Egyptian Journal of Medical Human Genetics

REVIEW Open Access

Exploring the multiple roles of guardian of the genome: P53

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Abstract

Background: Cells have evolved balanced mechanisms to protect themselves by initiating a specific response to a variety of stress. The *TP53* gene, encoding P53 protein, is one of the many widely studied genes in human cells owing to its multifaceted functions and complex dynamics. The tumour-suppressing activity of P53 plays a principal role in the cellular response to stress. The majority of the human cancer cells exhibit the inactivation of the P53 pathway. In this review, we discuss the recent advancements in P53 research with particular focus on the role of P53 in DNA damage responses, apoptosis, autophagy, and cellular metabolism. We also discussed important P53-reactivation strategies that can play a crucial role in cancer therapy and the role of P53 in various diseases.

Main body: We used electronic databases like PubMed and Google Scholar for literature search. In response to a variety of cellular stress such as genotoxic stress, ischemic stress, oncogenic expression, P53 acts as a sensor, and suppresses tumour development by promoting cell death or permanent inhibition of cell proliferation. It controls several genes that play a role in the arrest of the cell cycle, cellular senescence, DNA repair system, and apoptosis. P53 plays a crucial role in supporting DNA repair by arresting the cell cycle to purchase time for the repair system to restore genome stability. Apoptosis is essential for maintaining tissue homeostasis and tumour suppression. P53 can induce apoptosis in a genetically unstable cell by interacting with many pro-apoptotic and anti-apoptotic factors.

Furthermore, P53 can activate autophagy, which also plays a role in tumour suppression. P53 also regulates many metabolic pathways of glucose, lipid, and amino acid metabolism. Thus under mild metabolic stress, P53 contributes to the cell's ability to adapt to and survive the stress.

Conclusion: These multiple levels of regulation enable P53 to perform diversified roles in many cell responses. Understanding the complete function of P53 is still a work in progress because of the inherent complexity involved in between P53 and its target proteins. Further research is required to unravel the mystery of this Guardian of the genome "*TP53*".

Keywords: *TP53*, Tumour suppressor protein P53, Apoptosis, DNA repair, Cellular senescence

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Background

Despite 40 years of research studies about various functions of tumour suppressor protein P53, new roles of P53 are still a work in progress. "The *TP53* gene (encodes for tumour protein 53), founded in 1979, has been extensively studied in cancer" [1]. "The protein P53 is a transcription factor encoded by the gene *TP53* which is the most commonly mutated tumour suppressor gene in human cancers, it performs multiple regulatory functions by receiving information, modulating and relaying the information, carrying out multiple downstream signals such as cellular senescence, cell metabolism, inflammation, autophagy, and other biological processes which control the survival and death of abnormal cells" [2, 3]. "P53 also plays a crucial role in determining cell's response to various cellular stress like DNA damage, nutrient deficiency, and hypoxia by inducing gene transcription, which controls the process of cell cycle and programmed cell death (apoptosis)" [4].

Generally, in a cell, P53 is an unstable protein that is present in meagre amounts inside the cell because it is continuously degraded by Mouse double minute 2 homologue protein (*MDM2*) [5]. These multiple functions of P53 attributed to its interaction with many target genes, which were discovered by gene ontology enrichment analysis [6]. P53 has a complex array of functions, which makes it a challenging protein to study. This review explores multifaceted roles of P53, summarizes different mechanisms through which it inhibits cell proliferation, and explains its role in apoptosis, autophagy, and metabolism.

Outline of the P53 family

TP53 belongs to a large family of genes whose other members include *TP63* and *TP73*, which have broad and complementary roles. "As species evolved, *TP53* of higher eukaryotic species got deviated from its family members *TP63* and *TP73* before the advent of large aquatic animals" [7]. "*TP53* has evolved to exhibit tumour-suppressive activities, a unique characteristic not shown by its homologs *TP63* and *TP73* that exhibits a role in embryogenesis" [8]. "P53 family members have a preserved framework, as shown in Fig. 1. In the figure there is an N-terminal transactivation (TA) domain" [10] which is a 42 amino acid sequence and it is vital for transcriptional activity, "replacing the amino acids Phenylalanine 19, Leucine 22 or Tryptophan 23 results in transactivation deficient mutant proteins" [11, 12], a proline-rich (PR) region that contributes to transcription activation, is essential for restricting cell growth [13] and is a highly conserved sequence-specific DNA-binding domain (DBD) that is present in between amino acids 100, and 300 forms a protease-resistant core [14, 15] that "identifies a core sequence pattern of 10-base pairs (PuPuPuCA/T.A./TPyPyPy, where Pu=purine, Py=pyrimidine)" [16].

"The DNA binding domain (DBD) tucked into a four- and five-stranded β sheet scaffold, which is anti-parallel and two-α helices that interact with DNA" [17]. "Most of the cancer-associated mutations are present in this region [15]. Oligomerization domain (OD) consists of amino acids 324 to 355 and mediates in the formation of P53 tetramer, which is a dimer of dimers" [18]. P53 cannot form tetramers when this region substitutes hydrophobic amino acids [19]. This domain also contains a nuclear export signal (NES), which is masked by P53 tetramerization resulting in trapping of P53 inside the nucleus, whereas monomers and dimers are transported to the cytoplasm [20]. "One study suggested that oligomerization is crucial to cell fate decisions" [21]. "Studies have shown that alternative splicing at C-terminal exons of both *TP63* and *TP73* yields three isoforms of *TP63* (α, β, γ) and seven

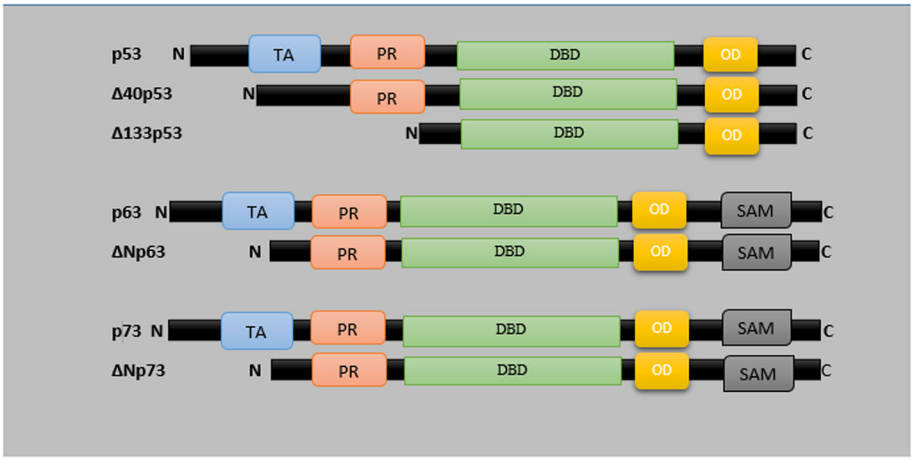

Fig. 1 The most important functional domains of the P53 protein family [9]

isoforms of *TP73* (α, β, γ, δ, ε, ζ, η) furthermore alternative promoter region in the gene family show possible transcriptional start sites that give rise to N-terminal truncated isoforms like Δ40P53, Δ133P53, ΔNp63, ΔNp73, these isoforms can show dominant-negative effects on P53, P63 and P73, on top of that N-terminal truncated isoform of P53 (Δ133P53) formed from the internal promoter in intron 4 of *TP53* gene lack transactivation and proline-rich domains" [22].

