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Review Article

# Crosstalk between P53 and DNA damage response in ageing

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ABSTRACT

Ageing is a sophisticated process, accompanied by reduction in general physiological capacity and increase in mortality and death, stemming from damage accumulation over time. Various signaling pathways are known to be involved in the functional decrease in various organs in ageing humans. One of the most prominent pathways is DNA damage response (DDR), which is responsible for maintenance of the genomic integrity and stability. Insufficient or dysfunctional DDR signaling and the subsequent accumulation of potential DNA lesions are associated with the initiation/progression of various human pathologies including ageing. As a tumor suppressor gene, with critical functions in the ageing process, p53 is considered as a DDR centerpiece. In this review, we aim to discuss the interactions between p53 and DDR signaling and their contributions in ageing.

## 1. Introduction

Ageing is a universal event that is common in almost all living organisms. The important aspects of ageing are the loss of functionality in organs, tissue degradation and reduction in the function at cellular and molecular level. In mammals and especially in humans, these characteristics are manifested in the development of pathologic processes and illnesses associated with ageing [1]. These include atherosclerosis, heart failure, neurodegeneration, Parkinson's disease, Alzheimer's disease, macular degeneration, osteoporosis, pulmonary insufficiency and renal failure, among others. Various processes are involved in the formation and progression of ageing. While some mechanisms promote ageing, others prevent its progress. DNA Damage Response (DDR) processes, constituting the cellular response to DNA damage (resulting from ionizing radiation, oxidative stress and chemical agents), is among the most important preventive mechanisms. DDR is a vast signaling network encompassing the repair mechanisms and numerous signaling pathways. Any defects in the DDR systems can cause related syndromes or complications, for example Xeroderma pigmentosum, Ataxia telangiectasia and Fanconi anemia [2]. Such conditions are related to ageing complications and affect the lifespan of patients. The DDR network is composed of its sensors, transducers, mediators and effectors. One of the DDR effectors is the p53 protein [3]. p53 is a famous tumor suppressor that has many interactions with other proteins, cell signaling pathways and networks in the human body [4]. This protein functions in controlling the cell cycle, apoptosis, cellular responses to stress and DNA repair. Also, activation of p53 can modulate and regulate the cellular senescence process and ageing. The increased p53 expression has been observed in senescent cells. The association of p53 with ageing mechanisms and proteins involved in the ageing process has several different angles, and DDR network communications with p53 have a significant impact on these interactions [5]. In this review, we will focus on the crosstalk between the p53 and DDR in the ageing process, as well as the interaction of DDR and p53 with proteins and mechanisms that are involved in ageing. Finally, we discuss the therapeutic advancements in ageing-related diseases by utilizing the therapeutic potential of p53.

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## 2. DNA damage response

All living cells are constantly threatened by exogenous hazards, which are capable of damaging the cellular DNA, rendering it dysfunctional. Throughout evolution, a signaling cascade has been formed which systematically recognizes the damage, and takes proper action [6]. This signaling pathway is referred to as the DDR pathway, and is composed of DNA damage sensor molecules, mediators, transducers and finally effector molecules. Many agents have the capacity to damage the DNA, including UV light, ionizing radiation and chemical toxic agents. Also the DNA is in constant threat by endogenous factors, such as replication errors or by-products of cellular metabolism [7]. DNA damage can be broadly classified into single strand DNA damage and double strand DNA breakage. These two classes have their specific damage sensors. γH2AX and the MRN complex is responsible for sensing damage in the double strand break, while RPA, and the complex of RAD1, RAD9, RAD17 and HUS1 are responsible for sensing single strand DNA damage [8]. These sensors play an indispensable role in promoting the function of transducer molecules, which are activated upon sensing of the DNA damage. The serine/threonine kinase ATM is the transducer of double strand breaks. ATM phosphorylates downstream DDR mediators, including CHK2, MDC1 and 53BP1 [9,10]. ATR, in combination with ATRIP, exerts the same role in the single strand DNA damage pathway, and phosphorylates CHK1, TopBP1 and Claspin. It is noteworthy to mention that although a distinction has been made between the function of ATM and ATR, they are closely linked and it is suggested that these two molecules are able to regulate each other's function [11–13]. For instance, one molecule involved in linking the two pathways, and also acting as a solo mediator of DNA damage is BRCA1. This molecule is induced by DNA damage, localizes to the damage site, and activates downstream effector molecules [14]. The fourth group of molecules, which are downstream of the aforementioned molecules and are thus regulated by their collective action, are the effectors. The interaction between various stages of DDR determines the cell fate, which ranges from DNA repair, cell cycle arrest and apoptosis to senescence [15]. One of the central effector molecules deciding cell fate is p53. p53 is activated by both damage sensing pathways, and also by BRCA1, and is capable of interacting with downstream effectors such as DNA repair enzymes [16], cell cycle proteins such as cyclin dependent kinases [17], apoptosis regulators such as BCL-2 [18], and also molecules involved in senescence [19]. The function of p53 is so crucial for DDR that mutations and aberrations are associated with wide-dysfunction of the entire cascade, best demonstrated in Li-Fraumeni syndrome [20], a condition which is known for sarcomas and invasive cancers in early periods of life [21].

