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Oxidative stress responsive transcription factors in cellular signalling transduction mechanisms

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ABSTRACT

Oxidative stress results from the imbalances in the development of reactive oxygen species (ROS) and anti-oxidants defence system resulting in tissue injury. A key issue resulting in the modulation of ROS is that it alters hosts molecular, structural and functional properties which is accomplished *via* various signalling pathways which either activate or inhibit numerous transcription factors (TFs). Some of the regulators include Nuclear erythroid-2 related factors (Nrf-2), CCAAT/enhancer-binding protein delta (CEBPD), Activator Protein-1 (AP-1), Hypoxia-inducible factor 1(HIF-1), Nuclear factor κB (NF-κB), Specificity Protein-1 (SP-1) and Forkhead Box class O (FoxO) transcription factors. The expression of these transcription factors are dependent upon the stress signal and are sometimes interlinked. They are highly specific having their own regulation cellular events. Depending upon the transcription factors and better knowledge on the type of the oxidative stress help researchers develop safe, novel targets which can serve as efficient therapeutic targets for several disease conditions.

1. Introduction

Oxidative stress may be also termed as “the disproportion between the formation and expression of reactive oxygen species”. A biological system has the capability to rapidly detoxify the reactive intermediates and also for repairing the resultant damage [1]. Oxidative damage of proteins, fats, nucleic acids and carbohydrates is due the imbalance between antioxidants and free radicals [2]. The resulting oxidative stress results in pathological disease conditions that include cancer, neurological problems, atherosclerosis, ischemia/perfusion, diabetes, acute respiratory distress syndrome and many others [3]. Antioxidants are capable of protecting the body from the harmful effect of free radicals [4]. Higher levels of oxidative damage will result predominantly in oxidative stress to cells, along with failure of repair mechanisms which include raise in levels of ‘biomarkers’ as a resultant of oxidative damage [5,6].

2. Oxidative stress

Oxidative stress denotes the instability between the generation of reactive oxygen species (ROS) and antioxidants [6]. Sies in the year 1989 proposed it as “a disruption in the pro-oxidant and antioxidant balance, that results in potential damage” often called the ‘oxidative damage’ [7]. The biomolecular damage resulting from the ROS is dependent upon the constituents of living organisms [8]. For example, ROS stress can exactly damage Na + /K + -ATPase [9] and regulate the actions of potassium channels by chemical reaction with amino acid [10]. Oxidative stress as a result of higher activity of muscle and other tissues is a limelight of high importance to sports medicine and to the subject of exercise in conditions like oxygen deprievation or hypoxia. As a result of oxidative stress, cells try to counterbalance the oxidant effects and reestablish the redox balance by stimulation or suppressing genes encoding defensive enzymes, structural proteins and transcription factors. For instance the ratio between oxidized and reduced glutathione is one of the causative factor of oxidative stress in our body. Higher generation of ROS may change the structure of DNA in the body, resulting in alteration of proteins and lipids, induction of several stress-induced transcription factors and render the production of pro-inflammatory and anti-inflammatory cytokines [11].

The molecular mechanism underlying the progression of oxidative stress is not well understood. Several signalling mechanism has a key role in the induction of oxidative stress. In this review, we spotlight on

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understanding the portrayal of several stress-related TFs and their expression.

2.1. NF-κB

The nuclear factor-κB (NF-κB) a prime transcription factor which governs gene expression in disparate cellular processes like innate immune response, organ development, embryogenesis, cell proliferation and programmed cell death. NF-κB comprise five specific homo and heterodimer proteins, REL subfamily proteins (p65/RELA, RELB, and c-REL) and the NF-κB subfamily proteins (p50, and p52, and its precursor p105 and p100, respectively). The two main signalling pathways of NF-κB are the canonical or the classical pathway and the non-canonical or the alternative pathway that lead to the activation of NF-κB target genes [12]. NF-κB pathway is of ample interest in the field of free radical biology because it can be stimulated by ROS and this activity can be regulated by antioxidants. It is an important biomarker for oxidative stress as the ROS produced under various prophylactic conditions, uses the evaluation of NF-κB stimulation to look to look into the aetiology of these disorders [13]. In case of diabetic nephropathy, one of the causes is oxidative stress. One proposed pathway for this is the stimulation of the oxidative stress sensitive NF-κB. Lower glycemic control has been shown to activate NF-κB in *exvivo* isolated peripheral blood mononuclear cells (PBMC) of Type I insulin-dependent diabetes mellitus patients that correlates the degree of diabetic nephropathy. NF-κB stimulation is in part dependent on oxidative stress since thioctic acid (a-lipoic acid) decreased NF-κB binding activity [14]. The mechanism of NF-KB activation is promoted by its release from IκB, the cytoplasmic inhibitor protein and subsequent translocation of active NF-κB into the nucleus. The action of inflammatory cytokines like tumor necrosis factor alpha (TNF-α) and Interleukin- 1a (IL-la); which are the tumor promoter and activator of protein kinase C, phorbol myristate acetate (PMA); lipopolysaccharides of bacteria (LPS); DNA-damaging agents; double-stranded RNA and infection by viruses including human immunodeficiency virus type 1 triggers the release of NF-κB from IκB [15] (Fig. 1a). AP-1 belongs to a group of basic leucine zipper (bZIP) TFs comprising of the Fos (c-Fos, FosB, Fra1, and Fra2) and Jun (c-Jun, JunB, and JunD) families is found closely related with NF-κB in the mechanism of regulation [16]. A study showed that endotoxin tolerance inhibited lipopolysaccharide induced pulmonary inflammation as a result of unresponsiveness of NF-κB. NF-κB is also found responsible to control proapoptotic JNK signalling triggered by TNFα [17]. Nifedipine, a synthetic compound is efficient in constraining NF-κB activation and therby susceptible to decrease in the inflammation followed by higher endothelial function in the coronary circulation [18]. Interestingly, a study proposed that regular exercise at older ages, results in a predominant increase in oxygen intake and thereby it potentially generates higher oxidative stress and attenuates, antithetical to expectation, the increase in the activity of NF-κB in the rat liver. Regular exercise not only halts the age-associated increase in NF-κB activity, but also results in the down-regulation of ROS production [19]. There are several evidences to prove the stimulation of NF-κB signalling by ROS. Some of which includes the experiments carried out in cell types like human breast cancer cell line MCF – 7 [20]. Glenn *et al* studied the significant induction of NF-κB by OS induced through UVA solar radiation in the nuclear extracts of skin fibroblasts [21]. Several *in vitro* studies concludes that a variety of antioxidants can prevent the activation of NF-κB or by the overexpression of antioxidant enzymes [22]. Blackwell *et al* proved *in vivo* that treatment with antioxidant *N*-acetyl cysteine (NAC) before endotoxin injection will inhibit NF-κB activation [23]. It is a common cause for the progression of several medical complications in diabetic cases. This correlates with the fact that NF-κB activation in diabetic patients and is thus decreased by treatment with antioxidant alpha-lipoic acid [24].