Main text

P53 and DNA damage response

P53 plays a central role in DNA damage response and considered "Guardian of the Genome". DNA damage response is dependent on the nature of the stress signal, the cell type, timing, and intensity of the stress signal. "DNA damage promotes Post-translational modifications (PTMs) on P53" [23], "whereas oncogenic stress activates Alternative reading frame (ARF) tumour suppressor protein to inhibit *MDM2*" [24]. "In response, P53 can activate cell cycle arrest, repair the damaged DNA, activates specific cell death pathways, and metabolic changes in the cell, as shown in Fig. 2" [26]. "DNA damage causes P53activation which induces an array of genes spanning multiple functions, using various genetic studies the best known P53 targets" [27] are (i) DNA damage response genes (e.g., damage specific DNA-binding protein 2 (*DDB2*) and *XPC* complex subunit, DNA damage recognition, and repair factor (*XPC*), (ii) "cell cycle arrest genes (cyclin-dependent kinase inhibitor1 (*CDKN1A*) encoding protein P21, Growth arrest and DNA-damage inducible alpha (*GADD45A*)" [27], (iii) "genes involved in apoptosis (*BCL2* binding component 3 (*BBC3*) (also known as *PUMA*) and *BCL-2*-associated X, Apoptosis regulator (*BAX*)" [27], (iv) metabolism (*TP53*-induced glycolysis regulatory phosphatase (*TIGAR*) and Aldehyde dehydrogenase one family, member A3 (*ALDH1A3*), and (v) "Post-translational regulators of P53 (*MDM2* proto-oncogene and *PPM1D* (protein phosphatase, Mg2+/Mn2+ dependent 1D) (also known as Wild-type P53-induced phosphatase 1(*WIP1*)" [27]. Expression profiling study identified many target genes of P53 whose number ranged from less than 100 to more than 1500 based on the conditions of P53activation and approaches used for data processing [28], "the main drawback was that they could not differentiate among the direct and indirect targets of P53" [28].

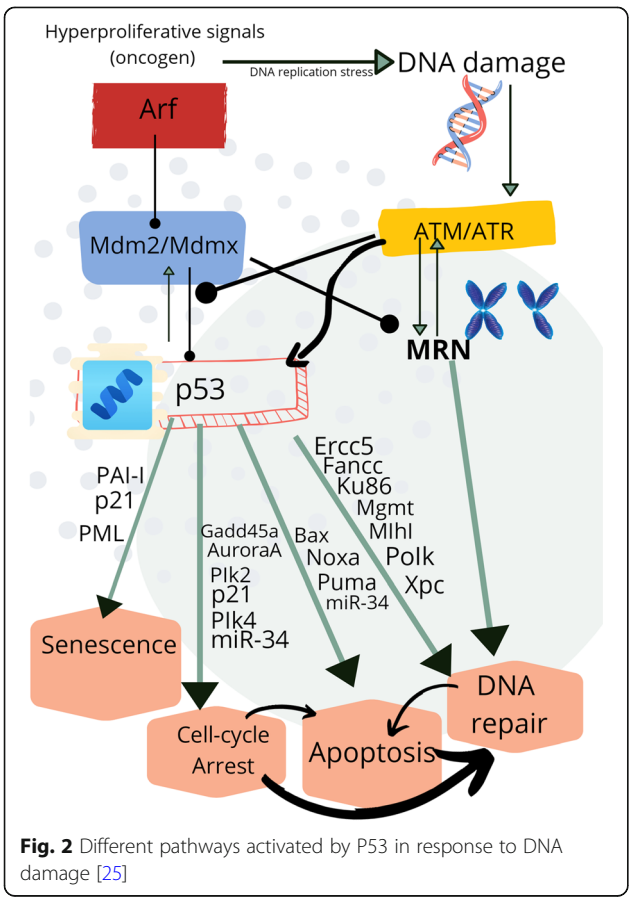

Fig. 2 Different pathways activated by P53 in response to DNA damage [25]

P53 dynamics in DNA damage response

P53 dynamics are also important in DNA damage response, and many profiles of P53 relating to time were identified using various models. "One important study conducted by Purvis et al. by using a mathematical model to explain the feedback loop of various stress signals like inactive P53, active P53, MDM2, and WIP1, based on the assumption that a constant source produced inactive P53 which was degraded by MDM2 and whenever the cell subjected to DNA damage, would result in the conversion of inactive P53 to active P53, and this conversion rate was reliant on the degree of DNA damage" [29]. "Later on, the active form of P53 is degraded by MDM2 protein" [29]. "In the model, Purvis showed that the levels of MDM2 levels were increased by P53 stimulation, whereas DNA stress induces reduced levels of MDM2 protein" [29].

"This model showed that various P53 targets associated with different cell fates like cell cycle control and DNA repair (*CDKN1A*), growth arrest and DNA-damage-inducible protein alpha (*GADD45A*), MDM2 and post-translational regulators of P53 (protein phosphatase 1 (PP1)) displayed a periodic fluctuation similar to P53 protein, for example when P53 was at the sustained level some target proteins like P21 and MDM2 also increased to a sustained level" [29]. "A significant observation in this study was that P53 target genes for apoptosis and senescence such as Apoptotic peptidase activating factor 1 (*APAF1*), *BAX*, *PML* nuclear body scaffold (*PML*) and Yippee-like 3 (*YPEL3*) were induced only at sustained P53 level but not by P53 pulse" [29].

"This model also studied how P53 dynamics influenced the cell fate and showed that cells with pulsing P53 dynamics recovered well from DNA damage whereas sustained P53 levels in cells lead to cellular senescence" [29]. More of such studies are necessary for understanding the effect of P53 dynamics on cell fate decisions.

P53 induces cell cycle arrest

In response to various cellular stress, P53 can activate the transcriptional upregulation of *CDKN1A*, which encodes for cell cycle inhibitor P21 [30]. P53 can also activate other genes like *GADD45A*, which also contributes to cell cycle arrest [31]. Following DNA damage, a myriad of DNA-protein activation occurs. For example, DNA damage kinases like ATM serine/threonine kinase (ATM) or ATR serine/threonine kinase (ATR) are activated and phosphorylate various proteins Checkpoint kinase 1 (CHEK1) or Checkpoint kinase 2 (CHEK2), Nibrin (NBN of the MRN repair complex), MDM2, and P53 to arrest cell cycle [32]. "In a cell cycle to progress from G1 to S phase, it requires active G1 cyclin/CDK complexes (Cyclin-dependent kinase), activated P21 inhibits cyclin D/CDK4 and cyclin E/CDK2 complex and thus blocks the phosphorylation of protein substrates essential for the onset of S phase" [33]. "Cyclin/CDK complexes also phosphorylates tumour suppressor RB transcriptional corepressor 1 (RB1), which results in dissociation from E2F family transcriptional factors and progression of DNA synthesis" [34]. "P21induced by P53 also inhibits phosphorylation of RB protein and blocks cell cycle, thus linking two tumour suppressor genes in same cell cycle checkpoint" [34].

