in the activation of NOX through the alteration of redox balance, thereby influencing the differentiation of tumour cells [90].

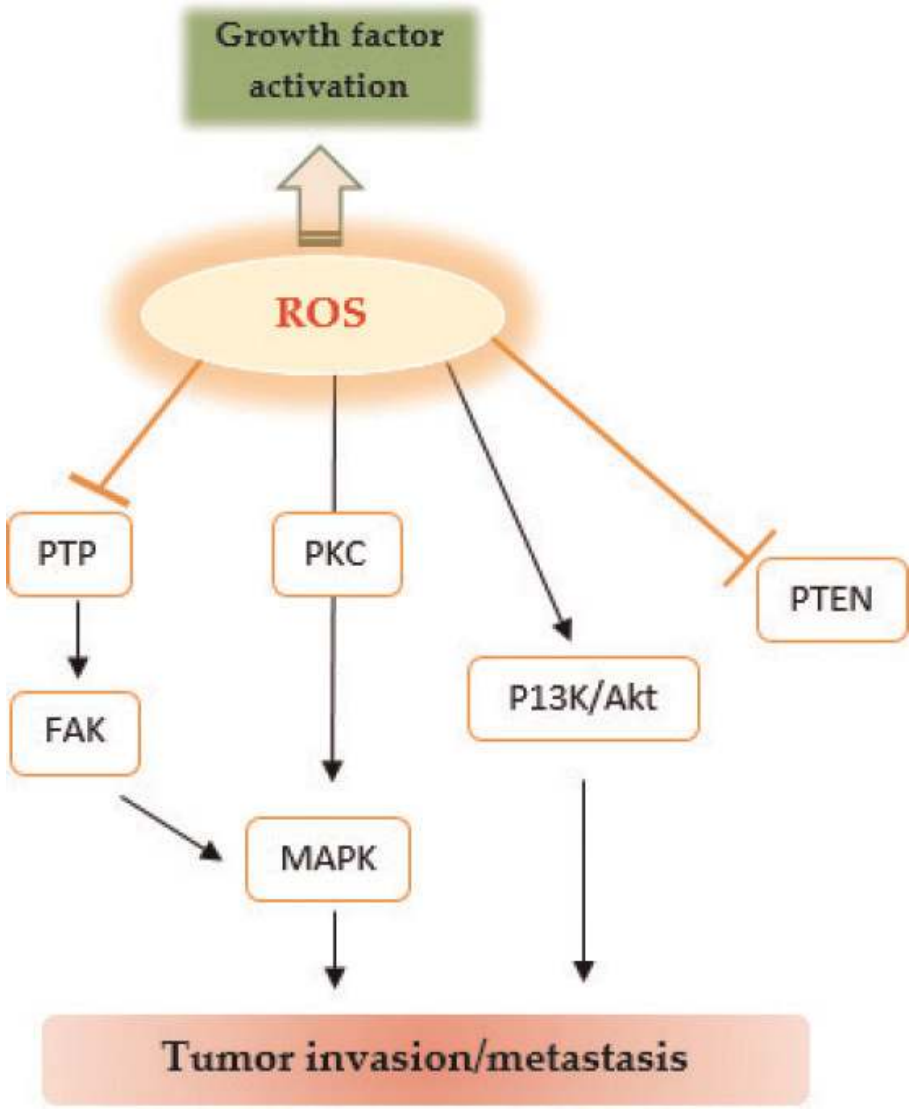

Figure 2. Effect of ROS imbalance in some pathways. Imbalance in the levels of ROS in the cell causes inhibition of PTEN and PTP dependent phosphorylation and consequent inactivation of FAK. The PI3K/Akt and PKC signals are activated in the process leading to invasion/metastasis.