2.2. Sp-1

Sp-1 belongs to the TF family associated with oxidative stress-induced neuronal cell death. Sp-1 is a member of the family of DNA-binding proteins that consists of three zinc finger motifs and bind to guanosine and cytosine-rich DNA. The role of Sp-1 have been demonstrated to change in response to apoptosis inducing stimuli like oxidative stress (Fig. 1b). In neurons according to researchers huntingtin protein induces neuronal toxicity which is mediated by Sp-1 sequestration and also its coactivators, TATA binding protein-associated factor II 130 (TAFII30). Sp1 modulates prosurvival proteins (*e.g.*, the inhibitor of apoptosis (IAP) protein) and manganese superoxide dismutase proteins. The regulation of Sp1 in cell death depends on the cell type and the death stimulus. Oxidative stress predominantly induce Sp1 and Sp3 protein levels and DNA binding in neurons *invitro* and *invivo* which reinforce the survival in cortical neurons [25]. The first cloned mammalian transcription factor was Sp-1. Sp-1 has high functional importance as highlighted in a study which states that the gene disruption in mice is lethal at embryonic day. Sp1 binds to G/C-rich nucleotides that includes GC and CACCC boxes. Identification of GC/ CACCC boxes called housekeeping genes gives the initial hint that Sp1 is a basal transcription factor [26]. Sp1 also has a role in inducible gene expression and the interaction of Sp1 with other transcription factors and/or cofactors such as CBP, p300 or CRSP 84 represent a prime transcriptional control mechanism. Recent studies made it clear that Sp1 can be regulated through changes in its phosphorylation state and altered signalling pathways like Ras dependent activation of the MEK1/ERK cascade targets [27]. A pleiotropic immunomodulatory cytokine, Interleukin-4 (IL-4), which is secreted by T-helper 2 (TH2) induce oxidative stress which further upregulate *VCAM-1* gene expression in human endothelial cells by the stimulation of the transcription factor [28]. A rate-limiting enzyme called Cyclooxygenase (COX), which is also referred to as prostaglandin H synthase converts arachidonic acid into prostaglandin H_2, thromboxanes, and prostacyclins. COX-1 and COX-2 are the two isoforms of COX. Cyclooxygenase-2 is induced by Sp1 in neuronal oxidative and DNA damage response [29]. Tranactivation of SP1 that interacts with c-Jun, has been shown to bind to the CYP2E1 promoter (Cytochrome P450 (CYP) enzymes) [30].

Receptor tyrosine kinase superfamily which comprise hepatocyte growth factor (HGF) receptor is encoded by c-met protooncogene. Studies reveal that a promising transcriptional regulatory system by which Egr-1 sequesters Sp1 by activating c-met through physical interaction mediated *via* downregulation of *Hepatocyte Growth Factor (HGF)* receptor gene expression by oxidative stress [31]. In 2003, Ryu et al., analysed the understanding of SP-1 in oxidative stress mediated cell death in neurons both *in vitro* and *in vivo*. *In vitro* studies observed that the basal DNA binding activity of SP-1 and SP-3 is very low under no stress condition while the prevalence of oxidative stress reflected in the increased levels of SP-1 and SP-3. Similarly, *in vivo* models in which neuronal death has been attributed due to oxidative stress responded with the high and sustained levels of SP-1 and SP-3 [32]. Another study reported that the regulation of TP53- independent glycolysis and apoptosis regulator (TIGAR) in brain is mediated by the transcription factor SP-1 [33]. H_2O_2 resistant HP100 cells were studied to deciper the regulation of the catalase gene promoter by SP-1 [34]. It is said that the accumulation of ROS intermediates is dependent on age. Experiments performed with the nuclear extracts of young and aged rat tissues serve as a proof for the above mentioned fact as the efficiency of SP-1 inducing to its cognate DNA sequence decreases largely with age [35]. This can also be restored by incubation with reducing agents like dithiothreitol [36].

2.3. AP-1

The transcription factor Activator Protein 1 (AP-1) is heterodimeric comprising of various members of the Jun and Fos families (Fig. 2a).