"Numerous studies showed evidence for the above mechanism, for example, cells when exposed to gamma radiation lead to the expression of P21 causing inhibition of CDK activity" [35]. "In another study defect in DNA damage-induced G1/S checkpoint was seen in mouse embryo fibroblast derived from a cyclin-dependent kinase inhibitor 1($P21^{WAF1/CIP1}$) deficient mice" [36]. "The cell cycle arrest activity of P21 is well studied, but there are many other P53-induced genes that play a role in cell cycle arrest" [37]. "For example, protein phosphatase, Mg2+/Mn2+ dependent 1D (*PPM1D*) is a growth-suppressive protein phosphatase, which is a vital regulator of DNA damage response and oncogenesis may also play a role in G1/S phase arrest" [37]. "WIP1 dephosphorylates the DNA damage-induced phospho sites in H2AX variant histone (H2AX), ATM and CHK2 kinases" [38, 39], "leading to reduced signalling and activation of P53 which is a transcription factor for turning 'ON' expression of many genes involved in DNA repair, cell cycle, cell death" [40, 41]. Transcription factor P53 also targets Cyclin G1, which is a novel member of the cyclin family. P53-mediated transcriptional upregulation of 14-3-3 phospho-serine/phospho-threonine binding proteins (14-3-3σ) expression also plays a role in cell cycle arrest. Upon DNA damage, dephosphorylated P53 binds to promoter region 1.8 kb upstream of 14-3-3σ transcription start site leading to increased expression of 14-3-3σ which results in detachment of CDK1/Cyclin B complex in the cytoplasm and blocked interaction of Cell division control protein 2 homologue (CDC2) with CDK1 and entry of cell into mitosis thus sparing time for repair of DNA [42–44]. .

P53 role in cellular senescence

"Temporary cell cycle arrest may not be the permanent solution because a cell with oncogenicity that cannot repair may resume proliferation and develop a tumour" [3]. "Cellular senescence is permanent cell cycle arrest that inhibits further replication of the cell but leaves a functioning cell" [26]. "P53-induced cellular senescence occurs in cells in which telomeres shortening is seen as well as in cells with oncogene activation and oxidative damage" [45]. Cellular senescence mediates via P53-induced transcriptional activation of the cyclin-dependent kinase (CDK) inhibitors $P21^{CIP1}$ (*CDKN1A*) and $P16^{INK4A}$ (*CDKN2A*) [46], but it is not enough on its own [46]. The dynamics of stress can influence senescence, that is, if the stress that initiates senescence is transient, then P53 induction can implement a quiescent state and activate the DNA repair process and, after the stress resolves, the cell can start cycling [47]. Persistent stress or prolonged P21-mediated cell cycle arrest can activate $P16^{INK4A}$, an inhibitor of CDK4 and CDK6, as well as subsequent activation of the RB1 transcriptional regulator, resulting in long-lasting cell cycle arrest [48]. The role of $P21^{CIP1}$ may be to initiate senescence, whereas $P16^{INK4A}$ may be responsible for durable growth arrest [49].

"Senescence is also associated with β-galactosidase (SA-β-gal) activity and expansion of cytokines that constitute the senescence-associated secretory phenotype" [49]. Apart from $P21^{INK4A,}$ there are other target genes like PML nuclear body scaffold (*PML*) and *SERPINE1* (Serpin family E member 1) also known as "Plasminogen activator inhibitor-1" (*PAI-1*) which are transcriptionally activated by P53 and plays a role in senescence [50]. "Kortlever and his colleagues reported that *PAI-1* is not only an essential marker but also a crucial advocate of cellular senescence in vitro" [50]. "They examined the role of P53 and its target gene *PAI-1* in cellular senescence and stated that fibroblasts with negative P53-and *PAI-1*-were immune to cellular senescence and multiplied longer than wild-type fibroblast" [50]. "There most prominent observation was that in the absence of cellular P53, overexpression of *PAI-1* is sufficient to induce senescence in fibroblasts and they reported that *PAI-1* regulates cellular senescence through PI3K-PKB-GSK3-cyclin D1 pathway" [50].

Another important P53-induced target gene is *PML* nuclear body scaffold (*PML*); it is a ubiquitously expressed nuclear phosphoprotein that belongs to the tripartite motif-containing (*TRIM*) protein superfamily [51]. The mechanism through which *PML* plays a role in senescence involves the RB and P53 tumour suppressor proteins [52, 53], which can directly interact with *PML* [54]. "Induction of cellular senescence not only results in irreversible cell cycle arrest but also releases Senescence-associated secretory phenotype (SASP)" [55]. A senescent cell is a persisting metabolically active cell that has undergone an array of changes in protein secretion and expression, finally developing SASP, which is phenotype and named as senescence-messaging secretome [55]. "SASP also play a role in tumorigenicity based on P53 status, for example in the stellate cells of liver stroma, the senescent stellate cells secrete factors that induce tumour clearance activity in nearby macrophages which are mediated by P53, whereas P53 null stellate cells employee macrophages that activate tumorigenesis" [56]. "In the colon, P53 deletion results in changes like SASP, increasing the expression of Tumour necrosis factor-alpha (TNF-α) and thus increasing its ability to induce invasion and multiplication of tumour cells" [57].

P53 role in the DNA repair process

"Under the low level of cellular stress and when there is a scope for the repair process, P53 activates a temporary cell cycle arrest and initiates the DNA repair process, thus limiting the proliferation of oncogenic mutated cells" [58]. The important P53-induced transcriptional gene target in this process is *CDKN1A*, which encodes the protein P21, which causes a transient arrest of cell cycle along with its role in cellular senescence [30, 36]. In the phase, when the cell cycle arrests, P53 is involved in the regulation of DNA repair pathways [59]. These repair pathways are specific for a particular class of DNA lesions and directed at re-establishing the integrity of the molecular structure of DNA [60]. The DNA repair system is a very complex network, and it is one of the most critical and powerful determinants of cell fate for survival, senescence, or apoptosis [61].

The repair mechanisms for Single-strand breaks (SSBs) and Double-stranded breaks (DSBs) are outlined as, "In eukaryotes, in response to SSBs and DSBs there are five main DNA –repair processes, Nucleotide-excision repair (NER), Base-excision repair (BER) are involved in the repair of DNA lesions affecting only one strand of the double helix (SSB), Non-homologous end-joining (NHEJ) and Homologous recombination repair (HRR) are involved in the repair of DNA lesions affecting both strands of the double helix (DSB), the Mismatch repair process is involved in the repair of mismatched nucleotides, insertion and deletion loops due to replication errors" [62–64]. Single-strand annealing (SSA) is one more unique DNA repair process that makes use of components from both HRR and NHEJ [65]. P53-mediated response to DNA damage may not be a part of its function as a tumour suppressor [66]. However, it does support cell activity. P53 target genes in the NER process are *DDB2* and *XPC*, which encodes for the proteins damage-specific DNA-binding protein 2 and *XPC* complex subunit, DNA damage recognition, and repair factor [67, 68].

"On prolonged exposure to U.V. radiation through sunlight leads to the formation of DNA lesions like Cyclobutane pyrimidine dimers (CPDs) and (6-4) pyrimidine-pyrimidone photoproducts (6-4PPs) which can lead to the development of genome instability and skin cancers if not repaired" [69, 70]. "Removal of this mutagenic DNA lesion takes place by the NER pathway, and it is activated by two different DNA damage identification paths, which depend on the precise location of the DNA lesion. Furthermore, NER reaction is transcription induced and induced by RNA polymerase II (POLII) - blocking lesions and thus eliminates DNA lesion from that strand of DNA in which genes are under transcription" [71, 72]. Conversely, Global-genome NER (GG-NER) utilizes lesions sensors *DDB2* and *XPC* to identify and eliminate DNA lesions from transcribed as well as non-transcribed templates of the whole genome [73, 74].

