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Role of Wnt-p53-Nox Signaling Pathway in Cancer Development and Progression

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Authors' contributions

This work was carried out in collaboration between all authors. The concept and idea behind this paper has been conceived by author RKA. Data and literature review is done by authors DK, SS and SV. The artwork has been carried out by authors DK and PK. Paper is written by author RKA. Final editing is done by all the authors. All authors read and approved the final manuscript

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Review Article

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ABSTRACT

Signaling pathways play an intricate role in regulating the homeostasis of a normal cell and any chronically altered activity in such signaling pathways causes cancer. Such aberrantly activated Wnt and vanished p53 signaling contribute to the development of various carcinomas. Majority of cancer cells exhibit elevated production of reactive oxygen species (ROS) in an NADPH oxidases dependent manner that further enhances cellular damage. However, Nox family enzymes regulate various physiological functions; for instance, gene regulation, cellular signaling, host defense and cell differentiation. All of these processes get affected in cancer thereby signifying the role of Nox in controlling various signaling pathways such as Wnt and p53. Therefore, unraveling of complex signaling pathways underlying tumorigenesis is enforcing the development of next-generation anticancer drugs directed against specific molecular targets.
This review provides an insight about Nox in regulation of Wnt and p53 pathway to govern the pathogenesis of cancer. Therefore, implementation of NOX inhibitors for inhibiting aberrant Wnt and p53 signaling could provide novel opportunities for therapeutic intervention.

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1. INTRODUCTION

1.1 Wnt Pathway: A Key Player in Cancer

Wnt signal transduction pathway controls tissue homeostasis, cell fate decisions, tissue patterning, proliferation and other biological phenomena throughout embryonic development and adult life making it one of the most important developmental pathways. The proto-oncogene Int-1 was the first identified Wnt-gene isolated from mice in 1982 and was named Wnt1 later on. Its homolog a segment polarity gene 'Wingless' required for wing formation was found in Drosophila. Requirement of Wnt begins from the first cleavage of zygote and continues till adulthood which may lead to diseases such as cancer, diabetes type-2, aging if dysregulated [1]. Wnt proteins ~40 kDa in size are highly conserved glycoproteins containing conserved cysteine residues and has a role in forming concentration gradient near the developing tissue [2]. There are 19 Wnt genes in 12 conserved Wnt superfamilies. Secreted from the cells Wnt proteins are found to be palmitoylated on the conserved cysteine residues and initiate signaling by binding to the cell surface receptors (i.e. Frizzled-LRP complex)while mutation or removal of palmitate from the Wnt protein leads to loss of activity indicating that this lipid modification is important for its activity[3]. This pathway is responsible for activating intracellular cascades; a) Canonical or the β-catenin dependent pathway and b) Non-canonical or the β-catenin independent pathway that further divided into Wnt-planar cell polarity (Wnt-PCP) pathway and Wnt-calcium (Wnt-Ca^{2+}) pathway (Fig. 1) which regulates cell migration and cell polarity playing a central role in developmental morphogenesis, promoting malignant progression and invasiveness of human cancers [4].

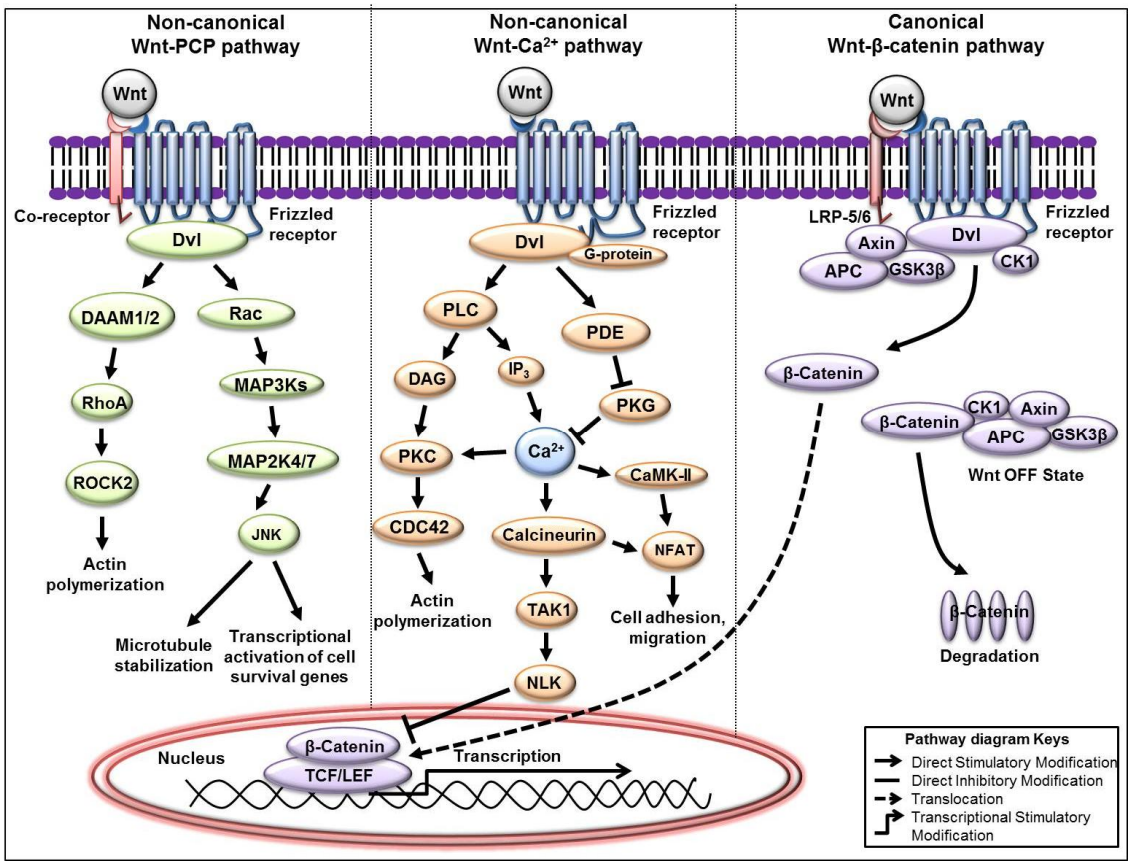

Fig. 1. Wnt pathways: Non canonical Wnt (PCP and Calcium) pathway and Canonical Wnt β-catenin pathway (Adapted from Berwick and Harvey 2013) [5]

1.2 Wnt Pathway Receptors

A wide array of Wnt receptors (Frizzled and LRP) contribute to the complexity and diverse action of this pathway. Frizzled receptors are seven transmembrane G-protein coupled receptors (GPCRs) rich in cysteine residues in their large extracellular N-terminal domain which provides a binding site for Wnt ligand. Structure of frizzled receptors comprised of an N-terminal signal peptide, conserved extracellular cysteine rich domain, variable length linker region, seven-pass transmembrane domain and a variable C-terminal. LRP (Low density lipoprotein related receptor 5 and 6) is another wnt receptor also known as ARROW in drosophila and LRP5/6 in vertebrates are single pass transmembrane proteins that play an important role in canonical Wnt pathway by binding to frizzled receptor upon ligand binding [6]. Structure of LRP-5/6 comprises of an extracellular domain with beta motifs and LDL ligand binding domain [7].

Since Wnt pathway is chronically activated in many human cancers, the frizzled receptors play a central role in propagating oncogenic signals. For instance, Frizzled homolog 3 receptor has been found to be upregulated in certain cancers such as gastric cancer, esophageal cancer and colorectal adenoma [8]. Another Wnt receptor Frizzled homolog 7 is found to be overexpressed in triple negative breast cancer, colorectal cancer and hepatocellular carcinoma, and is responsible for increase in cell proliferation and cancer invasiveness [9]. LRP-6 is also found to be overexpressed in triple negative breast cancer [10]. Likewise Frizzled-8 receptor and its ligand Wnt-2 are upregulated in non-small cell lung cancer [11] whereas Frizzled-1 and 2 are upregulated in breast cancer [12].