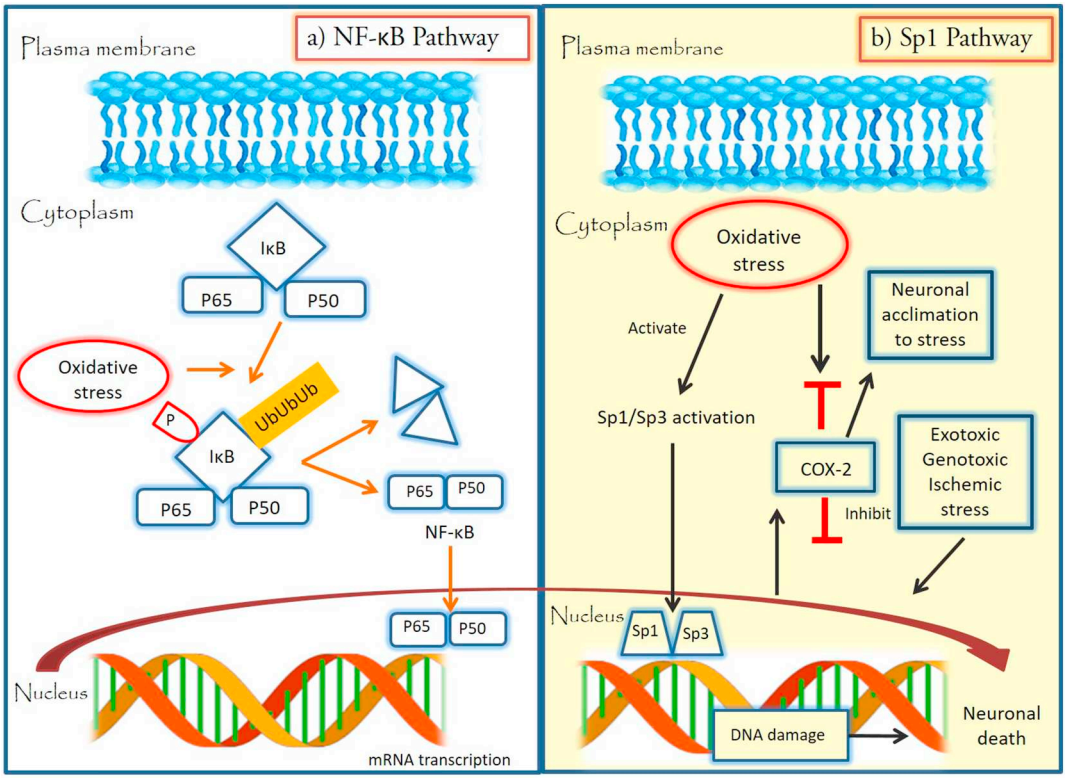

Fig. 1. A). Schematic representation of NF-κB pathway. Under normal conditions, IκB is bound to P65 and P50 thereby inhibiting transcription. Upon stimulation by oxidative stress, the NF-κB transcription complex consisting of P65 and P50 dimer subunits bound to the inhibitory complex IκB becomes free. The activated kinase phosphorylates IκB and undergoes ubiquitinylation that triggers its degradation which leads to the release of P65 and P50 subunits. Then the P65 and P50 dimerization unit moves into the nucleus and binds to the κB motifs present in the promoter of its target genes, stimulating their transcription. The target genes of NF-κB are *Fas, Bcl-2, Bcl-2 L 1, MCP-1, IL-18*, different interleukins and cell adhesion molecules namely *ICAM-1* and *VCAM-1* that plays important role in cell survival, proliferation, apoptosis, morphogenesis, inflammation, angiogenesis and differentiation. B). Schematic representation of Sp-1 pathway. A prototypic C_2H_2-type zinger finger named Sp1 is ubiquitously expressed that contains DNA binding protein that can either activate or repress transcription in response to physiological and pathological stimuli. COX-2 inhibitors are used for treating inflammation. Due to oxidative stress, kinases phosphorylates Sp1/Sp3 transcription factor that gets activated and it also inhibits COX-2 inhibitors which will overcome neuronal accumulation, exotoxic, genotoxic and ischemic stress thus preventing from neuronal death. Sp1/Sp3 moves to nucleus leading to damage of DNA that cause neuronal death. The target genes are *p53, p73 and YAP* that induces DNA repair and apoptosis.

The activity of c-Jun is enhanced through the phosphorylating activity of Jun NH_2-terminal kinases (JNKs)/stress-activated protein kinases (SAPKs), which are selectively initiated by a variety of oxidative stress. The activity of AP-1 can also be dictated between AP-1 and ER protein–protein interactions. Studies have shown that a compound called tamoxifen can operate as a agonist in co-inducing ER/AP-1 on promoters which are regulated by AP-1 site [37]. The two major signalling pathways are Jun N-terminal kinase (JNK) and p38 mitogen –activated protein kinase (MAPK) that induces the stimulation of *Jun* and *Fos* genes. JNK and p38 catalytic activities are interestingly raised by TNF, IL-1, LPS and dsRNA indicated through several knockout experiments. In response to H_2O_2, ASK1 and ASK2 (two related MAPKKKs called ASK1 (MEKK5) and ASK2 (MEKK6)) stimulate dimerization, which results in autostimulation through transphosphorylation. The most probable reason would be ASK1 and ASK2 forming heterodimers which act as direct sensors of oxidative stress [38]. Since H_2O_2-induced growth-related events are very sensitive to inhibition by nordihydroguaiaretic acid (NDGA), studies were carried out to assess whether 12, 15-hydroperoxyeic osatetraenoic acid (HPETE), mediated oxidative stress induction of c-Fos and c-Jun expression. Studies further revealed that H_2O_2 induces the synthesis of 12 and 15-HPETE in vascular smooth muscle cells (VSMC) and these eicosanoids has the ability to stimulate AP-1 and lipoxygenase inhibitors which exhibit antiproliferative activity [39]. Comparative analysis of the transcriptional activity of progressively deleted GADD153 promoter fragments intimated that an AP-1 binding element provide significant contribution to transcriptional activation by UVC or oxidant treatment. [40]. Luteolin, a flavanoid compound can greatly inhibit the activity of AP-1 thereby inhibiting the generation of ROS proven by in *in vitro* studies [41]. Another study carried out in human fibroblasts reveals that PUFA (poly unsaturated fatty acids) induced intracellular oxidative stress which activates AP-1 [42]. The oxidative stress inducible nitric oxide (NO) synthase (iNOS) has been studied in cases of hyperoxia. Pepperl et al., proved that hyperoxia upregulates NO pathway and the activation of AP-1 as studied in alveolar macrophages [43]. Activation of AP-1 can be achieved by a PKC activator which is ROS dependent [44]. The role of AP1 is depicted in the Fig. 2a.