"P53 induced Ribonucleotide Reductase Regulatory *TP53* Inducible Subunit M2B (*RRM2B*) gene encodes for Ribonucleotide Reductase (RR) which helps in DNA repair process by providing precursors" [75]. Proliferating cell nuclear antigen (PCNA) is a ubiquitous nuclear protein, which is a crucial part of replication fork also plays a vital role in the DNA repair process by providing replicative DNA polymerases and other proteins required for duplication of entire genome [76–78]. P53 can also activate DNA Polymerase Eta (POLH) and specifically recruit a DNA polymerase to replicate damaged DNA [79] accurately. In humans, the POLH gene encodes for DNA polymerase eta (Pol η); the other name for POLH gene is Xeroderma pigmentosum variant (XPV) gene because of a mutation in a group of patients, diagnosed with XP disease that did not carry mutations in *NER* gene [80]. Cells have many repair mechanisms through which they can repair there DNA damage lesions [81]. However, for those cells which have unrepaired lesions, the replication process of damaged DNA utilizes translesion synthesis (TLS) polymerases, and these polymerases can bypass the lesions [82]. "Human cells can develop genetic syndromes like Xeroderma pigmentosum (XP) and Cockayne syndrome (CS) as a result of the failure of these mechanisms furthermore XP and CS exhibit complex phenotypes of cancer or severe neurodegeneration and ageing" [81, 82].

Role of P53 in apoptosis

Apoptosis is a significant type of regulated cell death in human cells, and it is an evolutionarily conserved process with many ranges of functions like maintenance of tissue homeostasis [83, 84], prevention of cancer [85], and essential for proper embryonic development [86]. "Apoptosis winds up in the activation of Cysteine-aspartic proteases (CASPASES), which causes proteolytic degradation of intracellular components followed by phagocytic clearance with least stress to the surrounding environment of cells and tissues" [87, 88].

The activation of caspases ensues by one of the two pathways—the extrinsic pathway and the intrinsic pathway. "The extrinsic apoptotic pathway also called as death receptor-mediated is initiated by binding of various death ligands such as FS-7-associated surface antigen (FAS) or TNF superfamily member 10 (TNFSF10, also known as TNF-related apoptosis-inducing ligand (TRAIL) to Death receptors (DR) family member like Tumour necrosis factor (TNF) –receptor superfamily member 10a (TNFRSF10A, also known as TRAILR1), Tumour necrosis factor (TNF) – receptor superfamily member 10b (TNFRSF10B, also known as TRAILR2), Fas cell surface death receptor (FAS, also known as CD95) or TNF receptor superfamily member 1A(TNFR SF1A) present at the cellular membrane and thus leads to activation of caspases (mainly caspases 8) resulting in extensive cleavage of caspases substrates and cell death" [89]. "The intrinsic apoptotic pathway also named as the mitochondrial pathway initiated by a wide variety of intracellular stresses such as cytokine distress, DNA damage and endoplasmic reticulum dysfunction which activates single significant event that is Mitochondrial outer membrane permeabilization (MOMP) leads to the release of cytochrome *c* from the inner mitochondrial membrane into the cytoplasm through a cytoplasmic complex (apoptosome) which activates the cascade of caspases leading to cell death" [90].

"One of the major biological roles of wild-type P53 is its capability to induce apoptosis in genetically unstable cell" [91]. "P53 transcriptionally activates many pro-apoptotic *BCL-2* family proteins like *BCL2* antagonist/killer 1 (*BAK1*), *BCL-2*-associated X, Apoptosis regulator (*BAX*), *PMAIP1* (Phorbol-12-myristate-13-acetate-induced protein 1 also known as NOXA) and P53 upregulated modulator of apoptosis *PUMA* (also known as *BBC3* (*BCL-2*-binding component 3)) which are essential elements of MOMP in reply to death signal" [92, 93]. "P53 can directly interact with pro-apoptotic and anti-apoptotic proteins present in the cytoplasm and the membrane of mitochondria" [94]; thus, "P53 can act as both a sensitizer as well as an activator of apoptosis" [92]. "However, P53 can also inhibit B-cell Lymphoma 2 (*BCL-2*) and *BCL2* like 1 (*BCL2L1*) which enable pro-apoptotic members (*BAK* or *BAX*) to detach from heterodimer complexes following the oligomerization of *BAX* and *BAK* into mitochondrial outer membrane (MOM) thus forming lipid openings into MOM through which the initiators of apoptosis released in response to death signal" [95–99].

"P53 can activate Apoptotic peptidase activating factor 1 (*APAF1*) and cytochrome *c*, which releases from mitochondria binds to *APAF1* and procaspase 9 to form apoptosome" [100, 101]. Another P53 target gene Apoptosis-enhancing nuclease (*AEN*) also supports apoptosis by digesting double-stranded DNA [102]. P53 also upregulates the ceramide synthase-encoding genes like Ceramide Synthase 5 (*CERS5*) and Ceramide Synthase 6 (*CERS6*) [103] and induces ceramide production [104] which can activate apoptosis. "Even though most of the P53 target genes encode for apoptosis-inducing proteins, the P53 target, *TP53* Regulated Inhibitor of Apoptosis1 (*TRIAP1*), encodes for an inhibitor of apoptosis" [105]. The decision between apoptosis and cell survival depends on the members of the *BCL-2* family, regulated by P53 in both transcription-dependent and independent manner.

Role of P53 in autophagy

"Another cellular pathway triggered by cellular stress and P53 is autophagy" [106]. This mechanism can restrain the activity of P53 by preventing various signals for cellular stress like DNA damage and oxidative stress and by also directly degrading P53 [107]. "On the other hand, P53 can activate various target genes that play a role in autophagy like DNA-damage-regulated autophagy modulator 1 ((*DRAM1*), UNC-51-like autophagy-activating kinase 1 (*ULK1*) and cathepsin D" [108–110]. "P53 mediated autophagy also plays a role in suppression of tumour" [111]. The following are the target genes for P53: Tuberous Sclerosis Complex subunit 2 (*TSC2*), Phosphatase and Tensin Homologue (*PTEN*), protein kinase AMP-activated catalytic subunit alpha 2 (*PRKAA2*), or Sestrins 1 and 2 which are *PRKAA2* activators, and these pro-autophagic factors further signal the autophagic process through mechanistic target of rapamycin kinase (mTOR) inhibition [112–115]. "Damage regulated autophagy modulator 1 ((*DRAM1*) is also a target gene for P53 in cell stress response [109], and (*DRAM1*) also denotes a lysosomal protein that intervenes in various stages of autophagosome formation" [116].

"Several pro-apoptotic proteins transactivated by P53 also play a role in the activation of autophagy" [117, 118]. "This can occur in two ways, either by downregulating the expression of genes like *BCL-2*, *BCL2L1* and *BCL2* Interacting Protein 3 (*BNIP3*), or by upregulating the expression of *BAX*, *BAD* or *BBC3* which ultimately releases Beclin-1 that initiates autophagy" [119]. P14ARF (encoded by *CDKN2A*) is a tumour suppressor protein that is

regulated by P53, and it can also induce autophagy by directly interacting with *BCL2L1* [120, 121]. Death-associated protein kinase 1 (*DAPK-1*) is an essential regulator of both apoptosis and autophagy in the ER stress-induced apoptotic pathway [122]. It can activate autophagy either by phosphorylating Beclin-1, which inhibits *DAPK-1* degradation by anti-apoptotic proteins or possibly by inhibiting the anti-autophagic Microtubule-associated protein 1 light chain 3 alpha (MAP1LC3A)-interacting Microtubule-associated protein 1B (MAP1B) [123, 124]. The effect of P53 on autophagy may be dependent on its intracellular localization. Under cellular stress, P53 activates autophagy by translocating to the nucleus, whereas, under normal physiological state, cytoplasmic P53 inhibits autophagy. "This inhibition of autophagy by cytoplasmic P53 is via the same canonical *PRKAA2*-mTOR pathway and independent of P53 transcriptional activity" [106]. "Contrary to nuclear P53, cytoplasmic P53 protein inhibits the AMP-dependent kinase (a positive regulator of autophagy) and activates mTOR" [106]. A vital observation is that when P53-deficient cancer cells are exposed to hypoxia and nutrient depletion, the survival of these cancer cells improved because of enhanced autophagy. "This study also highlighted that inhibition of P53 degradation barred the activation of autophagy in several cell lines" [106].