## 3. P53: a DDR effector

p53 is the central effector molecule in DDR, and is a key regulator of multiple downstream signaling pathways leading to apoptosis, DNA repair, senescence and cell cycle arrest. Under normal conditions, p53 is targeted via MDM2 (human homolog of mouse double-minute-2), which ubiquitinates p53, resulting in its degradation. But if the DDR cascade is activated, ATM and ATR phosphorylate p53 on Ser15, while downstream kinases phosphorylate it at Ser20 [22]. This enables p53 to evade degradation, and accumulate in the nucleus, promoting the downstream signaling of DDR in both transcriptional and non-transcriptional manners [23]. Based on the extent of DNA damage, p53 takes role in pro-survival and anti-survival pathways. In its pro-survival role, p53 induces cell cycle arrest and DNA repair. p53 regulates proteins such as ADD45, BTG2, REPRIMO, B99 (GTSE-1), hematopoietic zinc finger protein (HZF) and MCG10, which promote G2/M arrest. It also activates p21 and 14-3-3 proteins, which induce S phase arrest. p21 is also able to induce G1 arrest by inhibiting cdk2 and cdk4 [24,25]. Regarding DNA repair, p53 regulates a wide array of genes, the most important being XPC, DDB2 and XPE from nucleotide excision repair and global genome repair, MLH1, MSH2, PCNA and PMS2 from mismatch repair and RAD51, WRN, RECQ4 from Homologous Recombination pathways. p53 is also capable of regulating base excision repair in a cell cycle-dependent manner, as it is able to induce cell cycle progression in G0-G1, while repressing it G2 [16,26].

Regarding the role of p53 in anti-survival pathways, multiple interactions have been found between apoptosis and p53. p53 can promote the intrinsic and extrinsic apoptosis pathways [27]. In the extrinsic pathway, p53 induces the expression of Fas, DR5 and PERP, which are transmembrane proteins responsible for initiating the apoptotic signaling [28]. It also induces DR5/KILLER, an organ specific receptor found in the spleen, intestine and thymus [29]. In the internal pathway, p53 effects the BCL-2 family of molecules, and up-regulates those members of this family that promote apoptosis, shifting the balance between pro-apoptotic and anti-apoptotic molecules [27].

## 4. Molecular mechanism of ageing

In order to promote the human longevity, determination of responsible molecular processes and their effect on the senescence is necessary. Many age-related diseases result from dysregulation of pathways engaged in a healthy ageing process, such as proteostasis and autophagy. Indicating the effect of molecular mechanisms involved in ageing and age-related diseases such as Alzheimer's and Parkinson's diseases [30], will lead to a more profound understanding of the healthy ageing process and thus, will help to improve the quality of life in elderly, who are vulnerable to age-related diseases.

Telomeres, the repetitive sequences at the terminal portions of chromosomes, protect genetic information on chromosomes from damages throughout each division cycle [31]. Telomere length is an important predictive factor of the lifespan of the cell, as many studies reported the significance of telomeres for extended longevity of cells in zebra finch, mice and other organisms [32]. Long telomeres in *Caenorhabditis elegans* are associated with increased resistance against environmental stress [33]. On the other hand, studies reported significant telomere shortening after each replicative cycle and due to stressful conditions in human cells. Additionally, Hayflick limit, which is the number of possible cell division cycles before the occurrence of cellular senescence, is reported to be due to telomere shortening. Moreover, telomere shortening is associated with many age-related conditions such as Alzheimer's disease and deteriorated innate immunity in the elderly [30].