1.3 Non Canonical WNT Pathway

Non canonical Wnt-PCP pathway promotes actin cytoskeleton changes by signaling through Rac, Rho and small GTPases that controls cell movements and tissue polarity through activation of various signaling cascades. For instance, RHOA signaling cascade through DAAM1 and DAAM2 Formin homology proteins transduce disheveled dependent signals while JNK signaling cascade through MAPKKK and MAPKK 4/7 [13]. Non canonical Wnt ligands (WNT5A, WNT5B, WNT11) transduce signals through FZD3, FZD6 receptors and ROR1, ROR2 co-receptors [14] and are known to cause cancer via promoting invasiveness, metastasis and tumor aggressiveness. For instance elevated Wnt5 through activation of JNK and Rac promotes breast, prostate and lung cancer [15]. Apart from Wnt-PCP pathway, Wnt Ca^{2+} pathway plays an important role in actin polymerization, cell adhesion and migration where binding of Wnt to frizzled receptor causes G-protein mediated activation of phospholipase C which increases the intracellular Ca^{2+} level that further activates protein kinase C and other downstream effectors [16].

1.4 Canonical WNT (β -catenin) Pathway

Canonical Wnt β-catenin signaling pathway controls cell division, migration and adhesion in a tightly regulated manner. Wnt binding at the transmembrane receptors (Frizzled and LRP5/6) leads to phosphorylation of LRP5/6 at its conserved serine/threonine residues with 'PPSPXS' motifs by G-protein-coupled receptor kinases 5 and 6 (GRK5/6) thereby recruiting Dishevelled (Dvl), AXIN and GSK3β proteins to the phosphorylated site [17]. Thus destruction complex of beta-catenin gets disrupted and stable beta-catenin enters the nucleus for transcriptional activation of target genes such as cyclin-D, c-myc, survivin by forming a complex with transcription factors T-cell factor/Lymphoid enhancer factor(TCF/LEF) and co-factors Pygopus, Bcl9, p300 [18]. While in absence of Wnt signals, destruction complex marks β-catenin for ubiquitination and subsequent degradation [19].

1.4.1 Role of beta-catenin in canonical pathway

The β-catenin is an armadillo protein and acts as a key mediator of Wnt-signaling made up of 781 amino acids consisting of a central core domain with 12 armadillo repeats (ARM) conserved at N and C-terminal domains which mediates protein-protein interactions whereas the core domain enables β-catenin to function and act as a scaffold for multi protein assembly [20]. An armadillo repeat consists of three alpha helices on an average with first repeat present in the N-terminal. N-terminal is an intrinsically disordered region with a conserved binding linear motif for β-TrCP binding (an E3 ubiquitin ligase). C-terminal acts as a trans-activator motif and is highly negatively charged. β-catenin has multiple functions in cells like stabilization of adhesive molecules in plasma membrane, transcriptional regulation and chromatin interactions in nucleus. While its level is influenced by certain factors

such as hypoxia, E-cadherin-cell adhesion molecule, inflammation [21].

1.5 Regulation of WNT-Pathway

Wnt pathway regulation is mediated through destruction complex which comprised of AXIN1, AXIN2, Glycogen Synthase Kinase-beta (GSK3β), Adenomatous polyposis coli (APC) and Casein Kinase-1α (CS1α) a priming kinase. The assembly of destruction complex begins with β-TrCP (an E3 ubiquitin ligase) that uses beta catenin as a substrate for its proteasomal degradation. Casein Kinase 1α primes beta catenin through which GSK3β is recruited, phosphorylating the serine residues in the linear motif which is pre-requirement for β-TrCP to function. As AXIN1 and AXIN2 are scaffold proteins they function in bringing GSK3β and beta-catenin in close proximity along with APC thereby disrupting β-catenin [22]. Other measures of regulation include antagonists to keep the beta catenin levels low which could be done through the interaction of antagonist with ligand or with the Wnt receptor. For instance, Dickkopf (DKK) protein family are secreted Wnt antagonists which binds to LRP5/6 and halts the formation of ternary complex Wnt-Fzd-LRP5/6 thereby halting the canonical Wnt signaling [23].

Since Wnt signaling pathway get unceasingly activated in numerous cancers therefore certain natural inhibitors of this pathway (Table 1) could be a potential candidate for cancer therapy. One such example is secreted Frizzled related protein (sFRP), a secreted glycoprotein structurally related to frizzled protein receptors which antagonize deleterious Wnt signaling by binding to Wnt proteins preventing its activation [24]. Moreover evidences suggested that exogenous expression of sFRP is helpful in inhibiting colorectal cancer cell proliferation in sFRP deprived cancer cell as a result of promoter hypermethylation [25]. Another protein Dickkopf-1 plays a role in inhibiting angiogenesis, decreased tumor vascular density and in suppressing tumor growth [26]. Likewise Norrin, a secreted signaling molecule has been found to regulate angiogenesis in colorectal cancer tumor microenvironment [27]. Other negative regulator of Wnt pathway includes ICAT which is reported to inhibit colorectal tumor cell proliferation in mutated APC [28]. These evidences suggest the effectiveness of these inhibitors in treatment of cancer.

1.6 Role of WNT Pathway in Cancer

Stem cells in embryo and adults have been shown to require β-catenin Wnt pathway to maintain cells and their transition to adult stem cells along with their tissue specification; any aberrant changes in this closely regulated pathway leads to cancer [40]. Mutations in genes involved in Wnt β-catenin pathway such as loss of APC function or mutations in β-catenin leads to constitutive expression of proteins involved in cell proliferation thereby resulting in tumor formation [41]. β-catenin mutations completely block axin mediated degradation of β-catenin leading to its accumulation while mutations in axin lead to an elevation of the Wnt-signaling pathway. APC a tumor suppressor, which suppresses wnt canonical pathway for its regulation harbors most of the mutations in its functional site resulting in C-terminal protein truncation thereby leading to familial adenomatous polyposis (FAP) predisposition, to colorectal cancer development and other cancers such as intestinal carcinoma, liver cancer [42]. Accumulation of beta catenin is a result of loss of APC hence its nuclear localization results in activation of transcription factor TCF/LEF leading to transcription of the responsive genes ultimately leading to uncontrolled cell proliferation [43]. Moreover, β-catenin nuclear expression has been shown to be associated with poor outcomes in treating the cervical squamous cell carcinoma and has been predictive indicator of early diagnosis of the disease [44].

In course of cancer development, only oncogenic transformation of proto-oncogenes are not sufficient but alteration in multiple gene systems are required to put into effect. Such a genetic system involves inactivation of tumor suppressor genes along with the activation of oncogenes. Therefore in cancerous cell apart from aberrantly activated Wnt pathway, inactivated tumor suppressor p53 gene has significant contribution for tumor progression.

2. p53 PATHWAY: A LINKAGE BETWEEN LIFE AND DEATH

When a cell is subjected to UV radiations, chemical carcinogens and cancer causing viruses, its key regulatory elements can be damaged which may cause uncontrolled growth that results in a tumor. A key defense mechanism in the body against the type of damage is p53 (a tumor suppressor protein) that was identified by Arnold Levine, William old and David Lane simultaneously in 1979. It has been

described as 'the guardian of genome' as it plays a major role in preventing genome mutation and providing stability to the cell. TP53 gene (located on the short arm of chromosome no 17) is known as the longevity assurance gene due to its impact on longevity of the cell through its tumor suppressor function [45]. This gene encodes p53 protein, a tetrameric transcription factor that reduces somatic mutations and mutated cell proliferation providing longevity to the cell and thereby reducing cancer occurrence [46]. p53 protein is a major defense system in the body having the ability to trigger cell cycle arrest transiently or permanently. Moreover, under stressful conditions like hypoxia, oncogenic activation, viral infection and nucleotide depletion or DNA damage, p53 might lead the cells to death and thus protects the cell from developing to cancer.