Role of P53 in metabolism

"P53 is also involved in the metabolism by helping the cells to adapt and survive under nutrient-deprived conditions like glucose [125], glutamine [126] and serine deprivation" [127]. "In response to nutrient deprivation the temporary activation of P21 (*CDKN1A*) plays a role in protective responses by arresting cell cycle –for example in response to serine starvation, P21 helps in de novo synthesis of serine into glutathione rather than nucleotide synthesis" [127] and also "in response to cysteine starvation P21 helps in delaying ferroptosis" [128]. Thus, P53 plays an essential role in nutrient deprivation by initiating alternative pathways to maintain cell survival and also plays a role in the death of the cells when recovery seems impossible.

Glucose metabolism

P53 plays an essential metabolic role by decreasing the rate of glycolysis and supplementing mitochondrial respiration. It downregulates the initial step of glycolysis (cells take up the glucose) by directly repressing the expression of various glucose transporters like Solute carrier family 2 member 1 (SLC2A1, also known as Glucose transporter type 1 (GLUT1)) and Solute carrier family 2 member 4 (SLC2A4, also known as Glucose transporter type 4 (GLUT4)) [129] and indirectly P53 controls Solute carrier family 2 member 3 (SLC2A3, also known as Glucose transporter type 3 (GLUT3)) expression by repressing IKK-NF-κB pathway [130]. "P53 can also inhibit glycolysis by activating *TP53*-induced glycolysis regulatory phosphatase (TIGAR), also known as fructose-2,6-bisphosphatase and this activation allows TIGAR to hydrolyze fructose-2,6-bisphosphate which is an allosteric activator of Phosphofructokinase 1 (PFK1, the enzyme for the rate-limiting step in glycolysis) which results in low levels of fructose-2,6-bisphosphate" [131].

"P53 inhibits glycolysis by downregulating the expression of glycolytic enzyme Phosphoglycerate mutase (PGM), which act as a catalyst for the conversion of 3-phosphoglycerate into 2-phosphoglycerate during glycolysis in fibroblasts in a P53-mediated transcription-independent manner" [132] but "P53 can directly transactivate the transcription of PGM in cardiac myocytes". "Another mechanism by which P53 inhibits the transport of glucose is by direct transcription of Ras-related glycolysis inhibitor and calcium channel regulator (*RRAD*), which results in inhibition of translocation of GLUT1 at the cellular membrane" [133]. "P53 can also inhibit the expression of mitochondrial Pyruvate dehydrogenase kinase 2 (*PDK2*) which is a negative regulator of Pyruvate dehydrogenase (*PDH*)" [134]—resulting in increased activity of *PDH* and this increased activity stimulates the conversion of pyruvate to acetyl-CoA for use in the TCA cycle and enhances mitochondrial respiration. Another gene that is activated by P53 is Parkin RBR E3 ubiquitin-protein ligase (*PRKN*), which encodes for an E3 ubiquitin ligase called as parkin [129] that increases the expression of Pyruvate dehydrogenase E1 subunit alpha 1 (*PDHA1*), which is a part of *PDH* complex.

"P53 transcriptional target gene Glutaminase 2(GLS2) is a mitochondrial protein that catalyzes the hydrolysis of glutamine to produce glutamate, which is promoted into mitochondrial TCA thus supporting mitochondrial respiration and production of ATP" [135, 136]. P53 also controls lactate levels in cancer cells by suppressing the lactate transporter Malonyl-CoA-acyl carrier protein transacylase (MCAT), which results in lactate accumulation that inhibits glycolytic rate in cancer cells [137]. "P53 also regulates the expression of Synthesis of cytochrome *c* oxidase 2 (SCO2), required for mitochondrial cytochrome *c* oxidase assembly, thus regulating the normal functioning of Electron transport chain (ETC) and oxidative phosphorylation" [138]. P53 directly induces the expression of mitochondrial Apoptosis-inducing factor mitochondria associated 1 (*AIFM1*), which plays a role in maintaining ETC [139]. In another study, P53 also induces Mitochondria-eating protein (MIEAP), which promotes the removal of oxidized proteins and sometimes mitochondria itself to aid mitochondria [140]. Thus, "On the whole, P53 seems to enhance energy metabolism through mitochondrial respiration and maintain mitochondrial integrity over glycolysis thus

opposing the Warburg effect (which increases aerobic glycolysis seen in rapidly dividing normal and cancer cells), but some studies challenge these ideas for example, "In telomerase knockout mice with severe telomere dysfunction activation of P53 triggers the suppression of PGC-1α and PGC-1β (positive regulators of mitochondrial synthesis) which leads to mitochondrial dysfunction and reduced oxidative phosphorylation" [141]. Thus, it implies that the effect of P53 on glucose metabolism depends on cellular context.

"P53 is also involved in Pentose phosphate pathway (PPP), an alternative pathway of glycolysis to supply ribose required for the synthesis of nucleotides and NADPH for reductive biosynthesis and antioxidant control by regulating TIGAR which promotes metabolic intermediates of glycolysis like fructose-6-phosphate to move towards oxidative PPP or through activation of AKT serine/threonine kinase 1 (AKT1) which increases PPP gene expression" [142, 143]. P53 can also inhibit PPP through direct binding and inhibition of Glucose-6-phosphate dehydrogenase (G6PD), which is an essential enzyme of PPP [144]. P53 also regulates gluconeogenesis. However, the role is not clear since it reported that P53 could promote [145] as well as inhibit [146] the expression of enzymes involved in gluconeogenesis. "P53 promotes gluconeogenesis through direct activation of Pantothenate kinase-1 (*PANK1*), which catalyzes the initial and rate-limiting step in CoA synthesis" [147]. "In one study, it was reported that stabilization of P53 in response to starvation is crucial for gluconeogenesis and catabolism of amino acid in the liver" [148]. "Goldstein et al. reported that P53 activation leads to induction of enzymes involved in gluconeogenesis like Glucose-6-phosphatase catalytic subunit (*G6PC*), Phosphoenolpyruvate carboxykinase-1(*PCK1*) and by providing glycerol through P53-dependent activation of Glycerol kinase (GK) or glycerol transporters like aquaporin 3 and aquaporin 9" [145]. "Conversely, P53 can suppress gluconeogenesis by activation of deacetylase Sirtuin 6 (*SIRT6*), which deactivates Forkhead box protein O1 (FOXO1), a positive regulator of Phosphoenolpyruvate carboxykinase-1 (*PCK1*) and Glucose-6-phosphatase catalytic subunit (*G6PC*)" [149].