Sirtuin proteins, e.g. SIRT3 and SIRT4, also play an essential role in cell durability. In some organisms such as *Saccharomyces cerevisiae*, by modifying the fragmentation of the nucleolus, sirtuins induce shifting of telomeres into the nucleolus, leading to progressive malfunction of the cell. As a result, the degradation of nuclear shape and dissociation of heterochromatin from the periphery occurs in ageing [34]. On the other hand, mutations in insulin-like growth factor 1 (IGF-1) signaling lead to compensation of these defects and extended cell lifespan (Ref).

Transcriptional regulation is one of the most critical molecular aspects of ageing since all other age-related changes take place through transcriptional modification of signaling pathways such as Target Of Rapamycin (TOR) and IGF-1 Signaling (IIS) pathways as well as Heat Shock Factor (HSF-1) and SKN-1/Nrf transcription factors [35]. TOR is a stress and stimuli reactive pathway, which modifies other signaling pathways by regulating the expression of various genes. IIS pathway induces the co-translocation of PQM-1 and DAF-16/FOXO into the nucleus [36]. These genes are associated with maintaining cellular health and could promote some responses such as growth, development, stress response, and longevity. As a result of cellular senescence, the coexistence of these two factors and consequently, deteriorates the cellular health. HSF-1 modifies protein quality control, cytoskeletal integrity, and heat stress resistance, which affects cellular durability (Ref). SKN-1/Nrf factor also affects longevity and extracellular collagen matrix in ageing [37,38]. Protein translation is an another important

control mechanism in the regulation of senescence; in some organisms (worms and flies) [39], down-regulation of translation occurs after reduced nutrient availability via TOR and IIS/FOXO signaling, causing an increase in lifespan [40]. Another example of modulating protein translation for prevention of ageing is shown in *C. elegans* (loss of eukaryotic initiation factor 4 F (eIF-4 F)*/ife-2*) [41].

Another important phenomenon related to ageing is proteostasis. Proteostasis is a mechanism for maintenance of protein quality and is necessary for longevity of the cell. In this mechanism, misfolded and damaged proteins are removed from the cellular pool and replaced with newly synthesized proteins [42]. Molecular chaperones play an important role in this process by modulating the misfolded proteins. Small heat shock proteins are members of these chaperone family. Dysregulation of proteostasis leads to ageing of the organism [43]. IIS and FOXO regulate the healthy ageing and can modulate proteostasis. It has been shown that protein aggregation is decreased in human cells with reduced IIS (Ref). Misfolded proteins are involved in the pathology of many age-related diseases; therefore, healthy proteostasis is correlated with health in ageing [44]. One of the other mechanisms involved in ageing is the unfolded protein response (UPR) which is related to ER-associated degradation (ERAD) pathway, and monitors the unfolded amino acid chains [45]. The disruption of UPR is associated with Alzheimer's and Parkinson's diseases. SIR-2.1 regulates the UPR in an insulin dependent or independent manner [46]. In "premature-ageing" diseases such as Hutchinson–Gilford progeria, the lamins at the nuclear envelope are organized incorrectly. This condition makes cell susceptible to oxidative damage and DNA breaks, indicating that nuclear organization is essential for maintaining tissues in a healthy condition [47]. Hutchinson–Gilford progeria patients display extreme ageing phenotypes at a young age [48].

Autophagy is an important process necessary for longevity. Autophagy degrades useless organelles and proteins and can be subdivided to three types: macroautophagy, microautophagy and chaperone-mediated autophagy. Reduction in the normal rate of autophagy in Alzheimer's disease can cause accelerated ageing. Yet another type of autophagy seen in the mitochondria called mitochondrial autophagy (mitophagy) is also critical for prevention of ageing [49].

The oxidative stress and ROS levels in the body correlate with ageing. In a study on *C. elegans*, it was shown that defects in the oxidative phosphorylation can result in extending lifespan [50]. Furthermore, oxidative stress products and ROS can damage the extracellular matrix (ECM) proteins. Cytoskeletal disruptions can cause age-related degenerative neural diseases such as Alzheimer's disease. The SM22 actin filament cross-linking protein has been identified as a biomarker of ageing across a range of organisms, including yeast, *Drosophila*, and also humans [51]. Another aspect of ageing is replicative ageing that is related to number of cell divisions. Replicative ageing is associated with TOR signaling and SIRT2 [52,53], and results from a combination of events that include the instant reduction of telomeres length during cell proliferation. The cells which undergo ageing communicate their internal status to their neighboring cells through senescence-associated secretory phenotype (SASP). SASP has been demonstrated in mice, flies and humans and plays a significant role in regulation of ageing [54].