2.1 p53 Structure

It is a homo-tetramer with 393 amino acid residues each consisting of a DNA binding domain(also known as core domain) which is highly conserved and rich in arginine residues. These residues are responsible for interacting with DNA to find the regulatory sites on it. Apart from core domain p53 consists of a proline rich region, a transcription activation domain, a tetramerizing domain, an N-terminal and C-terminal. Both N-terminal and C-terminal are flanked by disordered regions [47]. Transcription activation domain mainly functions in activating the reading machinery of DNA and is mainly located at the end regions of each arm of p53 monomer. Whereas N-terminal of the p53 functions as a transcriptional activator. The tetramerizing domains located at the center of p53 binds the four identical chains together and C-terminal through its nuclear localizing sequences also help in tetramerization of the p53 monomers and is rich in lysine residues. A majority of mutations usually occur at the DNA binding domain of p53 called as a 'hot spot' [48]. In a normal cell, p53 is found to interact with DNA through its carboxyl terminal domain providing anchorage to DNA thereby stabilizing the complex [49].

2.2 Role of p53 Pathway

The levels of p53 are usually maintained at a low concentration in the cell but when the DNA is damaged, its level rises in the cell that halts the cell division process in G1 and G2 phase so as to repair the damage or mark the cell for apoptosis if the damage is not repairable. In response to stress, ATM (Ataxia telangiectasia mutated), a serine/threonine protein kinase/ATR phosphorylate p53 at ser-15 and Chk-2 (checkpoint kinase 2) phosphorylates it at Ser-20 residue in N-terminal region [50]. In absence of ATM, ATR takes over the role to activate p53 and is mediated through Chk-1 [51]. In response to phosphorylation the transcription co activators CBP, p300 through their acetyl transferase activity acetylate p53, which results in p53 stabilization and activation of downstream processes [52]. Acetylation of p53 regulates its transcriptional activity and results in disrupting the interaction of Mdm-2 with p53 and therefore leading to its dissociation. It is also essential for promoting gene transcription by binding p53 to p53 binding elements such as p21, Noxa, PUMA and Bax resulting in cell cycle arrest or apoptosis [53]. p53 activation involves three steps: i) p53 stabilization, ii) binding of p53 to DNA at specific sequence and iii) activation of target genes through transcription [54].

A serine/threonine protein kinase, i.e. Nemo-like kinase blocks Mdm2 mediated p53 ubiquitination thereby stabilizing, activating p53 and also increasing its activity [55]. P300/CBP also works to inhibit Mdm-2 by acetylating it and preventing its ubiquitination activity. Depending on the action of p53 i.e. apoptosis, DNA damage repair or cell cycle arrest, p53 activates transcription of proteins involved in DNA repair. Cell cycle arrest mechanism involves activation of p21 by p53, which functions to inhibit cyclin dependent kinases and thereby inhibiting S phase and M phase of cell cycle [56]. Another transcriptional protein GADD45 (growth arrest and DNA damage 45 family genes) acts as stress sensors and regulates cell survival, repair or apoptosis in stressful conditions [57]. Proteins involved in mediating apoptosis include PUMA, a p53 up-regulated modulator of apoptosis, which is located on the long arm of chromosome number 19 [58]. It is a BH-3 only pro-apoptotic protein induced by p53 upon DNA damage which promotes apoptosis by disrupting the interaction of p53 and Bcl-2 displacing Bax [59]. Bax is another protein from this category, a Bcl-2 family member activated by p53 induces cytochrome-c release from mitochondria for the formation of apoptosome complex leading to cell death [60]. Moreover, DNA repair proteins include p53R2, a subunit of ribonucleotide reductase, is a p53 inducible homologue that repairs the damaged DNA by supplying nucleotides to it [61]. Various roles played by p53 in a cell are explained in Fig. 2.

Table 1. Canonical Wnt-pathway inhibitors and activators

Protein	Action	Interacting component	References
Norrin	Enhanced signaling	Frizzled4	[29]
R-spondin	Enhanced signaling	Bind to LGR family receptors	[30]
ZNRF3	Downregulate Wnt signaling	Frizzled	[31]
WIF	Inhibits Wnt/beta catenin signaling	Wnt	[32]
DKK1	LRP5/6 antagonist downregulate it from surface through receptor Kremen	LRP 5/6	[33,34]
Wise/SOST	LRP5/6 antagonist disrupt wnt-Fz-LRP6 formation	LRP 5/6	[35,36]
Shisa	Inhibit Wntsignaling	Bind to and degrade Fzd proteins	[37,38]
sFRPs	Antagonist for canonical and non canonical pathway	Wnt and Fzd	[24]
IGFBP-4	Inhibitor of canonical pathway	Frizzled 8 and LRP6	[39]

IGFBP-4: Insulin-like growth-factor-binding proteins; sFRP: secreted frizzled related proteins; DKK: Dickkopf; WIF: Wnt inhibitory proteins; SOST: Sclerostin protein;

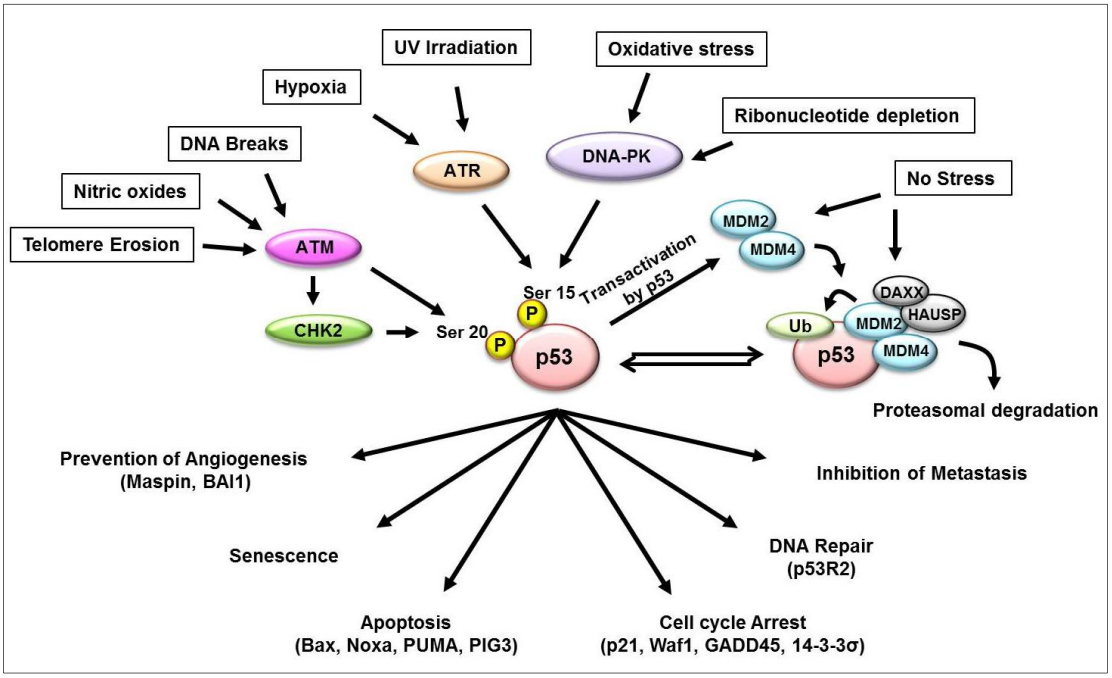

Fig. 2. Role of p53 in regulating cellular homeostasis to prevent cancer development