Lipid metabolism

Apart from regulating glucose metabolism, P53 also plays a role in regulating lipid metabolism by enhancing Fatty acid oxidation (FAO) and inhibiting fatty acid synthesis. Thus it is believed that P53 acts as a negative regulator of lipogenesis [150]. P53 regulate several genes that directly plays a role in lipid metabolism including three carnitine acyltransferases Carnitine O-Octanoyltransferase (*CROT*), Carnitine palmitoyltransferase 1A (*CPTA1*), and Carnitine palmitoyltransferase 1C (*CPT1C*) [151, 152]. "P53 induced activation of Carnitine palmitoyltransferase1C (*CPT1C*) promotes the transport of activated fatty acids into the mitochondria" [153]. "Lipin1 (*LPIN1*) is another gene that is activated by P53 and in response to nutrient deprivation" [154]. "*LPIN1* translocates to the nucleus where it acts as a transcriptional coactivator and activates the expression of genes involved in FAO, resulting in increased FAO" [154]. P53 inhibits fatty acid synthesis (FAS) through direct protein-protein interaction, for example, P53 binds directly to and inhibits G6PD, which results in reduced NADPH production and thus decreased FAS [144].

"P53 downregulates the expression of Sterol regulatory element-binding proteins (SREBP), which plays a key role in driving expression of FAS genes" [155]. P53 mutant protein binds directly to SREBP and increases their transcriptional functions, which result in increased activity and thus increased sterol biosynthesis in human tumour's [156, 157]. In response to metabolic stress, P53 is activated by AMPK via serine 15 phosphorylation, which results in temporary cell cycle arrest [125]. In contrast, under genomic stress P53 can activate AMPK via sestrin 1 and sestrin 2, leading to inhibition of mTOR and thus arrest of cell growth and proliferation [115]. Conversely, mutant P53 binds to and inhibits *PRKAA2* resulting in increased FAS and invasive cell growth of tumour cells [156]. "P53 is involved in transcriptional inhibition of Stearoyl-CoA-desaturase 1 (SCD1), which is an endoplasmic reticulum enzyme that catalyzes the rate-limiting step in the synthesis of Mono-unsaturated fatty acids (MUFAs)" [28].

Amino acid metabolism

P53 also regulates amino acid metabolism via transcriptional regulation of GLS2. "In response to impaired pyruvate oxidation P53 regulates GLS2, which replenishes TCA intermediates and also contributes to various metabolic pathways, this response is essential to continue the redox status of cells by driving glutathione production" [135, 136, 158]. "In response to glutamine deficiency, firstly P53 induces the expression of arginine transporter Solute carrier family 7 member 3 (*SLC7A3*) which increases transient levels of arginine inside the cell to endure mTORC1 activity" [159], "secondly P53 induces the expression of amino acid aspartate transporter *SLC1A3* to support cellular respiration and synthesis of nucleotides" [160]. "Serine deprivation may initially promote survival of the cell via MDM2/ATF-4 facilitated control of serine synthesis and also through the P53-P21 pathway, but when this deprivation is prolonged or severe, it may start a brutal cycle during which P53 induced suppression of Phosphoglycerate dehydrogenase (PHGDH) and activation of *PMAIP1* and *PUMA* via Activating transcription factor 4(*ATF4*) results in cell death" [161, 162]. Overall, many of the P53 related

metabolic functions rest on the capability of the cells to handle metabolic stress and survive the stress.

P53-reactivation strategies

"The cancer genome sequencing showed that 42% of cases across 12 types of tumour bear *TP53* mutant" [163], but it is to be noted that the *TP53* mutation rate also varies across tumour types. "Most *TP53* mutations in cancer are missense mutations contributing to nearly 75% and located in the DNA-binding core domain that results in disrupting DNA binding and oncogenic gain-of-function leading to exacerbation of tumour progression" [2]. Various mouse models have shown that restoration of wild-type P53 function in cancer cells results in the induction of tumour cell death and tumour eradication. Thus, P53 reactivation can be a crucial strategy to fight cancer, and various small molecules identified to rescue and reactivate missense-mutant P53 protein as well as by induction of mutant P53 degradation (Fig. 3). These small molecules bind and stabilize mutant P53, but the accurate and precise mechanism of the refolding of mutant-P53 is not entirely clear. Another mechanism of P53 reactivation is through inhibition of MDM2-P53 interaction. Various compounds have been identified that reactivate P53 by blocking MDM2-P53 interaction.

Compounds that restores wild-type P53 activity

In Table 1, we have provided an overview of small molecules that directly target mutant P53 via reactivation of its tumour-suppressive transcriptional activity.

Compounds that deplete mutant P53

Another method to target oncogenic mutant P53 is via compounds that particularly deplete mutant P53 with minimal effect on wild-type P53. "The underlying principle of depleting mutant P53 based on the observation that mutant P53 proteins are inherently unstable in healthy cells, and it can accelerate tumour development once it is stabilized" [194].

In Table 2, we have provided an overview of small molecules that directly target and degrade mutant P53.

HSP90 inhibitors

"In human cancer cells, mutant P53 shows more stability than wild-type P53, mainly because of the interaction of