## 5. DNA damage response in ageing

Ageing is preserved in all mammals, and is characterized by telomere attrition, mitochondrial malfunction, stem cell depletion, dysfunctional cell signaling, genome instability, epigenetic abnormalities, reduced proteostasis and altered nutrient sensing [55]. It is hypothesized that the aforementioned alterations in previously normal functions, lead to accumulated damage to the cellular DNA, resulting in the initiation of DDR, and its two important end points, apoptosis and senescence. p53 is an important effector in both of these functions, and alongside other DDR molecules such as p21 and ATM, directs the cells toward these pathways [56]. Another important functionality of DDR in preventing the premature ageing is the initiation of DNA repair. Studies have shown that any sorts of defects in DNA repair proteins in different DNA repair pathways, consisting of base excision repair, non-homologous end joining, homologous recombination, nucleotide excision repair and cross-link repair are associated with premature ageing [57]. This is best shown by syndromes characterized by DNA repair defects. Patients affected by these syndromes, present lesions and pathologies common in the elderly. Examples are Xeroderma pigmentosum, Fanconi anemia, Nijmegen breakage syndrome and Ataxia telangiectasia [58]. Other examples are cancers and degenerative diseases. Individuals effected by defects in the DDR process are effected by malignancies in their early decades of life, which are normally presented in other individuals within their sixth or seventh decade [59]. A similar pattern is also true for neurodegeneration, as individuals affected by DDR related syndromes show early signs of decreased mental capacity and dementia [60]. Further evidence in this regard relates to less characterized molecules which are not considered as part of the DDR cascade, but are localized to DNA damage sites involved in the ageing process. Examples are Ubiquitin-Specific Protease 3, N-Terminal RCC1 Methyltransferase 1 and RecQ-Like Helicase Sgs1. Malfunctioning of these molecules is associated with premature ageing, infertility, reduced body mass, and other degenerative changes [61–63].

## 6. Regulation of ageing process by P53

p53 is an ageing regulator gene because of its role as a tumor suppressor and also in cell cycle control which is directly linked to senescence. Moreover, p53 can perform its functions as a tumor suppressor through regulation of senescence. In the mouse model studies it is shown that persistent low level activation of p53 causes premature ageing. In this line, p53 interacts with some important molecules and various pathways. p53 can control the ageing process via its effects on many mechanisms and molecules. Some of them, discussed below, are E2F7, sirtuins, mTOR, reactive oxygen species (ROS) and autophagy [64].

### 6.1. P53 interaction with E2F7 in ageing

E2F7 is a transcription factor and a member of the E2F-family [65]. E2F transcription factors are essential components of the Retinoblastoma (Rb) pathway. These proteins are involved in controlling cell-cycle progression. E2F7 is induced by E2F1 in late G1 phase of cell-cycle. Aksoy et al. noted that E2F7 is up-regulated in a p53-dependent manner; they also reported that this new target of p53 is involved in senescence and cell-cycle arrest. It has been seen that cell-cycle progression is accelerated upon E2F7 loss. E2F7 binds to DNA and represses the expression of E2F1 and several other E2F target genes [66]. Some studies indicated that E2F7 may be a necessary protein for such a negative feedback loop that controls the function of E2F proteins and their targeted genes. Furthermore, inhibition in the expression of other genes essential for mitosis, for instance cyclin A, cyclin B and cdc2/cdk1, occurs in aↄ E2F7-dependent fashion. E2F7 interfere in modulation of senescence by p53 and Rb [66,67]. Mitxelena et al. found that E2F7 activity is associated with the suppression of DNA repair reactions. They also noted that E2F7 is recruited to the promoter regions of FANCE, FANCI, RAD51, CTIP, BRIP1 and BARD1, which are associated in cell-cycle control, DDR and even in ageing, implying their direct transcriptional repression by E2F7 [68].

