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The crosstalk between Wnt/β-catenin signaling pathway with DNA damage response and oxidative stress: Implications in cancer therapy

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ABSTRACT

DNA repair is essential for maintaining genomic integrity in cells. The dependence of cancer cell survival on proper DNA repair provides an opportunity to treat defective tumors by DNA damaging agents. Not only Wnt signaling has important functions in controlling gene expression, as well as cell polarity, adhesion and behavior, it also highly interacts with DNA damage response (DDR) in different levels. Furthermore, oxidative stress, which is responsible for majority of DNA lesions, affects Wnt signaling in different ways. A better understanding of the cross-talk between these pathways and events could provide strategies for treatment of cancer cells with deficient DNA repair capacity. As such, we will give a brief overview of the importance of the DNA repair machinery, signaling mechanisms of Wnt/β-catenin pathway, and DDR. We will further review the interactions between Wnt signaling and DDR, and the impact of oxidative stress on Wnt signaling. Finally, Wnt signaling is discussed as a potential treatment strategy for cancer.

Contents

1. Introduction

Survival and propagation of all organisms thoroughly depend on the accurate replication and transmission of genetic material, as well as on the maintenance of integrity and stability of genomic information [1]. Therefore, the existence of a system for sensing and repairing any potential damages interfering with genome health is critical [2]. DNA damage response (DDR), a hierarchical signaling pathway, is orchestrated by various proteins that sense DNA damages, transduce the signals to the effectors, and determine the cell fate [2]. In the case of repairable damages, DNA repair pathways are activated and subsequently remove any barriers against repli-

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cation. On the other hand, when DNA damages are too severe and unrepairable, cells are forced to undergo programmed cell death [3]. The importance of DDR is such that cells with any defect in these mechanisms are highly prone to various diseases and sensitive to DNA damage inducing agents [4]. Along with a wide range of environmental and endogenous genotoxic stimuli, reactive oxygen species (ROS), the by- product of normal cell metabolism, threaten the integrity of DNA and other macromolecules [5]. Superoxide and hydroxyl radical, H_2O_2, and other dangerous forms of ROS are produced upon cell exposure to multiple exogenous factors, UV and ionizing radiation (IR), growth factors, cytokines, environmental toxins, chemotherapeutic agents, hyperthermia and inflammation [6]. ROS-induced oxidative damage can cause substantial damages in DNA structure including single strand breaks (SSB), double strand breaks (DSB), DNA base modifications, and the formation of apurinic/apyrimidinic lesions, which are severely toxic and mutagenic [7]. In order to handle the mentioned oxidative DNA damages, cell cycle checkpoints are activated, cell cycle is arrested and DNA replication is halted, to create a window for repairing defects in DNA structure through excision repair pathways, which is the key repair system for oxidative stress-induced DNA damages [8]. Recent studies have reported that Wnt/β-catenin signaling pathway –which is pivotal for modulation of cell fate determination, cell proliferation and apoptosis, can induce DDR by regulating various proteins including γ-H2A.X, $p16^{INK4a}$, p53, and p21 [9]. Therefore, in this review, we will present a brief introduction about signaling mechanisms of Wnt/β-catenin and DDR pathways and then, focus on the involvement of Wnt/β-catenin signaling in the regulation of DDR and oxidative induced DNA damage.

2. Signaling mechanisms of wnt/β-catenin pathway

Wnt signaling pathway has important functions in controlling gene expression, as well as cell polarity, adhesion and behavior. Wnt signals are transduced to the canonical, non-canonical and the Wnt/Ca^{2+} pathways [10]. In canonical pathway, Wnt binds cell surface receptors, Frizzled (Fz) and LDL-receptor related proteins (LRP5/6), and the signal is propagated through β-catenin signaling cascade. When Wnt receptor complexes are not bound by ligand, the interaction between β-catenin, APC, AXIN and glycogen synthase kinase 3β (GSK-3) leads to β-catenin phosphorylation and subsequent polyubiquitination by hTRCP1 or hTRCP2 complex. These modifications lead to the proteasomal degradation of β-catenin [11,12]. In the presence of canonical WNT signaling, Dishevelled (Dsh or DVL) inhibits β-catenin destruction. The physical association between Fz and Dsh leads to the Dsh phosphorylation by PAR-1 and CKII kinases. Along with this, a direct binding is established between LRP and AXIN. Both Dsh phosphorylation and the latter event release β-catenin from GSK3β and CKIα phosphorylation, to continue its function in the nucleus [13].