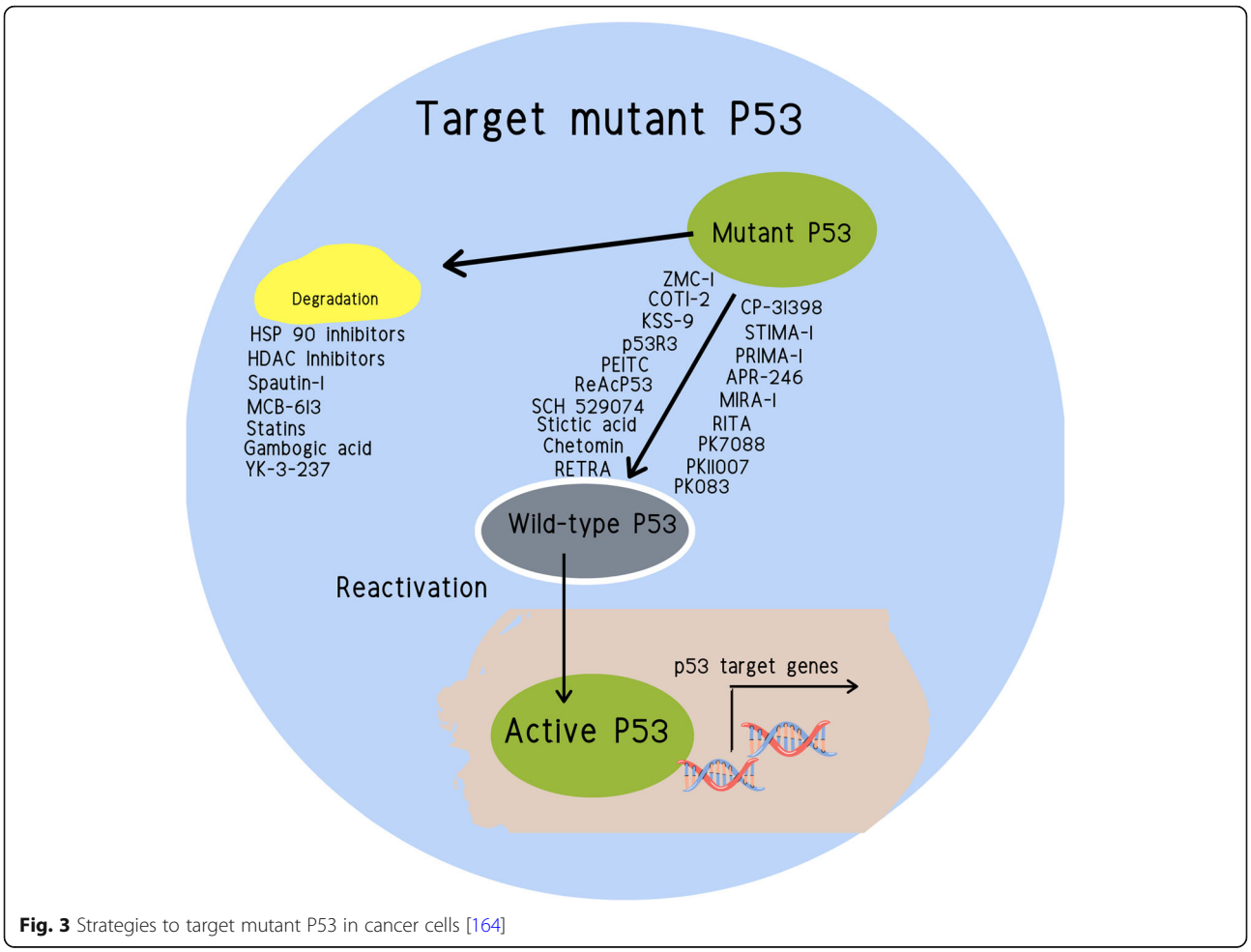

Fig. 3 Strategies to target mutant P53 in cancer cells [164]

Table 1 Compounds that target mutant P53 and induce reactivation

S. No.	Name of the compound	Type of mutant	Chemical name or class	Mechanism	References
1	CP-31398	V173A, S241F, R249S, R273H	Styrylquinazoline	"Stabilizes the DNA-binding core domain by promoting the proper folding of mutant P53 protein and triggering the P21 expression as well as inducing P53 reporter gene activity". It is the first molecule discovered that can reactivate mutant P53. It also exhibits anti-tumour activity in a mouse model of melanoma xenograft tumour and colon carcinoma as well as in urothelial bladder cancer that developed in SV40 large T transgenic mice. Currently, there are no undergoing clinical trials for this compound.	[165, 166]
2	STIMA-1 (SH group-targeting compound that induces massive apoptosis	R175H, R273H	Styrylquinazoline	STIMA-1 stabilizes wild-type P53 conformation by binding to the cysteine residues in the DNA-binding core domain and thus reinstates its transcriptional activity. STIMA-1 is a derivative of CP-31398. "It also induces the upregulation of mRNA expression of P21, *PUMA*, and *BAX* that results in mutant P53 dependent apoptosis".	[167]
3	PRIMA-1	R273H, R175H, R248Q	Quinuclidinone	"PRIMA-1 stimulates the refolding of mutant P53 and increases the expression of *BAX*, *PUMA*, and *CDK1NA* in cancer cells". "PRIMA is a prodrug that converts to its active form methylene Quinuclidinone (MQ) via hydrolysis and forms adducts with mutant P53 protein by Michael addition resulting in the reinstallation of wild-type P53 conformation and activation of apoptosis".	[168, 169]
4	APR-246 (PRIMA-1^{Met})	R273H, R175H	Quinuclidinone	APR-246 is a methylated form of PRIMA-1 and exhibits higher efficacy in terms of reactivating mutant P53 and promoting apoptosis. "It is also transformed to reactive electrophile MQ and binds covalently to cysteine 277 (Cys277) in P53. APR-246 also displays anticancer effect via depletion of glutathione content and elevation of Reactive oxygen species (ROS), leading to oxidative damage to cancer cells". It is a mutant-P53 independent effect. APR-246 is currently undergoing phase II clinical trials in combination with azacitidine (AZA) in patients who present with *TP53* mutant acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS). One trial is ongoing in France (ClinicalTrials.gov identifier NCT03588078) and another trial in the USA (ClinicalTrials.gov identifier NCT03072043).	[170–174]
5	MIRA-1	R175H, R248Q, R273H	Maleimide	MIRA-1, like STIMA-1, is a Michael acceptor and prevents unfolding of wild-type P53 as well as mutant P53. Thus, it restores native wild-type conformation. "Various studies using solid tumour models have demonstrated MIRA-1induced P53-dependent endoplasmic stress and caspase-9-dependent apoptosis that confirms that anticancer activity of MIRA-1 is not only through mutant P53 but also via other molecular targets". "MIRA-2 and MIRA-3 are structural analogues of MIRA-1 and inhibit cancer cell proliferation expressing P53R175H and P53R273H". Besides, MIRA analogues increased DNA-binding ability of mutant P53 and enhanced expression of P53 target genes like *MDM2* and *CDKN1A* in various cancer cells carrying mutant P53 protein.	[175]
6	RITA	R175H, R248W, R273H,	Thiophene derivative	"RITA (reactivation of P53 and induction of tumour cell apoptosis), induces a conformational change resulting in the restoration of normal	[176–179]

Table 1 Compounds that target mutant P53 and induce reactivation *(Continued)*

S. No.	Name of the compound	Type of mutant	Chemical name or class	Mechanism	References
		R280K		P53 function and activation of apoptosis in mutant P53". "RITA inhibits tumour growth of renal cell carcinoma cells by causing DNA-protein cross-linking and upregulation of wild-type P53 and P21".	
7	PK7088	Y220C	Pyrazole	PK7088 binds to the P53Y220C-specific surface cavity and stabilizes it while restoring wild-type P53 conformation. PK7088 targets cancer cells carrying the P53Y220C mutant and induces G2/M arrest of the cell cycle with increased expression of *NOXA* and *CDKN1A*. It also triggers the nuclear export of *BAX* into the mitochondria.	[180]
8	PK11007	Y220C, V143A	Sulfonylpyrimidine	"PK11007 is a 2-sulfonylpyrimidine that binds to Cys182 and Cys277 in both wild-type P53 and the P53-Y220C mutant P53 and alkylate thiols via nucleophilic aromatic substitution resulting in P53 stabilization and restored P53-dependent activation of target genes like *CDKN1A*, *PUMA* and *NOXA*". PK11007 anticancer activity is via both mutant-P53-dependent and mutant-P53-independent pathway, and like APR-246, PK11007 depletes GSH and increases the concentration of ROS in mutant P53-containing cancer cells.	[181]
9	ZMC-1 (zinc metallochaperone-1)	R175H, R172H (mouse)	Thiosemicarbazone	ZMC1 is a thiosemicarbazone derivative that displays selective toxicity towards cells carrying P53R175H, whereas it shows minimum toxic effect towards cells expressing wild-type P53 and other mutants of P53 like P53R248Q and P53R273H. "ZMC-1 displays mutant-P53 reactivation due to Zn^{2+} binding, which is essential for wild-type P53 structural stability". "Administration of ZMC1 results in higher toxicity in P53R172H (which is equivalent to human P53R175H) mice than in wild-type P53 in a dose-dependent manner".	[17, 182]
10	COTI-2	R175H, Y220C, R248Q, I255N, R273H	Thiosemicarbazone	COTI-2 is a thiosemicarbazone-related compound that promotes the refolding of mutant P53 and restores wild-type-P53 function. The mechanism of action of COTI-2 is still unclear. COTI-2 displayed superior activity at Nanomolar concentrations than traditional chemotherapy or targeted-therapy agents against tumour cells, in vitro, and in vitro, as well as being safe and well-tolerated in vitro. COTI-2 showed activity against different types of human cancer lines regardless of their tissue of origin and genetic makeup.	[183]
11	KSS-9	R175H,	Piperlongumine	KSS-9 and related C7-aryl piperlongumine derivatives displayed potent activity against human tumour cells. The cytotoxic activity, in particular, was more against the SKBR-3 breast cancer cells which carrying R175H mutation in P53 suppressor, and it also exhibited the ability to reactivate P53 mutation resulting in restoring of biological activity in SKBR3 cells. KSS-9-induced refolding of P53-R175H, and reactivation supplemented by increased expression of target genes like *MDMD2*, *P21CIP1*, and *PUMA*. Furthermore, KSS-9 induced abundant oxidative stress and actively disrupted the tubulin polymerization *in vitro*.	[184]
12	P53R3	R175H, R273H, R248W,	Quinazoline	The P53 reactivator (P53R3) compound identified in an *in vitro* DNA-binding assay. "It restores sequence-specific DNA binding of various	[185]