2.3 p53 Activation

Upon cellular stress the levels of p53 in the cell increases due to a decrease in its degradation by ubiquitin E3 ligase Mdm-2 and increase in translation of its mRNA. Daxx and Mdm-2 interaction stabilizes Mdm-2 thereby promoting its ligase activity towards p53 which upon DNA damage is disrupted, by phosphorylation through ATM of Daxx at serine 564 residue leading to p53 activation [62]. The disruption of Daxx-Mdm-2 complex stabilizes monoubiquitinated p53 and diverts its entry into Mitochondria where deubiquitination occurs through mitochondrial HAUSP leading to generation of apoptotically active non ubiquitinated p53 [63]. Whereas phosphorylation of Mdm-2 at serine 395 residue is required for p53 mRNA and Mdm-2 interaction. This interaction stabilizes p53 and is required for its activation after DNA damage. This also promotes SUMO-conjugation and nucleoli accumulation of Mdm-2 [64]. Therefore Mdm-2 play a dual role i.e. as a positive as well as a

negative regulator of p53 by targeting it either for its degradation or by binding to its mRNA and promoting its translation.

2.4 Regulation of p53

Since p53 is a tumor suppressor it arrests the cell cycle to repair the cell, if not regulated this could lead to a serious consequence which might result inleading to permanent cell cycle arrest and cell death therefore a tight regulation is required [65]. The inactivated p53 involved in cancer progression are depicted in Table 2. Proto-oncogene Mdm-2 (an E3 ubiquitin protein ligase) acts as dual both negative regulator and a positive regulator of p53 and degrades p53 by ubiquitinating it on at the lysine residue present at its C-terminal, in conjunction with Mdmx (also called as Mdm-4) which acts on the transcriptional activation domain of p53 [66]. Mdm-2 is a product of gene that is inducible by p53 and has the ability to regulate itself through auto-ubiquitination [67]. Poly-ubiquitinization of p53 is followed by its proteolytic degradation in 26S proteasomal complex so as to maintain a basal level in the cell [68].

The interaction of p53-Mdm-2 has remained conserved through the course of evolution. Both the proteins Mdm-2 and Mdmx consists of ring domain through this RING-RING domain association and interaction, Mdmx converts Mdm-2 mono-ubiquitination E3 ligase to poly-ubiquitination E3 ligase thus leading to poly-ubiquitination of p53 and therefore its degradation [69]. Mdmx is said to be involved in enhancing the proteasomal degradation rate of p53 mediated by Mdm-2 and also its E3 ubiquitin ligase activity [70]. Regulation of p53 begins with the negative feedback loop which involves p53 ubiquitination through its interaction and binding with the hydrophobic pocket at the N-terminal of Mdm-2 with its N-terminal peptide motif of p53 [71]. This binding leads to an allosteric change in the conformation of Mdm-2 thereby exposing its central domain to core domain of p53, thus leading to ubiquitination of p53 [72]. Overexpression of Mdm-2 results from deregulation of its gene resulting in low levels of p53 all the time thereby suppressing the tumor suppressive role which ultimately results in a tumor [73]. Since Mdm-4 also acts to keep the levels of p53 in control in a normal cell its deregulation also results in cancer [74].

2.5 p53 and Cancer

Two types of mutations result from cancer one that causes uncontrolled growth and the other that affects the defense system against the tumorous growth. Although p53 is a tumor suppressor and function in controlling the cell cycle, apoptosis, and DNA repair however mutations in p53 lead to uncontrolled cell growth, loss of tumor suppressor activity as well as defects in cell ultimately causing cancer. Sequence specific DNA binding domain of p53 (p53C) harbors most of the mutations. TP53, the tumor suppressor gene encoding protein p53 is mutated in certain cancer like ovarian cancer and colon cancer. Missense mutations in the gene result in a dysfunctional protein product [75]. Aggregation of p53 both mutant and wild type into amyloid oligomers and fibrils has been observed in malignant tumors and breast cancer leading to loss of tumor suppressor function and gain of function affecting prognosis of the disease [76]. Prion (infectious protein aggregates) like properties has been observed in cancers with mutant p53 aggregates and these p53 aggregates exert a negative regulatory effect on the wild type p53 [77]. These aggregates have the property to co-aggregate with the intrinsic p53 by penetrating the cell [78].

3. NADPH OXIDASES AND THEIR INVOLVEMENT IN CANCER

The NOX family NADPH oxidases are membrane-associated, multiunit enzyme protein complex that transfers electrons across biological membranes to reduce oxygen to superoxide. However, various physiological processes produce ROS as a byproduct including xanthine oxidase activation, cytochrome P-450 oxidase uncoupling, mitochondrial respiration, endothelial nitric oxide synthase (eNOS) uncoupling, and activation of various peroxisome oxidases. The NADPH oxidases also contribute significantly, to generate superoxide/ROS. The NOX family consists of seven members i.e. NOX1-5, and two dual oxidases (Duox); Duox 1 and Duox2. Although all NOX isoforms share common structural similarities with two heme molecules, six transmembrane spanning alpha helices with cytosolic N and C-termini, cytoplasmic domain with Flavin adenine dinucleotide (FAD) and NADPH binding sites, but each member seems to have a specific biological role [87]. In addition to this NOX5 contains an additional cytosolic NH_2-terminal transmembrane domain containing

four calcium-binding EF-hand motifs while Duox1 and 2 contain a seventh transmembrane domain with peroxidase homology. All NOX isoforms binds to a number of regulatory subunits and various stimuli which alter the expression or activity of NOX proteins and eventually the amount of ROS produced.

3.1 Reactive Oxygen Species and Cancer

Reactive oxygen species (ROS) are oxygen derived small molecules arising from oxygen reduction and their related precursor. ROS are classified into radicals [superoxide ($O_2^{\bullet-}$), peroxyl (RO_2•), hydroxyl (OH•) and alkoxyl (RO•)] and nonradicals [hypochlorous acid (HOCl), ozone (O_3), singlet oxygen ($^1O_2$) and hydrogen peroxide (H_2O_2)]. ROS possess beneficial as well as detrimental properties. Myraid antioxidant defence systems keep the ROS level in check [88]. ROS is essentially required in numerous biological processes such as extracellular matrix cross-linking, developmental and differentiation processes, responses to oxygenation (oxygen sensing), hormone biosynthesis, apoptosis, cellular senescence, cellular signalling responses to hormones, growth factors and cytokines [89]. An excess of ROS (oxidative stress) caused by an imbalance between ROS production and their removal by antioxidant systems or shortage of ROS (reductive stress) caused by excess of reducing agents in a cell, both are potentially deleterious. Moreover, reductive stress leads to oxidative stress [90]. Oxidative stress causes inflammation, abnormal cell growth, tissue damage and cellular damage by oxidation and nitration of lipids, proteins, RNA and DNA and thus serves as a causative factor in cancer via influencing cellular proliferation and angiogenesis [91]. Likewise, reductive stress regulates transcription and growth factors, alters intracellular calcium levels and modulates protein phosphorylation mediated by phosphatases and protein kinases [92].