Meanwhile, the non-canonical WNT signaling pathway is independent of β-catenin. In this pathway, the transcriptional activation of Fz receptors is done by Wnt which leads to activation of Dsh. Subsequently, the signals are transferred by small GTPase such as Rho/Rac and C-Jun N-terminal kinase (JNK) leading to moderation in cytoskeletal elements including actin and microtubules [14]. Many function of this pathway in vertebrate are still not well known (Fig. 1).

The Wnt/Ca^{2+} is a second branch of non-canonical Wnt signaling pathway. In this pathway, the interaction between Wnt and Fz receptors lead to release of Ca^{2+} from ER. The release of Ca^{2+} from ER is dependent on production of inositol 1,4,5-triphosphate(IP3) and 1,2 diacylglycerol (DAG) from phosphatidyl inositol 4,5-bisphosphate(PIP2), which is catalyzed by phospholipase C(PLC) The intracellular accumulation of Ca^{2+} activates several Ca^{2+}-sensitive proteins, including calcinurin (Cn), calcium calmodulin dependent protein kinase II (CaMKII) and protein kinase C (PKC). In turn, many regulatory proteins such as NFkB and CREB are activated by CaMKII and PKC and also Ca^{2+} ions released by IP3. Expressed Cn that can active nuclear factor associated with T cells (NFAT). Finally these factors (NFkB, CREB and NFAT) translocate to the nucleus and activate the transcription of downstream regulatory genes [15].

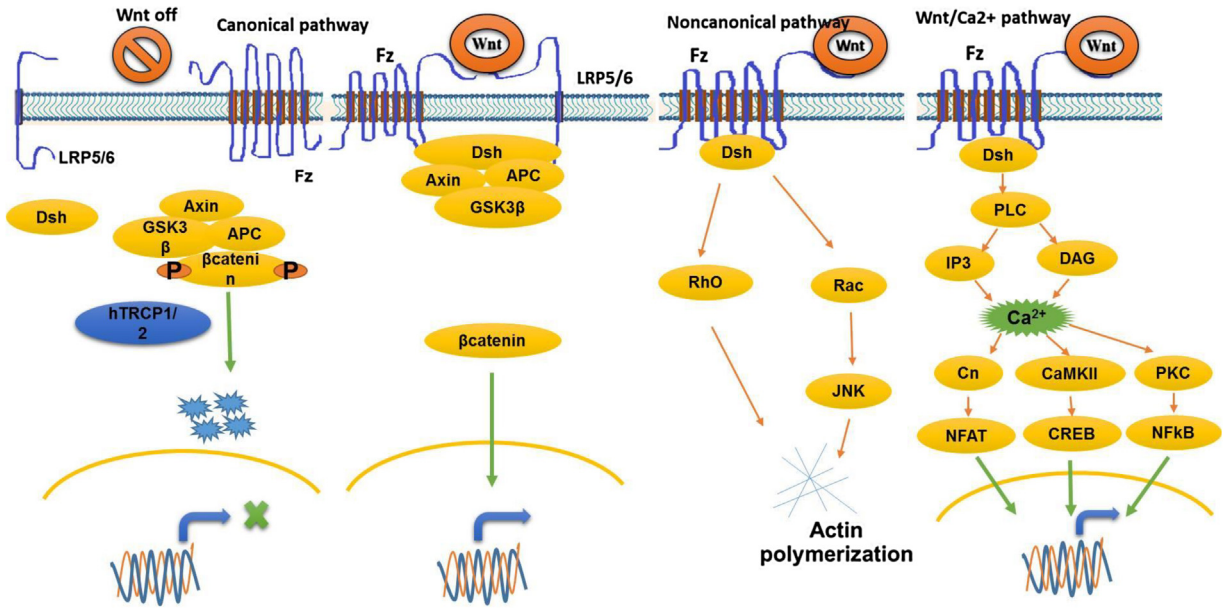

Fig. 1. A schematic representation of Wnt signaling pathway. Canonical pathway: activation of Fz receptors by the Wnt ligand leads to activation of β-catenin and finaly multiple cellular responses. Noncanonical pathway: activation of Fz receptors leads to activation of Dsh and then the translocation of signal through small GTPases Rho and Rac, which are involved in modulating cytoskeletal elements and are involved in actin polymerization. Wnt/Ca^{2+} pathway: binding of Wnt with Fz receptors leads to the activation of Dsh and PKC, CaMKII and Cn by increase in intracellular Ca^{2+}.