2.4. FOXO

The FoxO class of Forkhead transcription factors govern the progression of cell cycle and cell death. The insulin /IGF signalling pathway induces PKB/c-Akt to negatively modulate FoxO transcription factors [45]. Activation of oxidative stress in cardiomyocytes promoted FoxO1 and FoxO3 nucleus uptake and thereby activation of the target gene. Infection of cardiomyocytes with a dominant-negative FOXO1(256) adenovirus resulted in a significant increase in ROS and cell death, whereas when the FoxO1 or FoxO3 expression levels were increased it reduces ROS and cell death (Fig. 2b) [46]. The FoxO family of transcriptional regulators consists of a wide range of transcription factors like FoxO1, FoxO3, FoxO4 and FoxO6 [47,48]. Production of ROS in excess causes cardiovascular and neurodegenerative disorders

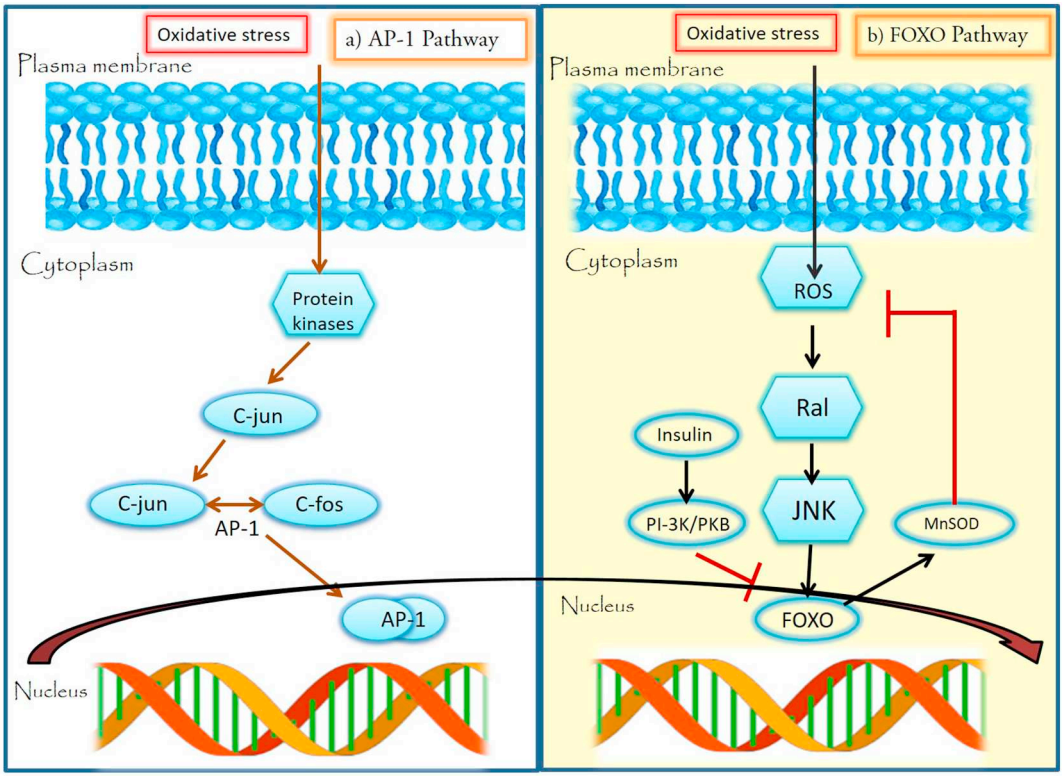

Fig. 2. A). Schematic representation of AP-1 pathway. Oxidative stress induces protein kinases that phosphorylates C-jun (encoded by *JUN* gene in humans) which combines with C-Fos forming the AP1. Regulation of Jun and its dimerization partner is achieved through extracellular stress stimuli such as peptide growth factors, pro-inflammatory cytokines and oxidative stress. The activated AP-1 moves into the nucleus and that triggers transcription which involves in migration, adhesion and inflammation. The target genes for AP-1 are *EGFR, FasL, Bcl3, JNK4A, proliferin, VEGFD, DNMTL1* that are responsible for DNA methylation, stimulates apoptosis, angiogenesis, proliferation and invasiveness. B) Schematic representation of FOXO pathway. FoxO class are negatively regulated by PI-3 K/PKB in response to insulin signalling that are involved in regulating cell cycle progression. FoxO upon ROS accumulation caused by stress, the small GTPase Ral gets stimulated to provoke the JNK-mediated activation of FoxO which ensures MnSOD production inhibiting cellular ROS. Few target genes of MnSOD involved in maintaining cell growth and apoptosis are *cyclin genes, p15, ATG, Fas ligand* and *Bcl-6.* Insulin responsive PI-3 K/PKB is a negative regulator of FoxO.

worsening the cell survival rate [49]. Oxidative stress activates an NAD + dependent protein deacetylase Sirtuin (SIRT1) that modulates p53 and FoxO transcription factors. Generally p53 upregulates BAX and PUMA leading to apoptosis. This effect is neutralized by SIRT1 as it deacetylates p53 promoting cell survival. Similarly FoxO induces apoptosis by expressing Fas, TRAIL and Bim proteins. On the other side they also transactivate ROS- detoxifying enzymes. Thus SIRT1 acts on FoxO in a way that downregulates apoptotic gene expression and transactivating detoxifying enzymes. Activity of SIRT1 varies with for different FoxOs ensuring resistance against stress [50–53]. The fact that Sirtuin regulates ROS by the activation of Foxo3a is presented by the one of the experiments carried out in microglia cells wherein over-expression of sirt3 activates Foxo3a leading to the expression of anti-oxidant genes [54]. Studies carried out *in vitro* in kidney mesangial cells supplemented with high glucose resulted in FoxO1 inhibition along with decreased expression of PGC-1a accompanied by mitochondrial dysfunction and ROS generation [55]. A study demonstrated that FOXO transactivation is prevented by the overexpression of catalase. Though it was stated that H_2O_2 induces transactivation and localization in various cell types, it is not reported in skeletal muscles [56]. The relationship between FOXO1 and sirt1 in oxidative stress response were studied wherein treating with sirt1 agonist increased FOXO1 levels [57]. FOXO causes the activation of free radical scavenging genes to protect against oxidative stress. In a study conducted with the osteoblasts, FOXO was proven to be indispensable for bone mass homeostasis. The study involved the deletion and overexpression of *FOXO* genes in mice osteoblasts which resulted in increased and controlled production of ROS respectively [58].