### 6.2. P53 interaction with mTOR in ageing

The mammalian target of rapamycin (mTOR) is a key molecule under starvation conditions. In the presence of nutrients, mTOR is active and promotes cell growth and anabolism in the organism; but when nutrients are unavailable, mTOR is inactivated and drives cell to catabolism and growth arrest [69]. mTOR controls the rate of protein

synthesis via phosphorylation of S6 kinase 1 and eIF4E-binding protein 1, resulting in the regulation of mRNA translation. mTOR is also known as the master regulator of senescence in animal models such as flies and mice [70,71]. In studies of caloric restriction for prolonging the lifespan of animals, it has been proven that mTOR is essential for the benefits of caloric restriction. On the other hand, sustained mTOR signaling promotes cell senescence and ageing of organisms [72]. Inhibition of mTOR can impede the expression of some senescence markers. In a study on *Drosophila melanogaster* during caloric restriction, inhibition of mTOR decreased ROS production in mitochondria, improved mitochondrial respiration and prolonged lifespan. These events resulted from increased translation of mitochondrial electron transport chain components, that in itself was mediated by activation of eIF4E-binding protein 1, a substrate of mTOR [50]. It is also known that Rheb (Ras homolog enriched in brain) which is an mTOR-activator protein, can initiate senescence in an mTOR-dependent manner. Moreover, p21 induces senescence in conditions when mTOR is inactivated or inhibited by rapamycin [73]. Thus, mTOR is pivotal for establishment of ageing in cell cycle arrested cells. Furthermore, mTOR is involved in controlling the ageing by autophagy. mTOR promotes senescence by suppression of autophagy using p53 [74]. In addition to the above-mentioned findings, p53 can inhibit the mTOR signaling pathway. p53 controls sestrins and they can repress the activity of mTOR. On the other side, p53 affects the AMPK (AMP-activated protein kinase) and this kinase inactivates mTOR. Also in the PI3K pathway, p53 can up-regulate PTEN, and this event results in down-regulation of mTOR. p53 can even have an anti-senescence role by interaction with mTOR and p21. P53 can reverse the p21-induced cell-cycle arrest, through inhibition of mTOR [75]. These data indicate that regulation of ageing by p53 is a complex function involving various pathways and molecules.

### 6.3. P53 interaction with sirtuins in ageing

An important element of the relationship between p53 and sirtuins is SIRT1. This crosstalk is involved in numerous biological processes such as ageing. SIRT1 belongs to a family of class III histone deacetylases [76] and was initially known as a longevity gene in some organisms. This $NAD^+$-dependent protein deacetylase plays roles in modulating the chromatin structure for DNA repair and processing. SIRT1 is also involved in transcriptional control network because of its role in deacetylation of some co-factors or transcription factors [77]. p53 is a substrate for SIRT1. SIRT1 can affect senescence, cell-cycle and stress resistance through deacetylation of p53. Both of SIRT1 and p53 are involved in the regulation of ageing through their roles in responding to DNA damage. While p53 directs the cells to apoptosis for removing damaged cells, SIRT1 promotes cell survival and repair. These opposite effects are coordinated between p53 and SIRT1. Several studies have shown that SIRT1 is suppressed in senescent cells. SIRT1 is also able to deacetylate target histone and non-histone proteins. Deacetylation of p53 can inhibit its effects on some genes in the cell, for example those involved in ROS production, apoptosis and specially senescence [78]. In another study, acetylation of p53 resulted in accelerated senescence, especially in cells in which the last seven lysine residues of p53 had acetyl-mimicking mutations; SIRT1 antagonizes these processes. In light of the above, it seems that SIRT1 hamper the induction of senescence by deacetylation of p53. This effect turns SIRT1 into an oncogene. However, in studies on mouse models, SIRT1 functions as a tumor suppressor and reduces cancer incidence [79].

### 6.4. P53 interaction with ROS in ageing

The ‘free radical theory of ageing’ states that cellular ROS has direct effects (mostly harmful) on the overall health of organisms. ROS is a major determinant of senescence at the molecular level [80]. If not detoxified properly and promptly, ROS species can damage cellular organelles and macromolecules. The oxidative damage from ROS can reduce lifespan by harming various contents of the cell. Mitochondria are the major source of ROS. The ROS produced in mitochondria cause vicious loop [81] where ROS damages mitochondria and mitochondria produce even more ROS. This event facilitates the process of senescence and ageing, leading to age-related diseases. p53 could affect ageing by its dual opposing functions in ROS regulation. For progression of senescence, p53 activates the apoptosis process in which intracellular oxidative content and ROS will increase. On the other side for prevention of ageing, p53 can up-regulate the antioxidant genes (i.e. glutathione peroxidase 1, superoxide dismutase 2) and increase the antioxidant contents of cell, which in turn reduce the intracellular ROS levels [82]. ROS has also been referred to in a hypothesis called ‘mitochondrial theory of ageing’. In this theory it is believed that the two mitochondrial functions, namely energetic metabolism and production of ROS, have such an important role in regulation of lifespan, that imbalances between these two processes can induce ageing. Furthermore, in a study on telomerase deficient animals, telomeres were found to link p53 and ROS in the ageing process. Shortened telomeres were shown to initiate DDR resulting in p53 activation and leading to age-related diseases. Active p53 inhibits expression of peroxisome proliferator-activated receptor gamma, coactivator 1 alpha and beta (PGC-1a/b) in cells with telomerase dysfunction. PGC repression leads to increased ROS levels and reduced mitochondrial biogenesis, because of the regulating role of PGC in mitochondrial energetic metabolism [83]. On the other hand, ROS can activate mTOR. Therefore p53 can affect mTOR and consequently senescence by its regulatory effect on ROS [84].