5.2. PI3K/AKT pathway

PI3K/AKT signalling pathway activates NOX with consequent ROS production and subsequent induction of instability to the genome of cancer cells [91]. Upregulation of PTEN suppresses ROS synthesis, thus regulating PI3K/AKT pathway [92]. ROS-mediated PTEN inactivity alters kinase-phosphatase stability favouring the signalling of tumorigenic-tyrosine kinase receptor via Akt (**Figure 2**) leading to the inhibition of apoptosis due to phosphorylation and inactivation of Bad and caspase-9 [93]. Akt improves cell survival by negatively regulating the activities of Bcl-2 homology domain 3 (BH3)-only proteins via binding and inactivation of pro-survival Bcl-2 family members. Akt survival effects on cells depend on the S136 phosphorylation on BAD [94]. Akt-mediated BAD phosphorylation is stimulated by survival factors on S136 leading to the creation of 14-3-3 protein binding site causing BAD to miss its protein target [94]. Akt phosphorylates FOXO proteins (FOXO1, FOXO3a and FOXO4) on T24 and S256 attaching onto 14-3-3 proteins in the cell nucleus causing displacement of transcription factors of FOXO from their gene target and consequent export out of the nucleus. This results in the blocking FOXO facilitated transcription of genes that can stimulate apoptotic processes and cell-cycle arrest, thereby encouraging cell survival. Akt also promotes survival by targeting HDM2 causing inhibition of BH3-only proteins by triggering degradation of p53. Akt induces phosphorylation of HDM2 on S166 and S186, causing HDM2 translocation to the nucleus to regulate p53 function negatively [94]. Deficiency of p53 in cancer results in higher cytokine transcription and consequent accumulation of ROS [95]. p53 is another tumour suppressor that has the potential to activate NRF2 and elevate antioxidant enzyme (SOD, GPX1 and NADPH) expression, thereby reactivating the antioxidant system (**Figure 1**) [10, 96]. Previous study has shown that 53 plays a pro oxidant role through the reduction of SLC7A11 expression, which is responsible for cysteine uptake during GSH synthesis [87]. Thus, the antioxidant activity of p53 is necessary because of its ability to avert cancer, thus implicating loss of tumour suppressors in upregulated intracellular ROS expression.

6. Conclusion

Redox homeostasis is achieved by the regulation of both ROS formation and removal. Shifts in ROS balance induce oxidative injury and tumour development. The balance between ROS production and subsequent detoxification is regulated by scavenging enzymes and antioxidant agents. Targeting the ROS generation pathway with anticancer medications can aid patient recuperation. Therefore, the modulation of ROS levels is a modern anticancer therapy. Further studies are needed to determine when ROS inhibition and activation can be applied in clinical cancer treatment.

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Conflict of interest

All authors declared that there is no conflict of interests.

Abbreviations

ROS	reactive oxygen species
SOD	superoxide dismutases
TRX	thioredoxin
GPX	glutathione oxidase
GSH	glutathione
mETC	mitochondrial electron transport chain
NOX	NADPH oxidases
LOX	lipoxygenases
XO	xanthine oxidase
Prx	peroxiredoxin
MnSOD	manganese SOD
CuZnSOD	copper-zinc SOD
GCLM	glutamate cysteine ligase modifier subunit
GSSG	S-glutathionylated Cys
PRDXs	peroxiredoxins
GR	glutathione reductase
GCLM	glutamate cysteine ligase modifier subunit
Ox-PTM	oxidative post-translational modification
DUOX	dual oxidases
mCTP	mitochondrial citrate transporter
IDH	isocitrate dehydrogenase
Sirtuin-3	silent information regulators of gene transcription-3
ATM	ataxia telangiectasia mutated
FAK	focal adhesion kinase
BAD	Bcl-2-associated death

FOXO	forkhead box
PI3K	phosphoinositide-3 kinase
PTP	protein tyrosine phosphatase
PTEN	phosphatase and tensin homologue
PKC	protein kinase C
Nrf2	nuclear factor erythroid 2-related factor 2

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