2.5. *Nrf-2*

The Cap'n'collar (CNC)-bZIP transcription factor family comprises of the Nuclear factor erythroid 2 (NF-E2) whose expression are confined to the hematopoietic tissues such as erythroid cells and megakaryocytes. While the only exception are the NF-E2 related factors 1 and 2 (Nrf1 and Nrf2) as they are expressed in multiple tissues [59].They are also noted as important activators of RNA polymerase [60]. An actin bound cysteine-rich repressor of Nrf2 is the Keap1 protein present in the cytoplasm. Usually Keap1-Nrf2 complex is found in the cytoplasm. Upon stimulation by the oxidative stress Keap1-dependent turnover and translocation of Nrf2 happens which in turn activate the transcription of its target genes [61,62]. To prove the impacts of Nrf2 and Keap1 during oxidative stress, the keap1 −/− MEFs (mouse embryo fibroblasts) were experimented. Subjecting to irradiation, the result was characterized by the increased levels of Nrf2 expression thereby reducing the ROS levels. It can be noted that the Keap1 −/− is a radiation resistant phenotype [63]. Collective *in vivo* studies in mice witnessed that Nrf2 controls gene expression mediated by the antioxidant response elements (ARE) [64]. These studies also prove that Nrf2 controls gene expression mediated by the antioxidant response elements (ARE) [64]. Keap1 promotes Nrf2 ubiquitylation especially *via* the cullin-3-dependent pathway in an unregulated manner [65]. Cysteine residues of Keap 1 are the target sites of ROS that makes Nrf2 escape cullin-3 mediated degradation [66]. Experiments proved that Nrf2 is vital in the defence against Acetaminophen [*N*-acetyl-p-aminophenol] (APAP) toxicity through the GSH (glutathione) synthesis pathway [67]. According to research several types of stresses including oxidative and electrophilic stress impair the proteosomal degradation of Nrf2