Superoxides are generated by reduction of molecular oxygen and are highly reactive, short lived and unable to cross biological membranes. Moreover, they activate pro-inflammatory nuclear factor jB (NF-jb), disable cellular antioxidants enzymes such as glutathione peroxidase and catalase, damages DNA through oxidation and has been associated with various acute and chronic diseases like cardiovascular disease and cancer [93,94]. Superoxide is rapidly reduced to hydrogen peroxide (H_2O_2), either spontaneously or enzymatically via superoxide dismutase (SOD) which is more stable and lipid soluble than superoxide due to its neutral charge. Hydrogen peroxide can diffuse through biological membranes and reach sites distant from its source and can alter cellular proteins via oxidation of methionine, cysteine and genetic material. Moreover, H_2O_2 has the ability to generate more reactive molecules such as OH• that can oxidize nucleotides and lipids leading to DNA damage and cellular dysfunction respectively [95].

3.2 The NADPH Oxidase Family

Among the Nox family, Nox2 was the first to be discovered as catalytic subunit and later 6 other homologous have been identified i.e. Nox1, Nox3, Nox4, Nox5, Duox1 and Duox2. All NOX isoforms are distinctively expressed and regulated in different tissues. They play a significant role in maintaining the redox regulation to govern various processes in the cell. For instance, Nox family enzymes are involved in controlling host defense, cellular signaling, gene expression, post-translational processing of proteins and cell differentiation [96].

3.2.1 NOX2 enzyme complex

NOX2 enzyme complex is composed of NOX2 ($gp91^{phox}$), $p22^{phox}$, $p47^{phox}$, $p67^{phox}$, $p40^{phox}$ and a small GTP-binding protein Rac1 or Rac2 (Fig. 3a) where $gp91^{phox}$ is the catalytic subunit. It was first described in neutrophils and macrophages for playing a crucial role in innate host defense. NOX2 gets highly expressed in secondary granules of resting neutrophils and acts against the foreign pathogen upon phagocytosis with help of generated superoxides thereby initiating various inflammatory and immuno-protective responses [97].

NOX2 activation requires translocation of cytosolic factors to NOX2/$p22^{phox}$ where $p22^{phox}$ is essential for the stability of NOX2 protein. During neutrophil stimulation, $p47^{phox}$ (NOX2 organizer/NOXO2) get heavily phosphorylated and undergoes conformational change in SH3 domains allowing its interaction with the proline-rich region in the C-terminus of $p22^{phox}$ subunit [98] and also translocate $p67^{phox}$ (NOX2 activator) and $p40^{phox}$ in close proximity to NOX2 [99]. Finally, the GTPase Rac initially interacts with NOX2 followed by $p67^{phox}$ leading to the activation of NOX2 enzyme complex [100] that transfers electrons from NADPH to oxygen and

generates superoxide. In a recent study, high expression of NOX2 has been observed in Gastric MALT lymphoma (GML) and melanoma cells [101].

3.2.2 NOX1 enzyme complex

NOX1 (mitogenic oxidase 1/mox-1) was the first homolog of NOX2 that exhibited high degree of sequence identity with NOX2. It gets highly expressed in colon epithelial cells and primarily produces superoxide that plays a substantial role in innate immunity, blood pressure regulation, angiogenesis, cell signaling, cell growth and motility [102-105]. NOX1 enzyme complex is composed of $p22^{phox}$, NOXO1 (NOX organizer 1/ $p47^{phox}$ homolog), NOXA1 (NOX activator 1/$p67^{phox}$ homolog), Rac1, PDI (protein disulphide isomerase) and TKS4/5 (tyrosine kinase substrate with 4/5 SH3 domain) (Fig. 3b) [106,107]. Like NOX2, it also requires subunits and regulatory proteins for its enzyme activity. For instance, $p22^{phox}$, TKS4/5 and PDI bind to NOX1 [100] while Rac interacts with the NH_2 terminal tetratricopeptide repeats of NOXA1 to activate NOX1 enzyme complex thereby eliciting superoxide production. Recent studies showed that ROS generated via NOX1 is mandatory for formation of invadopodia (actin-rich membrane protrusions) that degrade the extracellular matrix, in human colon cancer cell thereby imparting metastatic property to the cancer cell [108]. Moreover overexpression of NOX1 mRNA and protein has been observed in colon, prostate and gastric cancers [109-111].

3.2.3 NOX3 enzyme complex

NOX3 is also a multi-component enzyme complex (Fig. 3c) which displays high structural and amino acid similarity with NOX2. It was discovered in 2000 in the otoconia-deficient head tilt mice and found to be highly expressed in inner ear [112]. Furthermore NOX3 mutant mouse model revealed its role in gravity and balance perception. Studies on the mechanism underlying its activation displays contradictory results. Some studies showed that $p22^{phox}$ is essential for NOX3 activation and superoxide generation [113] while others indicate decreased activity of NOX3 when coexpressed with $p22^{phox}$. However, it has been found that NOXO1 enhances activation of NOX3 but there are conflicting results regarding the requirement of NOXA1. Some studies showed enhanced NOX3 activity through NOXA1 [114] while others deny the motion [115]. Involvement of Rac is also unclear [116]. There are no concrete evidence which show variations in the above studies but majority of studies accepts that $p67^{phox}$ and NOXO1 each universally activates NOX3. Further expression of NOX3 has been found in pancreatic cancer [117].

3.2.4 NOX4 enzyme complex

NOX4 is a 578 amino acid protein with 35% homology with NOX1 and 39% homology with NOX2 [118]. NOX4 was initially characterized as Renox (renal oxidase) due to its abundant expression in kidney. It is a H_2O_2 producing enzyme and it is highly expressed in kidney and blood vessels.

Unlike NOX1-3, NOX4 only requires $p22^{phox}$ for its stabilization (Fig. 3d) and ROS generation [113]. It does not require other cytosolic subunits for ROS generation. Role of Rac1 in NOX4 activity is contradictory for instance, in vascular smooth muscle cells (VMSCs,) Rac1 is required for NOX4 activity whereas NOX4 maintains its activity when transfected into Rac1 deficient cells [119,120]. NOX4 is considered constitutively active and regulation of ROS production is solely regulated via regulation of NOX4 expression [121]. However Poldip2 (Polymerase DNA directed delta-interacting protein 2) binds to NOX4 and enhance its activity [122] but Tks4/5 (tyrosine kinase substrate with 4/5 SH3 domain), PDI (protein disulphide isomerase) also binds to NOX4. Biochemistry underlying NOX4 mediated H_2O_2 production is still unclear [106,107] but it has been proposed that superoxide produced by NOX4 rapidly dismutases to H_2O_2 prior to its release from the enzyme and recent study provided evidence that extracytosolic loop (E-loop) of NOX4 is involved in this process [123].

Increased ROS generation by NOX4 has been closely linked with papillary thyroid carcinoma [124]. Moreover, ROS produced by NOX4 promotes pancreatic cancer by mediating antiapoptotic effect on growth factors such as TGF-β (transformation growth factor-β) and IGF-1 (insulin-like growth factor) [125]. Other than these, NOX4 expression has also been observed in melanoma cells [126], and renal carcinoma cells [127].

3.2.5 NOX5 enzyme complex

NOX5 is an 85kDa nonglycosylated protein which exhibits 27% similarity to NOX2. NOX5 is the least understood among all other NOX

enzymes because its gene is absent in rodents which make its study challenging [128]. It is highly expressed in testis, spleen and lymphoid tissue [129].

Like NOX1-3, NOX5 also produces superoxide but it is a $p22^{phox}$ independent enzyme (Fig. 3e). It neither requires cytosolic organizer nor activator subunits while its activation depends on Ca^{2+} levels. NOX5 protein has four EF-hands, Ca^{2+} binding domains at the N-terminus that regulate the activation of enzyme in addition to flavin and NADPH binding domain at C-terminus [128]. Binding of Ca^{2+} to the EF hands induces a conformational change in the N-terminus leading to its interaction with C-terminal thereby activating NOX5 [130]. However, Calmodulin and Hsp90 (heat shock protein 90) also known to regulate expression and activity of NOX5 [131]. NOX5 derived ROS have been implicated in cancer development and progression. For instance, overexpression of NOX5 has been observed in human cancers including breast, lung, ovary, colon, prostate and brain as well as in non-Hodgkin lymphoma and malignant melanoma [132]. Moreover, NOX5 is also involved in esophageal cancer, hairy cell leukemia and pancreatic cancer [133-135].