### 6.5. p53 interaction with autophagy in ageing

Autophagy is a process in which dysfunctional or unnecessary cellular organelles and excess intracellular materials are degraded. Autophagy is classified into three distinct types, including macro-autophagy, micro-autophagy and chaperone mediated autophagy. Macro-autophagy is initiated by the formation of the phagophore (isolation membrane), which is derived from the endoplasmic reticulum. The next step is the formation of the autophagosome and its fusion with lysosomes [85]. In the two other types, autophagosome is not formed and the lysosome acts as the initial site for degradation [86]. There is an extensive relationship between ageing and autophagy. Early studies have reported that loss of function mutations in genes such as Atg1 (Unc-51), Atg7, Atg18 and Beclin-1, all involved in the process of macro-autophagy, cause a decreased life span [87]. Further studies revealed that important signaling pathways including PI3K/AKT/mTOR signaling and insulin-growth factor signaling pathway, contribute significantly to autophagy, and thus longevity [88]. More specific studies regarding the role of autophagy on cellular and organismal health have suggested that autophagy plays an important role in neuronal health. For instance, autophagy reduces the cellular damage caused by polyglutamine expansion proteins, decreases inflammation in hepatocytes by clearing a mutant dysfunctional form of α-1-antitrypsin, and regulates the immune system, for example by presentation of intracellular antigens via MHC Class II antigen loading compartments [89–93]. As mentioned, autophagy is regulated by the activation or suppression of upstream signaling pathways, such as PI3K and growth factor singling. One other important pathway in regulation of autophagy is DDR; but autophagy itself, is a regulator of DDR proteins such as p53. As mentioned, p53 can direct cells in both pro-survival and anti-survival pathways. Autophagy is able to tilt this balance by promoting pro-survival signals, and also to negatively regulate the DDR cascade as a whole [94]. Interestingly, among the DDR molecules, p53 is able to exert great regulatory effect on autophagy. For instance, p53 indirectly regulates the expression of genes such as damage-regulated autophagy modulator, Isg20L1, Ulk1 and Atg7 [95–97]. This regulatory role is further explored in a study by Verma et al., where it was shown that p53-detective cells had increased rates of cell death resulting from

Advanced Glycation End products (AGEs), which are formed during prolonged episodes of diabetes mellitus. Interestingly, the major functional change that occurred in these cells was the reduction of autophagy, shown by impaired autophagosomes clearance. Interestingly, NF-κB was up-regulated in these defective cells, which up-regulated NEDD4, a molecule which targets Beclin-1 [98]. This interaction between inflammatory pathways such as NF-κB and survival pathways is important, as inflammation could act both to promote cell death and generate pro-survival signals, by effecting DDR downstream effectors such as the effector molecules of apoptosis [99,100]. Another major field in cell survival and ageing is cancer. It is widely recognized that cancer cells high-jack normal cellular coping mechanisms to endure the unfavorable tumor environment and evade cell death. Salminen A et al. found that pro-survival pathways such as AMPK signaling utilized transcription factors such as p53 to stimulate autophagy, and change cellular metabolism to evade cell death [101].

## 7. Crosstalk between P53 and DDR in ageing

As mentioned above, DDR consists of a protein collection, including DDR sensors, transducers, mediators and effectors. p53 is one of the main DDR effectors. There are two subsets of p53 target genes: a) negative regulators of cell cycle progression, for example growth arrest and DNA damage-inducible gene (GADD45a), the p21 cyclin-dependent kinase inhibitor 1A (CDKN1A) and 14 3-3 s; b) apoptosis-promoting genes, such as PUMA (p53 up-regulated modulator of apoptosis), BAK (Bcl-2 antagonist/killer) and BAX (Bcl-2-associated protein X) [102].