3. DNA damage response: an integrated genome-maintenance network

Early phosphorylation-driven signaling cascades trigger DDR following detection of any destructive damages in DNA. DDR is executed through three main steps with three main players: detection of damages by sensors, conveyance of damage signal by transducers, and repairing the damages by effectors [16]. The two distinct protein complex including the MRE11/RAD50/NBS1 (MRN) complex as DSB sensors and the replication protein A (RPA) and the RAD9–RAD1–HUS1 (9-1-1) complex as SSB sensors, play important roles in sensing DNA lesions[17]. At the next step, sensors mediate the recruitment of transducers, which amplify and transduce damage signals to downstream effectors. Three members of the phosphoinositide 3-kinases (PI3K)-like protein kinases family including, ATM, ATR and DNA-PKcs, regulate the cellular response to DNA damage [18]. ATM is recruited by MRN complex following detection of DSBs, and phosphorylates various substrates which control cell cycle checkpoint activation and DNA repair [19]. The 9-1-1 complex recruits ATR after sensing SSBs. ATR phosphorylates target substrates to regulate cell cycle checkpoint and genomic stability [20]. DNA-PKc is induced by detection of DSBs, phosphorylates itself and other various substrates and mediates DSB repair via non-homologous end joining [21]. In this regard, phosphorylation of the histone-variant H2AX, which produces γH2AX, is one of the earliest events following ATM activation. γH2AX function as a signal for DNA lesions and recruits the DDR proteins [22]. Signals from transducers activate and phosphorylate downstream effectors for eliciting appropriate responses in determining cell fate. The target proteins in the downstream of ATR and ATM, which include BRCA1, p53-binding protein 1 (53BP1), CHK1 (is dominantly phosphorylated by ATR) and CHK2 (is dominantly phosphorylated by ATM), spread DDR signals away from the site of lesions to the effectors such as p53 and cell division cycle 25 (CDC25) phosphatases [23,24]. p53 subsequently determines the cell fate by either arresting cell cycle and DNA repair or proceeding toward apoptosis after unrepairable DNA damage [25].

4. The interactions between wnt signaling pathway and DDR

The maintenance of genomic integrity after DNA damage depends on the activation of the tumor suppressor p53 which then coordinates the action of the DNA repair system and/or the cell cycle checkpoint [26]. The Wnt signaling pathway is one of the major targets of p53. In this context, the degradation of β-catenin has a central role. P53 induces SIAH-1 (E3 ubiquitin ligase) which subsequently ubiquitinates β-catenin for degradation. A number of scaffold protein have been identified that establish the interaction between SIAH-1 and β-catenin. This molecular bridge accelerates the degardation of β-catenin by E3 ubiquitin ligase or SIAH-1 that includes SIP, Skp1 and Ebi proteins. Therefore, the p53-mediated degradation of β −catenin is simultaneous with cell cycle arrest [27]. The p53-β-catenin loop is recognized as a pathway that has important functions in regulation of p53 upon DNA damage. Activation of β-catenin by Wnt signaling pathway leads to the expression of the ARF tumor suppressor protein. ARF binds to and inactivates MDM2. MDM2 inactivation induces constitutive activation of p53, leading to triggering of the cellular p53 response [28].