3.2.6 DUOX-1/2 enzyme complex

Dual oxidase 1 (DUOX1) and dual oxidase 2 (DUOX2) are also referred to as thyroid oxidases (ThOX) due to their abundant expression in thyroid and were initially recognized and cloned from thyroid gland. In addition to gp91phox homology domain and Ca^{2+} binding EF-hand motifs, DUOX proteins possess an extracellular peroxidase domain which is responsible for its dual nature [136]. DUOX2 is highly expressed as compared to DUOX1 in thyroid while in lungs and airway epithelial cells DUOX1 is more highly expressed than DUOX2. Like NOX5, DUOXs do not require $p22^{phox}$ or other cytosolic subunits for its activation (Fig. 3f) whereas they require Ca^{2+} for their activation which binds to EF-hands in Duox proteins for ROS production [137]. DUOX1 and DUOX2 also binds to DUOXA1 (Duox activator 1) and DuoxA2 (Duox activator 2) respectively [96]. DUOXA1 and DUOXA2 are maturation or activation factors essential for full processing of DUOX and are required for translocation of DUOX enzymes from the ER to plasma membrane [138].

Table 2. Inactivated p53 in different type of cancer

Mechanism of inactivation	Cause	Type of cancer	Effect of inactivation	References
Defect in p53 mRNA translation	Impairment of dyskerin function	Breast carcinoma	Reduced p52 levels	[79]
Interaction between BRCT seventh and eight domain of TopBP1 and p53 DNA binding domain	Overexpression of Top BP1	Breast cancer	Inhibition of p53 promoter binding activity	[80]
p53 codon 72 polymorphism and HPV 16/18 oncoprotein expression	HPV 16 E6 oncoprotein	Colorectal cancer, lung cancer	p53 protein degradation, reduced p53 transcriptional activity	[81,82]
Histone modification	Histone deacetylase-3	Pancreatic cancer	Repression of p53 gene transcription	[83]
Deletion of chromosome 17p13 region	Mutational deletion	Multiple myeloma	Loss of p53 proteins	[84,85]
Defect in post translation of p53	Germline mutation	Adrenocortical component tumor of Li Fraumeni syndrome	P53 deficiency	[86]

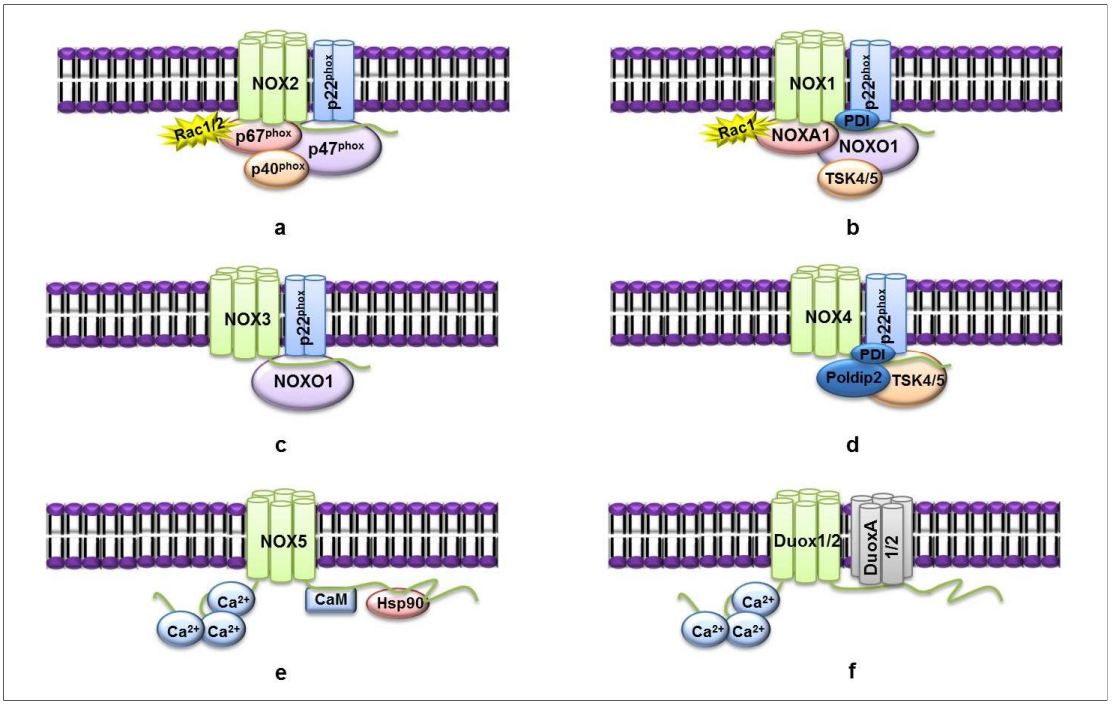

Fig. 3. Structures of NADPH Oxidases: a) Nox 2, b) Nox 1, c) Nox 3, d) Nox 4, e) Nox 5, f) DUOX1/2

Studies have shown that DUOX1 and DUOX2 are frequently silenced in human lung cancer [139]. Furthermore elevated levels of DUOX2 expression has been observed in cancer of breast, colon, lung and prostate [140].

4. CROSSTALK BETWEEN NADPH OXIDASE, P53 AND WNT PATHWAY

The cross talk emphasizes the role of Nox (NADPH oxidase) in redox regulation of Wnt mediated cell proliferation and p53, death receptor mediated cell apoptosis (Fig. 4). Several studies have revealed that ROS generation in a cell not only take place due to bactericidal activity and inflammation but can also be generated as a result of intracellular signaling processes. Such a process is Wnt signaling where role of ROS is little understood. Recent studies revealed the production of ROS on Wnt treatment via Nox1 (NADPH oxidase1) in intestinal and colon epithelial cells. Canonical Wnt signaling plays a vital role in the regulatory process of cell proliferation in developing as well as adult tissues. Earlier it was reported that upon Wnt binding to the frizzled receptors, signal transduction takes place via Src kinases that triggers Dvl2 (disheveled segment polarity protein 2) to translocate the β-catenin into the nucleus for transcriptional activation of Wnt target genes [141]. But an alternative path has also been identified recently that involve the role of nucleoredoxin (NRX) in canonical Wnt signaling. Here, Wnt stimulate Rac1 guanine nucleotide exchange factor (Vav2) via Src mediated tyrosine phosphorylation that further trigger Rac1 that regulate Nox1 activity and thus involved in Wnt induced ROS production [142]. Thus produced ROS leads to oxidative inactivation of NRX (a redox protein: nucleoredoxin) thereby dissociating NRX from Dvl that ultimately leads to Wnt-β-catenin TCF mediated cell proliferation [143,144]. Apart from Nox activating role, Rac1 (Ras-related C3 botulinum toxin substrate 1) also found to associate with β-catenin/TCF complexes to assist transcriptional regulation of Wnt target genes [145]. Furthermore, transcriptional activation of Wnt target genes cause the induction of ARF (ADP ribosylation factor) protein that in association with Mdm2 (Mouse double minute 2 homolog: an E3 ubiquitin protein ligase) suppresses the p53 mediated cell apoptosis via its proteasomal degradation [146].