ATR is a DDR protein which is activated in response to a replication stress and its activation can induce the senescence of cells even in the absence of actual DNA damage. ATR activation engages the p53/p21 and/or p16INK4a/pRB pathways, so effects of ATR for activation of ageing process, will be through p53 activation [103]. Chronic activation or over-expression of proteins such as p53, pRB, p21, or p16INK4a is generally sufficient to induce senescence and growth arrest [104]. On the other hand, ATM that plays an important part in response to ionizing radiation (IR) and is a DDR transducer, controls the initial phosphorylation of p53 after DNA damage. In other studies, it has been revealed that both ATM and ATR can phosphorylate p53 at its Ser15 site [105]. In a study by Armata et al., it was shown that the mice with non-phosphorylable alanine instead of Ser18 on p53 showed signs of accelerated ageing. This study demonstrated that physiological activity of p53 is necessary for preventing the age-related damage to tissues [106]. There is another phenomenon related to ageing known as oncogene induced senescence (OIS). After activation of oncogenes, the cell undergoes hyper-proliferation. This is a trigger for DDR, after which p53 is activated and induces senescence. In lack of ATM cells fail to execute senescence signaling [107]. Moreover, studies have shown that CHK2 (a DDR mediator) can phosphorylate p53 on Ser20 at the N-terminal transactivation domain [108].

It has been reported that stable suppression of p53 expression in senescent fibroblasts leads to their immortalization and rapid cell cycle re-entry. This indicate that p53 has an important role in initiation and even maintenance of senescence [109]. Indeed, p53 and pRB pathways control senescence as master transcriptional regulators. These regulators work by inducing widespread changes in gene expression. The ageing phenotype can be ameliorated by p53 mutation and depletion of PUMA, which is a target of p53 and has a significant role in survival and apoptosis of stem cells [110]. The downstream effector of p53 is p21. On the other side, p16INK4a is a positive upstream regulator of pRB; both are cyclin-dependent kinase inhibitors and potent negative regulators of the cell-cycle progression. It is proven that CDKN1A/p21 is up-regulated during replicative senescence. p21 is an essential mediator of p53-dependent cell-cycle arrest. The lack of p21 can abrogate senescence [111]. There are other pathways which work independently of the p53/p21 and p16INK4a/pRB pathways that can maintain the senescence arrest, but p53/p21 and p16INK4a/pRB pathways still play more important roles in the senescence program and ageing processes [112].

The crosstalk between p53 and DDR can affect the ageing process from different angles; for example, telomeres are affected in the process of ageing and cause ageing-related complications. Telomere dysfunction promotes DDR, but in this process, DNA repair is suppressed. Thus, DDR arrests cell division through p53 activation, and prevents genomic instability. Cells with dysfunctional telomeres experience persistent DDR signaling and p53 activation, so the senescence and growth arrest are enforced [113,114]. Also it is shown that genetic ablation of p53 can reduce the symptoms of ageing in mice with short telomeres [115]. In 2004 in a study by Scrable's group on mouse model with over-expressed p53 isoform, it was shown that accelerated ageing occurred in mouse and this mouse showed reduced lifespan and growth defect. In another study, the hyperactive p53 resulted in IGF signaling, which is a master regulator of ageing [35,116].

### 7.1. Clinical application of p53 and DDR in ageing

p53 is usually identified as a tumor suppressor gene with anticancer effects. But in fact, according to the studies discussed above, the other role of p53 is in the ageing process and its therapeutic potential can be considered in the treatment of age-related diseases (Table 1). In a study performed by Serrano's group using a super-arf/p53 mouse model it has been reported that the mice show increase in lifespan and improvement of age-related complications. This transgenic condition manifests p53