The β-catenin overexpression in Wnt signaling pathway induces the expression of H2AX, a variant of H2A histone protein. The overexpression of H2AX denotes the activation of DDR. DDR induces the expression of p21, p16 and p53 and these factors promote cellular aging and senescence [29]. Glycogen synthase kinase-3β (GSK3β) has a vital role in the advancement of Wnt signaling pathway. Different forms of DNA damages induced by several agents, have been shown to activate p53 and further activation of GSK3β by p53. This activation depends on direct binding of p53 and GSK3β, and underlies the translocation of GSK3β to the nucleus. Activation of GSK3 β by p53 promotes responses to p53 including increase in p21 levels and caspase-3 activity. In this case, these proteins initiate the DNA repair or apoptosis processes. On the other hand, the interaction between p53 and GSK3β stops phosphorylation and inactivation of β-catenin by GSK3β in Wnt signaling pathway and leads to expression of p21 and caspase3 in response to DNA damage [30]. As explained before, β-TRCP or hTRCP have critical functions in degradation of β-catenin in canonical signaling pathway. Yet another factor that is affected by β-TRCP is Cdc25A, a phosphatase essential for cell cycle progression because of its function in dephosphorylating cyclin-dependent kinase. In response to DNA damage, the checkpoint kinases (Chk1 and Chk2) are activated by ATM and ATR protein kinases and lead to hyperphosphorylation of Cdc25A. These events stimulate the ubiquitinatin and degradation of Cdc25A by β-TRCP in response to Chk-mediated phosphorylation, This process finally eventuates in cell cycle arrest [31]. β-Catenin is the downstream effector of the Wnt signaling pathway. The interaction of this protein with TCF (T-cell factor) and LEF (lymphoid enhancer factor) leads to transcriptional activation, because β-Catenin is a coactivator of these two protein. On the other hand, it has been demonstrated that poly(ADP-ribose) polymerase-1 (PARP-1) interacts with the TCF and β-catenin complex and enhances their transcriptional activity (Fig. 2).

In response to DNA damage, PARP-1 auto-polyADP-ribosylates itself, which leads to inhibition of its interaction with TCF and suppresses the transcriptional activity of this protein [32]. Ku is an antigen composed of two 70 and 80 kDa subunits which bind to the DSBs with high affinity and recruit the DNA-dependent protein kinase (DNA-PK). The Ku70/Ku80/DNA-PK join together and repair DSBs. It has been recently reported that Ku70/80 can remove β-Catenin from TCF/LEF/β-catenin complex and then inhibit the transcriptional activity of this complex [33]. Klotho is a protein that regulates aging in a fundamental level. After exposure of cells to DNA damage injury, the levels of klotho in damaged cells begin to rise. Along with this, factors that affect the klotho levels are also upregulated including H2AX, ATM and ATR. At this point, klotho will affect different pathways. Increase in klotho levels after DNA damage leads to inactivation of p21, p16 and p53 which are involved in DDR. On the other hand, klotho deactivates Wnt signaling by increasing the level of Calpin, a protease that cleaves β-catenin. Therefore, through the mentioned mechanisms, klotho prevents cell death and prolongs the cell lifespan [34,35].

5. Oxidative stress and wnt signaling pathway

Reactive oxygen species (ROS) highly affect the cell homeostasis by influencing numerous cellular processes. Cells attempt to counteract the adverse effects of ROS through different approaches such as upregulation of manganese superoxide dismutase (Mn-SOD), catalase, as well as DNA damage repair genes, such as Gadd45 [36]. This response requires the activation of Forkhead box O (Foxo), a family of ubiquitous transcription factors that promote cell survival by inducing cell cycle arrest and quiescence in response to oxidative stress [37]. Oxidative stress activates the expression of Foxo in the cells. The interaction of β-catenin with Foxo transcription factors (Foxo1, Foxo3a and Foxo4) promotes exit from the cell cycle and entry into quiescence or apoptosis. On the contrary, the interaction of β-catenin with TCF promotes cell proliferation [38]. Wnt signaling pathway has an important function in osteoblast differentiation. Alcohol consumption plays a role in induction of