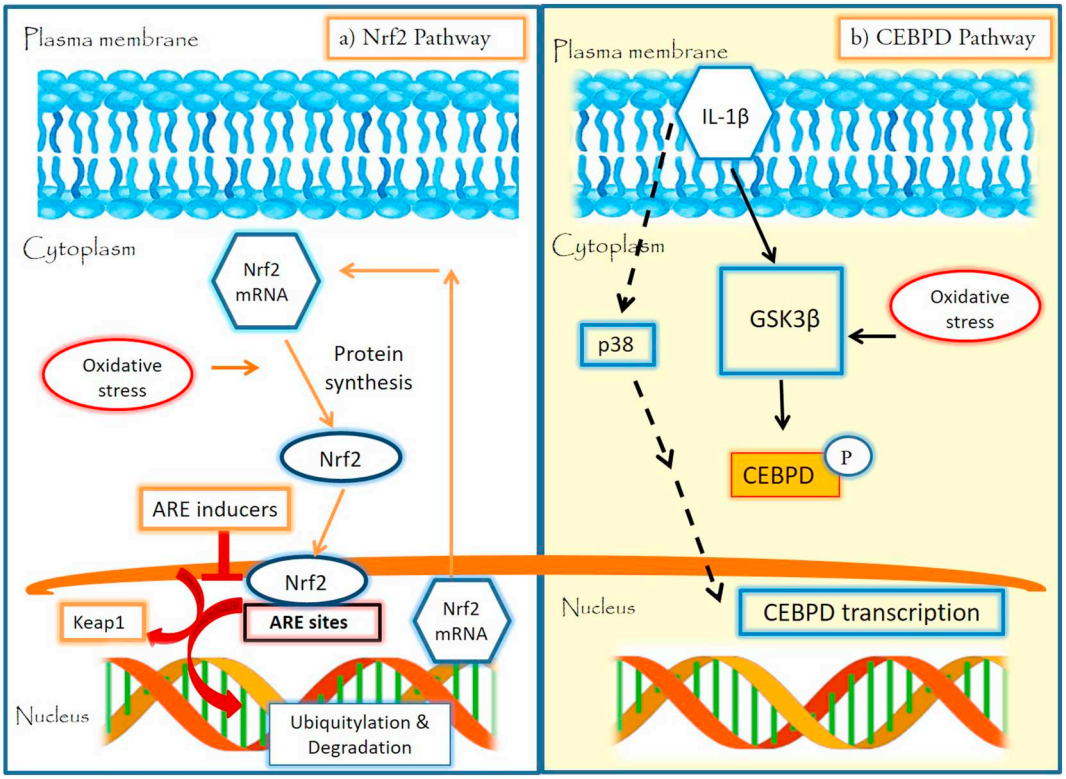

Fig. 3. (a) Schematic representation of Nrf2 pathway. Nrf2, transcription factor is encoded by the *NFE2L2* gene. Nrf2 mRNA is being transcribed in the nucleus and then is transported to the cytoplasm where it translates to Nrf2 protein. Nrf2 is associated with Kelch like-ECH-associated protein 1 (KEAP1) and Cullin 3, in cytoplasm which degrade Nrf2 by ubiquitintion. Cullin 3 is a protein which ubiquitinates Nrf2, while keap1 is a substrate adaptor protein which aid the process. Once Nrf2 is ubiquitinated, it will be presented to the proteasome complex, where it will be degraded and its components will be recycled. Upon stimulation by the oxidative or electrophilic stress, a cysteine residues in keap1 will be disrupted which in turn collapses the keap1-Cul3 ubiquitination system, When Nrf2 is not degraded by ubiquitinated, because of the absence of Keap1 it piles up in the cytoplasm and translocates into the nucleus. In the nucleus, the Nrf-2 associate with small Maf proteins and adheres to the antioxidant response element (ARE) in the upstream promoter region of many antioxidative genes and initiates transcription. The target genes for Nrf2 are *NAD(P)H quinone oxidoreductase 1 (Nqo1), HMOX1, GCLM* and *CPX*. (b) Schematic representation of CEBPD pathway. CEBPD is an important member of the family of CCAAT/enhancer-binding protein. In response to oxidative stress and inflammatory stimuli, IL-1β is activated that in turn stimulates many signalling pathways such as phosphatidylinositol 3-kinase, p38, JAK, JNK and PKA. This IL-1β activates cebpd transcription by recovering the activity of GSK3β and causes the phosphorylation and leads to the polyubiquitination and degraded. Also the signalling pathway p38 induces the cebpd transcription. The target genes for CEBPD are *PTX3* that inhibits phagocytosis, *MCP-1* that activates chemoattraction, *MMPs* that activates macrophages/microglia migration and *ZNF179* that induces antiapoptosis/ astroglios. CEBPD is thought to be involved in apoptosis regulation and cell proliferation.

mediated by Keap-1 (Fig. 3a). Deterioration of Nrf2 activity is the study material for dealing with various pathogenicity [68,69]. Studies conducted *in vitro* dealing with oxidative and electrophilic stress in vascular cells ensured that Nrf2 has both cytoprotective and anti-inflammatory effects. Application of gene therapy in vascular pathology combating oxidative stress is considered crucial as proven by several *in vivo* studies. *Nrf2* gene transfer eventually decreased inflammation rate in the vascular vessels [68,70]. Reduction of oxidative stress were reported in the cases of neurodegenerative disorders both *in vitro* and *in vivo* spotlighting the defensive effects of Nrf2 induction [71]. *In vitro* and *in vivo* studies carried out in oxidative stress induced cardiac cells explored the regulatory role of providing insulin resistance with the ERK-mediated Nrf2 suppression [72]. A compound called catechin significantly decreases the levels of lipid peroxidation, reactive oxygen species, and increases the activity of intracellular antioxidant enzymes glutathione peroxidase, glutathione reductase and total sulfhydryl groups [73]. DS/Cu (Disulfiram, a dithiocarbamate family member/ copper complex), as a result of Nrf2 suppression, is said to induce apoptosis [74].

2.6. CEBPD

CCAAT/enhancer-binding protein delta (CEBPD), a CCAAT/enhancer-binding protein family member plays a prominent role in cell cycle regulation (Fig. 3b) [75]. Research has shown upon overexpression of CEBPD levels of cyclin E and cyclin D1 were decreased and alternatively p27 levels were increased which resulted in growth inhibition in erythroleukemia cells and prostrate cancer. CEBPD has an important role in regulation of pro-apoptotic gene expression as a result of mammary gland involution thus CEBPD serve as a potent tumor suppressor which leads to apoptosis and growth arrest [76,77]. CEBPD belongs to the leucine zipper (LZ) transcription factor and are considered as the stress response genes being triggered by various stimuli [78]. Researchers have suggested that CEBPD are also highly expressed in the astrocytes which was found to have potential link in the Alzheimers disease. It has been identified CEBPD can upregulate two mediators that include $p47^{phox}$ and $p67^{phox}$, which are subunits of NADPH oxidase which in turn results in intracellular oxidative stress. In addition CEBPD was also shown to upregulate SOD1 specifically in astrocytes [79]. Several studies indicated that *CEBPD* gene expression is down regulated in breast cancer, leukemia and cervical cancer [80–82]. It has been noted as a potential mediator of differentiation which is sensitive to all-transretinoic acid (RA) and vitamin D3 treatment. CEBPD is therefore an important target for the development of chemotherapeutic agents [83]. It has been reported that during oxidative stress 1-(2-hydroxy-5-methylphenyl)-3-phenyl-1,3propanedione (HMDB) induces CEBPD transcription by stimulation of p38/CREB pathway and does not alter the DNA methylation status of the CEBPD promoter. Induced CEBPD enhances the transcription of PPARG2 and GADD153 proapoptotic genes [84].