NADPH oxidase play a key role in regulating the balance between cell proliferative and apoptotic pathways, for instance, ROS generated by Nox can up regulate cell proliferation and down regulate as well depending on cellular environment [147]. Under optimum level, ROS can mediate cell proliferation by not letting NRX to inhibit Dvl that in turn successfully translocate β–catenin into nucleus for transcriptional activation of target genes [148]. While on the other hand, high level of ROS can trigger cell death by activating FAS (death receptor) and p53 (tumor suppressor gene) that further stimulate Bax to cause mitochondrial mediated cellular apoptosis via caspase activation [149,150]. Moreover, ROS can also stimulate cell growth in an indirect manner by inhibiting PTEN which is known to suppress AKT formation thus allowing cell proliferation via PI3K/AKT pathway [151,152]. Moreover, activated p53 in response to DNA damage can induce NOXA (NADPH oxidase activator) to facilitate cell apoptosis via repressing Mcl1/A1 (Bcl2 proteins) mediated cell survival signal [153]. Since, NADPH oxidase complex has the potential to induce Wnt triggered cell proliferation as well as p53 mediated cell apoptosis in various carcinomas therefore activation or inhibition of NADPH oxidases depending on the case might be an additional therapeutic approach for targeting cancer.

5. NADPH OXIDASES INHIBITORS: THE POTENTIAL CANDIDATES FOR TARGETING CANCER

Targeted cancer therapies involve drugs or other substances that hinder the progress and expansion of cancer by obstructing specific molecular targets that play a direct role in tumor growth and progression. In contrast to chemotherapy targeted therapies differ in a variety of ways that involve i) specific molecular targeting, ii) blocking tumor cell progression and iii) direct interaction with the target. Presently scientists are paying attention towards targeted therapies via anticancer drug development. Such an example is of NADPH oxidase inhibitors that can serve as a novel approach for cancer therapeutics.

5.1 Nox2 Inhibitors and Underlying Mechanism

Celastrol, a bioactive compound extracted from the medicinal plant *Tripterygium wilfordii*, is a potent inhibitor of NOX2 which is used to treat states of chronic inflammation and has shown beneficial results in cancer, neurodegenerative disease and arthritis models. It precisely attaches to $p47^{phox}$ disrupting its binding with $p22^{phox}$ and inhibiting enzyme activity [154]. Another drug *Ebselen* prevents the binding of $p47^{phox}$ to $p22^{phox}$ thereby preventing NOX2 activation and thus is classified as NOX2 inhibitors [155]. *VAS2870* (3-benzyl-7-(2-benzoxazolyl)thio-1,2,3-triazolo[4,5-d]pyrimidine) is also NOX2 inhibitors [156].

S17834 (benzo(b)pyran-4-one derivative) inhibits NOX2 as it prevents the binding of $p47^{phox}$ to membrane complex of the enzyme and it is neither superoxide scavenger nor xanthine oxidase or eNOS inhibitor [157]. *Perhexiline* (prophylactic anti-anginal agent) directly inhibits NOX2 in neutrophils andit neither inhibits xanthine oxidase nor directly scavenges superoxide. Although *Suramin* inhibits biochemical NOX2 activity but it lacks cell penetrance and thus does not inhibit cellular ROS production [158]. *Berberine* (plant-derived alkaloid) inhibits NOX2 mediated superoxide anion production in macrophages [159]. Further, *Brilliant green* (triphenylmethane derivative) shows selectivity for NOX2 inhibition [160]. *Shionogi I & II* (pyrazolo pyrimidine derivatives) inhibits NOX2 indirectly while Bridged tetrahydroisoquinolines, 11g (*n*-pentane) and 11h (thiophene), are highly efficacious inhibitors of NOX2 [161]. Recently it has been demonstrated that Wild Alaska bog blueberries (*Vaccinium uliginosum*) prevents the association of $p67^{phox}$ with NOX2 and $gp21^{phox}$ in plasma membrane thereby impeding NOX2 assembly and disrupting ROS generation [162]. *Fulvene-5* inhibits NOX2 mediated ROS production and hindered NOX2 function [163]. Moreover, NOX2ds-tat (gp91ds-tat) is a biological inhibitor specific for NOX2 which is an 18 amino acid peptide where 9 amino acid sequence of NOX2ds-tat mimics cytosolic B loop of NOX2 and binds to $p47^{phox}$thereby hindering NOX2 assembly [164].

5.2 Other NOX Inhibitors and Underlying Mechanism

Like NOX2, *VAS2870* also inhibits NOX4 and NOX5. *VAS3947,* a close derivative of *VAS2870,* inhibits NOX3 and NOX4 [165]. Similarly *Fulvene-5* and *S17834* also inhibits NOX4 other than NOX2 [166].*GKT136901* and *GKT137831,* potent inhibitors of NOX1 and NOX4, were developed by GenKyoTex (Geneva, Switzerland) and both GKT compounds exclusively inhibits

xanthine oxidase-derived ROS [167,168]. *GKT136901* strongly scavenges peroxynitrite (a reactive nitrogen species) and inhibits NOX5 [169]. In addition to NOX2, *Celastrol* also inhibits NOX1 by interrupting the binding of $p22^{phox}$ to the SH3 domain of NOXO1 [154]. Likewise *Ebselen* is potent inhibitors of NOX1, NOX2 and NOX5 [155,170].

Both ML171 (2-acetylphenothiazine) and NOXA1dsinhibit NOX1 in a different manner i.e. ML171 effectively hinders invadopodia production in human colon cancer cell line [108] while *NOXA1ds* mimics a putative activation domain of NOXA1 and thus binds to NOX1 which prevents the formation of active NOX1 complex [171].

A plant-derived naphthoquinone- *Plumbagin* [172], triphenylmethane derivatives- *Imipramin blue*, *Gentian violet* and *Brilliant green*[160.173] and active compounds from edible plants- *ACD042* and *ACD084* (diarylheptanoid) inhibits NOX4 activity [174]. Moreover *Schisandrin B* (Sch B), a naturally occurring dibenzocyclooctadiene lignan, inhibits NOX4 derived ROS production [175] while another NOX4 inhibitor, *Grindelic acid* is not a direct ROS scavenger [174]. A cell-based screening of approximately 1000 compounds yielded phenantridinones and flavonoids as potent NOX4 inhibitors [176] which are not direct H_2O_2 scavengers. Apart from these NOXA1, DPI (diphenylene iodium), siRNA (small-interfering RNA) and intracellular calcium chelation inhibits DUOX enzyme [177,178]. These NADPH oxidase inhibitors are summarized in Table 3 that provide a new therapeutic intervention for targeting cancer.