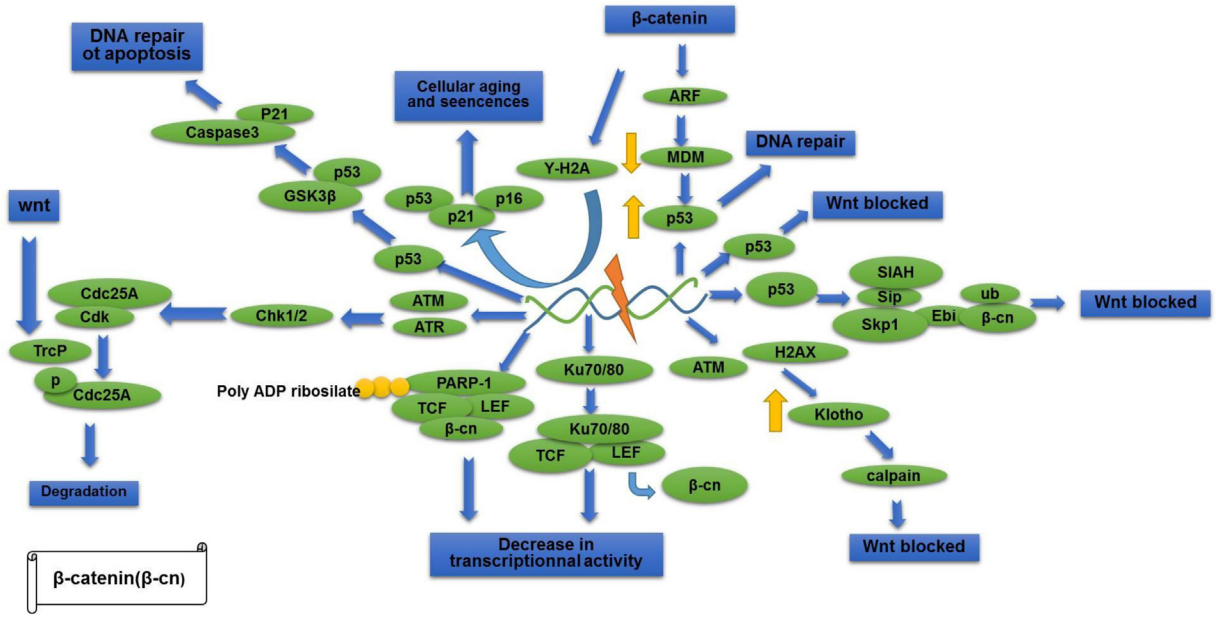

Fig. 2. The interactions between Wnt signaling pathway and DDR. DDR induces the expression of p53, SIAH (E3 ubiquitin ligase) and klotho. Subsequently, these factors block Wnt signaling either directly or indirectly. β-catenin induces H2AX expression which activates DDR. DDR induces the expression of p21, p16 and p53 and consequently leads to cellular aging and senescence. DDR induces the expression of p53, the interaction of which with GSK3β leads to activation of p21 and caspase-3. In turn, these factors can induce DNA repair or apoptosis. Cdc25A (a phosphatase essential for cell cycle progression), is phosphorylated by ATM and ATR, and is then degraded by TrcP. This process leads to cell cycle arrest. Expression of Ku antigen and PARP-1 in response to DNA damage and interaction of these factors with downstream elements in Wnt cascade such as TCF, LEF and β-catenin, eventually decreases the transcriptional activity.

oxidative stress, which then leads to osteoblast senescence and decrease in the rate of bone formation [39]. The effect of alcohol consumption on osteoblastogenesis gets back to the accumulation of oxidative stress and inhibition of Wnt signaling pathway. It has been suggested that alcohol has direct inhibitory effects on translocation of β-catenin from cytoplasm to the nucleus and also activation of GSK3β through Wnt induced TCF/LEF-dependent transcription [40,41]. Nitric oxide-donating aspirin (NO-ASA), consists of a traditional ASA to which a NO-releasing moiety is covalently attached. NO-ASA displayed a deep inhibitory effect in human colon cancer compared to the traditional ASA. Finding indicate that NO-ASA induces oxidative stress and promotes intrinsic apoptosis by inhibition of Wnt signaling pathway and disruption of adherens junctions. In this process, caspase3 expressed in intrinsic apoptosis cleaves β-catenin leading to the disassembly of the adherens junctions. Furthermore, the activation of caspase3 by NO-ASA also inhibits Wnt signaling, an affect which is also enhanced by caspase3-induced cleavage of β-catenin [42].