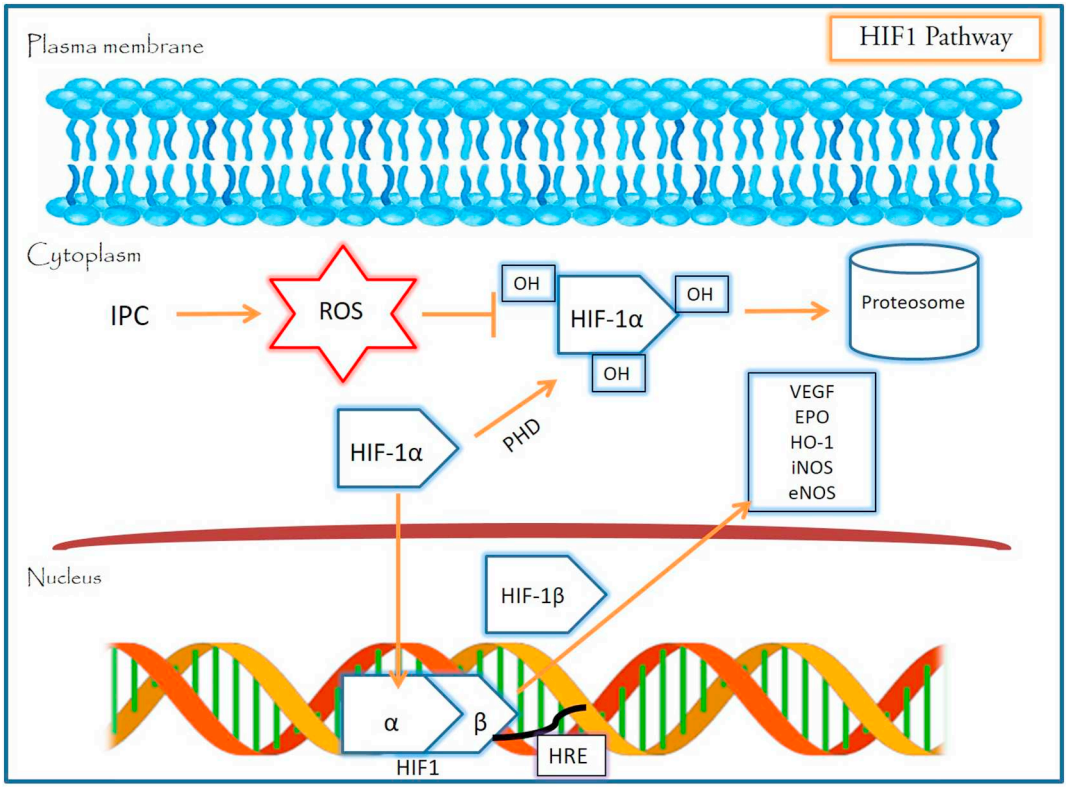

Fig. 4. Schematic representation of HIF-1 pathway. Hypoxia-inducible factor1 (HIF-1) is a key regulator of oxygen homeostasis. It comprises two subunits: an inducibly-expressed HIF-1a subuit and a constitutively-expressed HIF-1b subunit, in the nucleus that gets transcribed. The prolyl residues of the HIF-1a subunit undergoes hydroxylation followed by ubiquitin/proteosomal degradation during normoxia. In contrast, hypoxia results in HIF-1a stablization interacting with the coactivators such as p300/CBP to enhance its transcriptional activity. The target genes for HIF are *VEGF, EPO, HO-1, iNOS* and *eNOS*.

2.7. HIF-1

Hypoxia-inducible factor 1 (HIF-1) is an effective regulator of hypoxia-inducible genes and proangiogenic factors, such as vascular endothelial growth factor (VEGF). Structurally it is a heterodimer composed of HIF-1 alpha and HIF-1 beta (Fig. 4). The ubiquitin / proteosome degradation of HIF-1 alpha is triggered by the oxygen dependent prolyl hydroxylases (PHDs) which is mediated by the tumor suppressor protein von hippal lindau (VHL) [85,86]. In order to address the activation of HIF-1 under the context of ROS production, researcher's used low doses of H_2O_2 to create mild oxidative stress. This caused Sentrin/SUMO-specific protease SENP3 to quickly stabilize and promote the transcriptional activity of HIF-1 through deconjugation of Small uiquitin-related modifier SUMO2/3 from p300, the coactivator of HIF-1a. During normoxia and hypoxia conditons, the preceding mechanism becomes crucial for HIF-1 activation [87]. Temperature is a driving regulating factor for HIF protein. Cold temperature results in higher binding of HIF-1 to the DNA when compared interspecifically *i.e.*, polar *vs.* temperate species. Mammalian studies carried under normoxic conditions intimated that interaction with HSP90 stabilized HIF-1a. [88,89]. Atheletes have ventilatory acclimatization during acute hypoxia independent of oxidative stress by the sensitive regulation of HIF-1a mRNA. For example, a study conducted in a group treated for 1 day of hypoxic condition, showed increased expression of HIF-1a mRNA. While treated for 3, 7 and 14 days of hypoxic condition decreased its expression, thus promoting the relation with duration of hypoxic condition. The MDA (Malondialdehyde, product of lipid peroxidation) level in liver increased and persisted along the duration time of hypoxic condition insignificantly in the groups. While the levels of GSH (Glutathione) decreased significantly ($p < .005$) in all groups [90,91]. Prevention of normoxic oxidative death by stabilizing HIF-1 to actively initiate the transcription of its downstream target genes such as erythropoietin (*Epo*), glycolytic enzymes and *VEGF* is addressed by iron chelators [92].

The mechanism of hypoxia is stated to be biphasic. It involes up-regulation of beta-site APP cleaving enzyme (BACE1) in the beginning followed by a late up-regulation of BACE1. It is mediated by HIF-1 alpha activation due to the ROS released by the mitochondria, which accumulates amyloid-β in conditions like ischemia [93]. Hyperglycemia affected the stabilization of HIF-1a causing interstitial fibrosis. Availability of HIF-1a was reduced in a dose-dependent manner. Generation of ROS in regard to very low presence of nitric oxide greatly affected HIF-1a stability which also promoted tubulointerstitial fibrosis. [94]. Studies involving ROS production in U87 cells demonstrated that, a greater extent of HIF-1 signal transduction was achieved in cycling hypoxia, reflecting ROS mediated HIF-1a synthesis. A decreased HIF-1a degradation resulting from decreased prolyl hydroxylation was observed in non-interrupted hypoxia [95]. Various studies investigated that, the alteration of tumor growth and metastasis were correlated with a HIF-dependent ability of NAC (N-Acetylcysteine) in multiple orthotopic and syngeneic murine models of breast cancer, where NAC increased metastasis by preventing HIF-1a stabilization *in vitro* [96]. A hypoxia-regulated HIF-1 target gene involved in regulation of cell survival is the REDD1 whose inactivation induces ROS dysregulation and tumorigenesis [97,98]. HIF-1 also plays an important role in radiotherapy and angiogenesis [99].

3. Discussion

Oxidative stress is catastrophic to human health leads which leads to the generation of reactive oxygen species (ROS). Several signalling pathways are activated to regulate target gene expression. On a special note, the network of oxidative stress related transcription factors organize the expression of downstream target genes like antioxidant

Table 1
Transcription factors-mechanism, inhibitors and inducers.