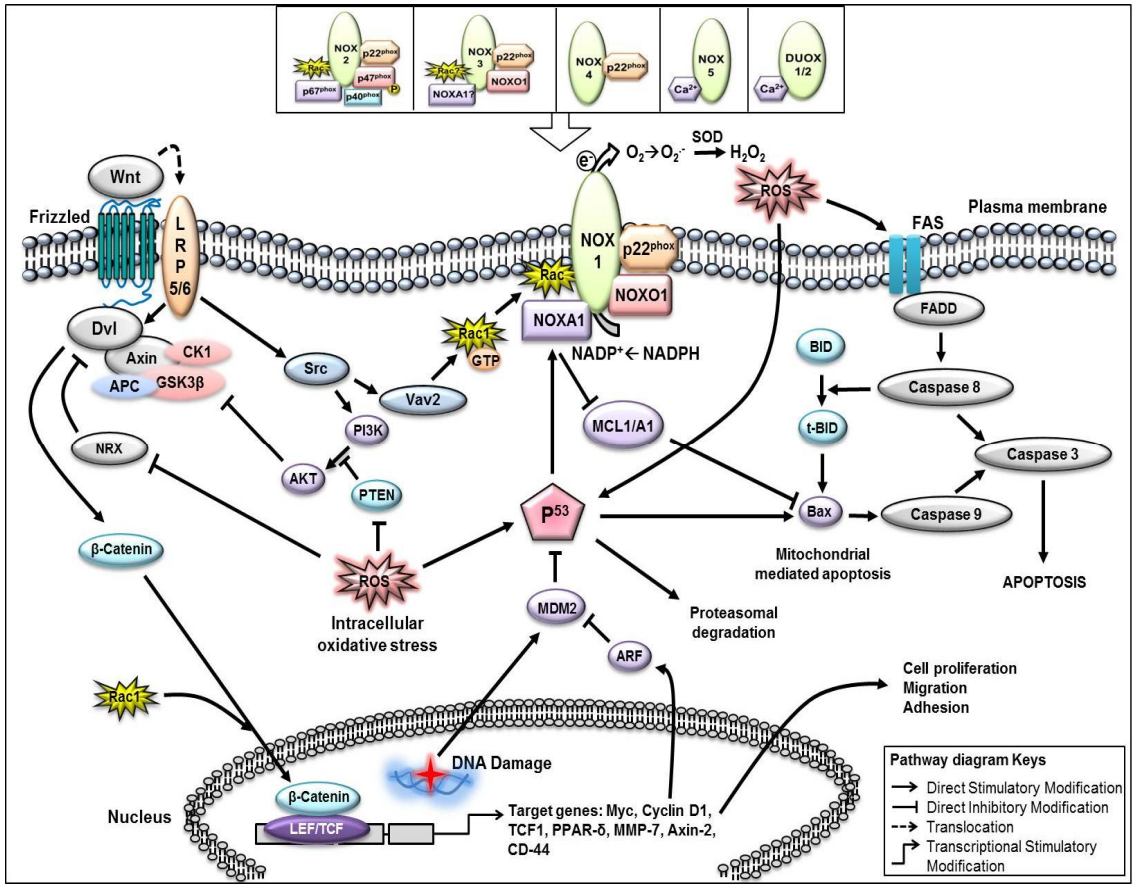

Fig. 4. Crosstalk between Nox, Wnt and p53 pathways

Table 3. NADPH Oxidases and their inhibitors in Cancer

NADPH Oxidase	Binding partner	Expressed in cancer	Inhibitors	ROS generated	References
NOX1	P22phox, NOXO1, NoxA1, Rac1, PDI, TKS4/5	Colon cancer, Prostate cancer, Gastric cancer	ML171, GKT136901 & GKT137831, Celastrol, NOXA1ds	$O2^{\cdot}$--	[108,154,167,171]
NOX2	p22phox, p67phox, p40phox, p47phox,Rac1/2	Gastric MALT lymphoma, Melanoma	Nox2ds-tat, Bridged tetrahydroisiquinolines, Berberine, Alaska bog blueberries, Perhexiline, Suramin, Shionogi I & II	$O2^{\cdot}$--	[158,159,161,162,164]
NOX3	p22phox,NOXO1	Pancreatic cancer	VAS3947	$O2^{\cdot}$--	[179]
NOX4	p22phox,PDI,TKS4/5, Poldip2	Pancreatic cancer, Melanoma, Renal cell carcinoma, Thyroid cancer	Plumbagin, ACD042 & ACD084, Sch B, Grindelic acid, Phenantridinones and Flavonoids	H2O2	[172,174-176]
NOX5	Ca2+, Hsp90, CaM	Prostate cancer, Hairy cell leukemia, Esophageal cancer, breast cancer, colon cancer, lung cancer, brain cancer, ovary cancer, melanoma, non-Hodgkin lymphoma, Pancreatic cancer	GKT136901, VAS2870, Ebselen	$O2^{\cdot}$--	[165,169,170]
DUOX1/2	Ca2+, DuoxA1/A2	Thyroid cancer, Lung cancer	DPI, siRNA, NOXA1	H2O2	[177,178]

6. CONCLUSION

Cancer has been the major cause of death in the world at present. A lot of research has been done to unravel the mystery of cancer development and progression in order to find out all possible ways to cure it. Uncontrolled proliferation of cells arising from virtually any cell type in body results in cancer. A cancerous cell differs from a normal cell in terms of its properties such as loss of anchorage dependency, loss of contact inhibition, loss of differentiation, chromosomal abnormality, large and irregularly shaped nuclei etc. causing uncontrolled cell proliferation. Knowledge of these characteristics enable us to understand the mechanistic pathway through which cancer causes destruction. Unlike a normal cell, caner cell does not obey the laws of biology i.e. normal life cycle of a cell- growth, division, differentiation, senescence and cell death. There are numerous causes of cancer development including infection (Virus), environmental (carcinogens), genetically (genetic or chromosomal aberration) and lifestyle (tobacco consumption). These factors alter various signaling pathways such as PI3K/AKT, MAPK, PTEN, p53, Wnt, Notch, and Hedgehog etc.

Activation of canonical Wnt signaling cascade and loss of p53 function are frequently found to be coupled in cancer. Wnt is majorly involved in tissue homeostasis, cell fate decisions and other biological phenomenon throughout embryonic development and adult life making it one of the most important development pathway. Genetic aberration in any component of this pathway such as APC, β-catenin, receptor results in uncontrolled cell proliferation. Here, destruction complex play a significant role in regulating Wnt/β-catenin pathway that include APC, Axin, GSK3β and CS1α. Loss of APC function causes nuclear deposition of β-catenin thereby leading to up-regulated transcription of responsive genes resulting in cancer. Experimental reports suggest that p53 has a role in suppressing transcriptional activity of β-catenin via targeting TCF/LEF complexes. P53, a sequence specific transcription factor plays a critical role in maintaining the genomic stability of an organism. Therefore it is the main target of cancer, hampering the defense system. Moreover, p53 mutant further aggregates with intrinsic p53 forming amyloid oligomers thus causing its inactivation. There is a significant correlation between Wnt and p53 pathway in a Nox (NADPH oxidase) dependent manner. Wnt stimulate Vav2 (Rac1 guanine nucleotide exchange factor) via Src facilitated tyrosine phosphorylation that further trigger Rac1 which regulate Nox1 activity and thus involved in Wnt induced ROS production. As a resultof ROS production it leads to oxidative inactivation of NRX (a redox protein: nucleoredoxin) thereby dissociating NRX from Dvl that ultimately causes Wnt-β-catenin TCF mediated cell proliferation. Thus targeting of Nox enzymes would be a beneficial therapeutic approach in controlling the Wnt mediated unregulated cell proliferation. Moreover ROS is required for other essential biological processes such as ECM cross-linking, hormone biosynthesis, apoptosis and cellular signaling etc. Excess (oxidative stress) or shortage (reductive stress) of ROS both are detrimental. Oxidative stress causes inflammation, abnormal cell growth, tissue and cellular damage. ROS is produced as a byproduct in various physiological processes such as xanthine oxidase activation, mitochondrial respiration, eNOS uncoupling etc. The primary function of Nox family is to produce ROS. Nox family comprises of seven members NOX1-5, DUOX1-2. ROS generated by Nox family is involved in pathophysiology of cancer development and progression making it a new target for cancer therapeutics. Nox derived ROS involved in cancer of prostate, colon, pancreatic, lung, breast and other diseases. Recent studies are targeting Nox enzymes to obstruct the cancer progression. There are several new small molecule Nox inhibitors have been identified such as ML171, GKT136901 and GKT137831, VAS2870 and VAS3947, FULVENE-5 etc. Since, NADPH oxidase complex has the potential to induce Wnt triggered cell proliferation in various carcinomas therefore inhibition of NADPH oxidases especially in wnt /p53 mediated cancer might act as an additional therapeutic approach for targeting cancer. Further research in this area is required to better understand and diagnose the cancer progression.

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CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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