Benzo(a)pyrene (B[a]P), is a ubiquitous compound found in coal tar, industrial processes, cigarette smoke, and many foods, especially grilled meats [43]. B[a]P exhibits destructive effects after exposure to biologically reactive epoxides by CYP1 isoforms of cytochrome P450 monooxygenases. B[a]P is known as a potent carcinogenic, mutagenic and preoxidative agent in experimental studies. Wnt signaling pathway is also affected by the mutagenic effects of B[a]P. β-catenin is an essential component of Wnt signaling that regulates the overall structure of the tissue and cell–cell adhesion in various tissues. B[a]P treatment disturbs the Wnt/β-catenin signaling pathway, by increasing the β-catenin levels and suppressing APC expression in the cell, which can collectively result in tumor formation [44].

Glucocorticoids (GCs) and inflammatory cytokines contribute to the age related decrease in bone density. GC administration or an endogenous rise in TNFα production has been causally related to an increase in the number of osteoclasts and a decrease in the number of osteoblasts, which eventuates in bone loss over time [45]. Oxidative stress induced by GC and TNFα causes bone loss through apoptosis in two ways, generation of ROS by GC and activation of the PKCβ/P66^{SHC}/JNK cascade by TNFα. Yet another mechanism underlying bone loss is the effect of oxidative stress on Wnt signaling pathway, which is mediated by GC and TNFα. GC and TNFα inactivate Akt and suppress the foxo/β-catenin interaction, thus reducing the effect of Wnt signaling pathway on osteoblastogenesis [46].

Peroxisome-proliferator activator receptor γ (PPARγ) are a group of nuclear receptor proteins that function as gene transcriptional regulators, and as such, play essential roles in energy homeostasis and inflammation. The exposure of the nuclear factor erythroid 2-related factor 2 (NRF2) to ROS leads to activation PPARγ and interaction of this factor with β-catenin, leading to inactivation of Wnt signaling pathway [47]. Phosphatase and tensin homolog (PTEN) is a tumor suppressor frequently mutated or inactivated in a large number of cancers with high frequency. PTEN is a phosphoinositide-3-phosphatase that negatively regulates the Akt/PKB signaling pathway [48]. Oxidation of PTEN by NADPH oxidase, superoxide dismutase or enzymatic peroxidation of arachidonic acid by COX-1, COX-2 or 5-LOX leads to inactivation of this protein. Inactivation of PTEN by oxidative stress increases the activity of proto-oncogene Akt, phosphorylation of Akt substrates such as GSK3β, increased nuclear β-catenin signaling and therefore proliferation of many different cancers [49]. Furthermore, senescence in aging stem cell can also be induced by Wnt/β-catenin signaling pathway. Generation of ROS leads to the activation of Wnt and induction of senescence in cells; however, the molecular mechanism of this cascade remains to be elucidated [9].

6. Targeting wnt signaling as a potential treatment strategy for cancer

In the last decade, the Wnt/β-catenin signaling pathway has turned out as an attractive target for developing anti-cancer drugs in big pharma [50]. The most important reason for the focus on this target, is that Wnt/β-catenin signaling plays a major role in the