Transcription factors	Cellular mechanisms	Inhibitors	Inducers
NF- κB	It controls the transcription of cellular genes needed for inflammatory response like the production of cytokines, chemokines and potential biomarker for oxidative stress and apoptosis	TPCA1, BMS 345541	Prostratin, PMA [100]
Sp-1	Regulates the transcription of prosurvival proteins and prodeath proteins depending upon the cell type and death stimulus	Arsenic trioxide, Celecoxib	Trichostatin A, PMA [101]
AP-1	Cellular transformation, proliferation, differentiation and apoptosis	SP100030, T-5224	Veratramine [102]
FOXO	Controls the transcription of regulatory genes involved in free radical scavenging and apoptosis	Carbenoxolone	Issothiazolonaphthoq-uinone (LOM612 – compound 1a) [103]
Nrf-2	Regulates the transcription of cytoprotective genes like anti-oxidative, anti-inflammatory for maintaining cellular redox reactions	Dexamethasone, Clobetasol propionate	Bardoxolone – methyl (CDDO-Me) [104]
CEBPD	Regulating oxidative stress, response to DNA damage, maintains genomic stability	Rosmanol	Corticosteroids [105]
HIF-1	Regulation of apoptosis by inducing pro-apoptotic proteins	Actinomycin-D, GL331	Deferoxamine, SNAP (S-nitro-*N*-acetyl-D,L-penicillamine) [106,107]

genes involved in secondary metabolism. Oxidative stress can lead to many types of DNA lesions and strand breaks. Activity of number of transcription factors are influenced by oxidative damage. Few of which includes the activation of NF-κB, Sp-1, AP-1, FoxO, Nrf-2, Cebpd and HIF-1 (Table 1).

NF-κB is a transcription factor that possess extreme importance in regulating the genes involved in physiological processes in response to injury and infection [12–14]. It is vital for human health as the activation of NF-κB impacts the hallmarks of cancer and inflammatory diseases through the transcription of genes involved in cell survival, cytoprotective genes, angiogenesis, inflammation, tumor progression and metastasis [20–24]. Oxidative stress induces Sp1 transcription factor in cortical neurons that positively regulates neuronal survival [25–27]. It adheres to GC-rich motifs to a greater extent and looks after the manifestation of a huge number of genes participating in a variety of processes namely cell growth and differentiation, programmed cell death and immune responses [32]. Sp1 can be used as a control protein while checking for the occurrence of the aryl hydrocarbon receptor and/or the estrogen receptor as it attaches to both and commonly occurs at a comparatively constant level [34,35]. AP-1 like transcription factors are definite regulators of oxidative stress in most filamentous fungi and yeast [39–41]. It is initiated in response to oxidative stress followed by its nuclear localization to trigger the synthesis of antioxidant stress genes in organisms [43]. An ample number of studies stated that AP-1 and its components orchester oncogenesis. *c-jun* and *c-fos* which were first noted as retrovirus-triggered genes with a potential to develop tumor in avian and mammalian cells. Concordant with the statement that *c-jun* encourages tumorigenicity, overexpression of this transcription factor is observed in some of the hostile CD-30 positive lymphomas [44]. FoxO is a family of transcription factors that are actuated by oxidative stress for the maintenance of cell proliferation and providing resistance against oxidative stress [46–48]. Members of the class O of forkhead box transcription factors (FOXO) are significant for controlling metabolism, cellular proliferation, stress resistance and apoptosis [52]. The activity of FOXOs is confined to various post translational modifications like phosphorylation, acetylation and ubiquitinylation. FOXOs themselves express the target genes and not straightaway binding to DNA. A study showcased that the overexpression a FOXO mutant was yet able to express target gene eventhough it lacked DNA binding activity. Furthermore, the FOXO factors paved the repair of damaged DNA by upregulating genes such as *GADD45* and *DB1* [54–57]. Other FOXO target genes maintains glucose metabolism, cellular differentiation, musclar atrophy and even energy homeostasis.

Studying the mechanism of Nrf-2 is crucial when dealing with oxidative stress and pathogenicity [60–63]. It is proven that Nrf-2 controls over the expression of several ARE genes (antioxidant response elements) by binding to it, ample of genes involved in the antioxidative and anti-inflammatory response as well as mitochondrial protection. Induction of Nrf-2 by compounds belonging to various chemical classes, directly associated the inhibition of proinflammatory responses (Cox-2 and iNOS expression) [66,67]. On the contrary anti-inflammatory effects of these molecules were partially Nrf-2 dependent and the exact relation between Nrf-2 induction and anti-inflammatory properties lies yet to be elucidated. Likely, the intracellular glutathione content impacts Nrf-2 to direct the cytoprotective effects through the inhibition of Fas- mediated apoptotic pathways [72,73]. The degree of expression of CEBPD at normal physiological conditions, is usually low in most of the cells [76,77]. It is quickly initiated by external stimuli including glucocorticoids, insulin and growth factors. CEBPD functions as a signalling hub which sums up the signalling pathways that promote stemness in breast cancer and glioblastoma in addition to embryonic stem cells. The process of inflammation is nearly identical in various disease states and CEBPD activation is highlighted in many chronic inflammatory diseases [81–84]. HIF influences various adaptive responses to hypoxia from the molecular, cellular to tissue levels [85,86]. Such activated HIF-1 plays a critical role in adaptive responses of the tumor cells to modify through transcriptional activation of over 100 downstream genes which governs indispensable biological processes needed for tumor survival and progression [91,92]. In a rapidly progressing tumor tissue, HIF-1 helps hypoxic tumor cells to switch the glucose metabolism from the efficient glycolytic pathway maintaining their energy production [97].

4. Conclusion

Oxidative stress resulting from excessive intracellular ROS accumulation is a key component of several pathological conditions. Higher ROS levels are general indicators of cell damage following exposure by stress signal which are induced by a number of factors including radiation and cancer and are generally harmful to cells. The redox status of such cells are usually different from that of normal cells. Addressing the role of signalling pathways mediated by the oxidative stress and identifying the modulators and cellular sensors help clinicians to better manage the disease state and to prime positive therapeutic impact.

Declaration of Competing Interest

The authors have no competing interest to declare.

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