**Table 1**
p53 roles in ageing-related diseases.

| Age-related Disease | Intervention | Mechanism | Reference |
|---|---|---|---|
| Alzheimer's Disease | Dominant-negative p53 | Prevention of mitochondrial changes and dendrite degeneration | [125] |
| | Inhibition of p53 activity | Increase in NFκB transcriptional activity and enhanced expression of NFκB downstream targets | [126] |
| | Osmotin (a plant protein extracted from *Nicotiana tabacum*) | Inhibition of p53-mediated activation of apoptotic pathways | [127] |
| | Thymoquinone (natural compound in black seed (*Nigella sativa* seed)) | Induction of p53 and p53-downstream targets | [128, 129] |
| | Endocannabinoids (AEA & 2-AG) | Prevention of association of p-p53$^{Ser-15}$ with the lysosomes | [130] |
| Parkinson's Disease | Synthetic p53 inhibitors (PFT-α or Z-1-117) | Suppression of Bax production and apoptosis, reduced damage to nigrostriatal dopaminergic neurons and reduced depletion of dopamine | [131] |
| Autosomal recessive forms of juvenile Parkinson's disease (AR-JP) | Ubiquitin ligase parkin | Reduced p53 expression (and activity) and inhibition of ceramide-induced upregulation of CHK | [132] |
| Type 2 diabetes | Inhibition of p53 activity in adipose tissue (p53-knockdown) | Decreased activity of senescence-associated β-galactosidase, reduced expression of pro-inflammatory cytokines and improved insulin resistance in mice with type 2 diabetes-like disease. | [133] |
| Age-related Macular Degeneration (AMD) | Hydrogen | Inhibition of of Sirt3 downregulation, reduced expression of p53, p21 and p16 and decreased expression of ATM, cyclinD1 and NF-κB | [134] |

and $p19^{arf}$ over-expression, but maintains endogenous regulation of p53. $p19^{arf}$ also prevents the MDM2-mediated proteasomal degradation of p53 [117]. This finding indicates that existence and physiological function of p53 is required for prevention of ageing. In another study on mice with eroded telomeres, it was shown that genetic ablation of p53 reduces the symptoms of ageing [115]. Demidenko et al. found that p53 can suppress senescence by induction of cell cycle arrest. They noted that in p21-arrested cells, p53 changes the direction against the senescence and in favor of quiescence [75,118]. Quiescence is identified as a reversible arrest with preservation of proliferation capacity and no senescent morphology. Although it was thought in the past that tumor suppressors except p53 suppress ageing, but with regards to this finding, it has been claimed that p53 also follows the same rule.

Moreover, in a study by Yue et al. it is shown that Rg1, a component of ginsenoside has anti-senescence effects in hematopoietic stem cells. This molecule performs its role through the p53-p21 and p16-Rb pathways, indicating that p53 signaling pathway is a potential target for regulation of hematopoietic stem cell ageing [119]. In a study by Chang et al., it was demonstrated that p53 inhibitors may act as a treatment for age-related neurodegenerative diseases such as Alzheimer's disease [120]. It is shown that pifithrin-α, a synthetic inhibitor of p53, was effective against neuronal death induced by DNA-damaging agents, Aβ and glutamate. This molecule performs its role via different mechanisms, one of which is decreasing p53 DNA-binding activity. Also neurons treated with pifithrin-α have more resistance to damage and focal ischemic injury [121]. In another study by Zeng et al., protosappanin B, a bioactive dibenzoxocin derivative could prevent apoptosis-related events, stimulate the expression of GAP-43, and promote degradation of p53 via activation of its MDM2-dependent ubiquitination process [122].

Furthermore, it has been seen that loss of p53 results in amplification of the senescence-associated secretory phenotype (SASP) and pro-inflammatory state that is usually associated with ageing in organisms [123]. As a result, prevention of premature ageing and increase in longevity will be possible by controlled modification of p53. Also, p53 is the focus of attention in cancer treatment. Consequently, cancer can be prevented by controlled induction of senescence in target cells. Reactivation of p53 in tumor cells have been shown in multiple studies, to lead to a robust tumor regression mediated by induction of senescence [124].

## 8. Conclusion

DDR signaling is responsible for maintenance of the genomic stability and integrity. Any disruptions in DDR signaling pathways results in the functional decline of cells and tissues, associated with various pathological conditions. p53 tumor suppressor is a centerpiece in responding to DNA damage. p53 also modulates the DDR cascade for adapting the ageing organism to DNA damage. Recent studies open new avenues in investigating the complexity of DDR and the consequences of persistent DNA damage in ageing. Understanding the longevity assurance mechanisms related to DNA damage and their impacts on the ageing process can play a major role in finding ways of combatting ageing. In this regard, the etiology of ageing-associated diseases, the thorough function of p53, and its target genes need to be more investigated. **Acknowledgements** The authors would like to thank Clinical Research Development Unit, Shohada Hospital, Tabriz University of Medical Sciences for kind supports.

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