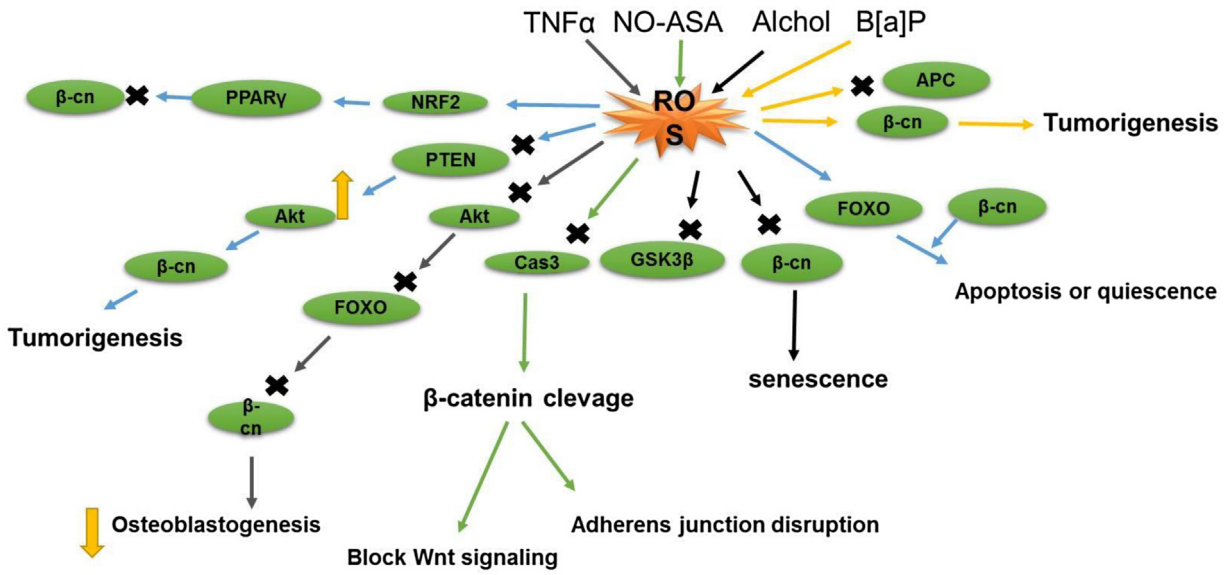

Fig. 3. The overall schematic representation of the interaction between oxidative stress and Wnt signaling pathway. Induction of oxidative stress by multiple factors, affects downstream proteins in Wnt signaling pathway, which can bring about numerous cellular responses including tumorigenesis, apoptosis and senescence.

regulation and maintenance of cancer stem cells (CSC) proliferation [51]. Currently, three main strategies are pursued for targeting Wnt signaling; 1) targeting receptor/ligand interactions, such as inhibition of the LRP5/6 co-receptors and Fzd family members, 2) targeting cytosolic signaling components, such as suppression of CK1 family, GSK3β and Axin and 3) targeting the nuclear signaling components by e.g. inhibition of members of the TCF/LEF family [51]. On the other hand, defects or upregulation of the target proteins with essential functions in DDR and repair are common in cancers, and may be triggered by both genetic and epigenetic insults [52]. Inhibition of the DDR proteins can be used to enhance the efficacy of radiotherapy and chemotherapy, and also to selectively kill cancer cells with deficiencies in special DNA repair pathway(s) based on the principle of synthetic lethality [53]. For example, it has been reported that canonical Wnt/β-catenin signaling has a pivotal role in determining the sensitivity of intestinal stem and progenitor cells (ISPCs) to DNA damage in the intestinal epithelium of mice. In line with these findings, cells with higher activity of Wnt/β-catenin respond better to DNA damage-induced depletion. More interestingly, the activation of canonical Wnt signaling causes a significant increase in radio-sensitivity of ISPCs, while suppression of Wnt signaling reduces it, both *in vitro* and *in vivo*. This finding and the results of other similar studies could be relevant for the accumulation of genetic changes in the context of DNA damage during carcinogenesis as well as for therapeutic targeting of Wnt signaling in cancer stem cells with high levels of DNA damage [54]. Another study investigated the effects of inhibiting Wnt/β-catenin signaling on the H_2O_2-mediated cell death. Treatment of human periodontal ligament fibroblasts (hPLFs) with Wnt1 was shown to suppress the H_2O_2- induced decrease in the viability and MMP levels, and targeting of Wnt/β-catenin signaling by specific siRNA blocked the protective effect of Wnt1 against H_2O_2-mediated damage to hPLFs. In other words, inhibition of Wnt pathway accelerated the H_2O_2- induced cell death [55]. However, more focused studies will be required to explore the potential application of targeting Wnt signaling in cancer (Fig. 3).

7. Conclusions

Targeting DNA repair machinery has been a hot topic in cancer treatment in the last decades. Inhibition of elements involved in DDR has the potential to enhance the efficacy of radiotherapy and chemotherapy. This can be used to selectively kill cancer cells with deficiencies in special DNA repair pathway(s) based on the concept of synthetic lethality. We have discussed the multitude of interactions that have been studied between Wnt signaling and DNA repair. Furthermore, we reviewed the ways by which oxidative stress can affect the Wnt signaling and therefore, DNA repair. The increase in our knowledge of these phenomena can help design better and more effective therapeutics to selectively target different components of these pathways to kill cancer.

Conflicts of interest

The authors have no conflicts of interest in regard to this research or its funding.

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