Table 1 Compounds that target mutant P53 and induce reactivation *(Continued)*

S. No.	Name of the compound	Type of mutant	Chemical name or class	Mechanism	References
		M273I		P53 hot spot mutants (P53R175H, P53R248W, and P53273H) and increases the recruitment of wild-type P53 and P53M273I to several target genes, such as *CDKN1A*, *GADD45*, *BAX*, *PUMA*, *PIG3* and *MDM2*. P53R3 also sensitizes glioma cells to apoptosis induced by TRAIL".	
13	PEITC	R175H	Isothiocyanates	Phenethyl isothiocyanate (PEITC) is a vegetable-derived compound that can reactivate the P53 mutant under in vitro and in vitro conditions. PEITC exhibits unusual antiproliferative activity against hotspot mutation P53R175H. From various mechanistic studies, it shows that PEITC induces apoptosis in a P53R175H mutant-dependent manner by restoring P53 wild-type conformation and transactivation. PEITC is a multifaceted compound that targets multiple pathways essential for the growth and development of cancer cells. The growth-inhibitory effects of PEITC is also due to increased ROS and depleted glutathione (GSH), leading to oxidative stress to kill the cancer cell.	[186]
14	ReACP53	R175H, R248Q	Peptide	ReACP53 is a cell-penetrating peptide that rescues and increases the levels of functional and wild-type P53 protein in high-grade serous ovarian carcinomas (HGSOC) triggering cell cycle arrest and cell death. ReACP53 disrupts mutant-P53 aggregates and exhibited activity in ovarian cancer organoids and decreased intraperitoneal growth of OVCAR-3 ovarian cancer cells carrying mutant-P53in mice. "ReACP53 can also induce interaction of mutant-P53 with *BAX* with resulting mitochondrial cell death in castration-resistant prostate cancer (CRPC) cells".	[187, 188]
15	SCH529074	R175H, L194F, R248W, R249S, R273H	Piperazinylquinazoline	"SCH529074 is a small molecule that explicitly binds to the P53 DBD in a saturable manner". "It acts as a chaperone and restores the PAb1620 epitope and increases the DBD activity of various P53 mutants". This activity results in increased expression of multiple P53 target genes like *CDKN1A*, *NOXA*, *BAX*, *cyclin G1*, and *PUMA*. SCH529074 also inhibits wild-type P53 ubiquitination and degradation by MDM2.	[189]
16	Stictic acid	R175H, G245S	1,4-Dihydroxy-10-methoxy-5,8-dimethyl-3,7-dioxo-1,3-dihydro-7H-2,6,12-trioxabenzo[5, 6]cyclohepta[1,2-e]indene-11-carbaldehyde	"Stictic acid is a natural product that binds to L1/S3 pocket with high-affinity in silico and thermostabilized P53-R175H and P53-G245S *in vitro* resulting in the restoration of wild-type P53 activity". "Stictic acid also reactivated P53-R175H and P53-G245S mutants with the increases expression of P21 in a mutant-P53-dependent manner".	[190]
17	Chetomin	R175H	Epidithiodioxopiperazine	"Chetomin (CTM) exhibits anticancer activity *in vitro* and *in vivo* in cells carrying P53R175H mutant with upregulation of *MDM2*, *CDKN1A*, and *PUMA*". "CTM increases the interaction of heat shock protein 40 (HSP40) with P53R175H, resulting in restoring the wild-type P53 conformation".	[191]
18	PK083	Y220C	Carbazole	PhiKan083 (PK083) is a carbazole derivative that binds to and thermodynamically stabilizes P53-Y220C. PK083 causes mutant P53Y220C wild-type reactivation.	[192]

Table 1 Compounds that target mutant P53 and induce reactivation *(Continued)*

S. No.	Name of the compound	Type of mutant	Chemical name or class	Mechanism	References
19	RETRA	R273H, R248Q, R280L, G266E	Ethanone hydrobromide	"Reactivate transcriptional activity (RETRA) increased β-galactosidase activity only in cancer cells carrying mutant P53 but also induced expression of P53 target genes. The increased β-galactosidase activity is absent in cells with wild-type or null P53. RETRA suppressed the growth of mouse tumour xenografts derived from human A431epidermal carcinoma cells expressing P53-R273H".	[193]

mutant P53 with the HDAC6/HSP90 chaperone complex" [195]. "Treatment of cancer cells with 17-AAG (first HSP90 inhibitor), an analogue of Geldanamycin promotes degradation of various P53 mutants by inactivating HSP90 and decreases the viability of cells carrying mutant P53" [196]. "Ganetespib, also known as STA-9090, was shown to display > 50-fold more potency than 17-AAG in degrading P53R175H and P53R248Q using mouse models" [205]. Currently, there are more than a dozen of HSP90 inhibitors under preclinical and clinical studies.

Histone deacetylase inhibitors

"HDAC inhibitors can reduce the enhancement of mutant P53. Blagosklonny et al. reported the first line of evidence of histone deacetylase inhibitors (HDACi) such as trichostatin A and FR901228, on mutant P53 (P53R175H, P53R280K, P53V274F, and P53P223L)" [206]. "Suberoylanilide hydroxamic acid (SAHA, also known as Vorniostat) is an HDACi that inhibits class I, II, and IV HDACs resulting in disruption of HDAC6/HSP90, mutant P53 complex. This disruption leads to mutant P53 ubiquitination by MDM2 and CHIP" [195, 207]. "SAHA shows higher cytotoxic effects on cancer cells carrying mutant P53 than wild-type or null for P53" [207]. "SAHA also increases the sensitivity of cancer cells to camptothecin, a topoisomerase inhibitor in a mutant P53-dependent manner" [195]. "Interestingly, HSP90 inhibitors synergize the effect of SAHA on the degradation of mutant P53 and

Table 2 Compounds that target mutant P53 and induce degradation of mutant P53

S. No.	Name of the compound	Type of mutant	Mechanism	References
1	HSP90 inhibitors (heat shock proteins)	R175H, L194F, R248Q, R273H, R280K, R172H (mouse)	"Reverse the HSP90's function to inactivate MDM2 and CHIP".	[195, 196]
2	HDAC inhibitors **(**histone deacetylase inhibitors**)**	R175H, R280K, V274F, P223L	These compounds target HDAC6 by inhibiting it and thus disrupting the HDAC6/HSP90/mutant P53 complex. "HDAC/HSP90 chaperone complex stabilizes mutant P53 by averting its degradation, which is mediated by E3 ubiquitin ligase". "HDAC inhibitors or HSP90 inhibitors can disrupt this HDAC/HSP90 complex and induce degradation of mutant P53".	[194–196]
3	Spautin-1	R175H/C/D, S241F, R248Q/W/L, G245C, E258K, R273H/L, R280K, R282W	"Spautin-1 induces degradation of a broad range of mutant P53 proteins via the chaperone-mediated autophagy (CMA) pathway". "Spautin-1 also induces cell death under non-proliferating conditions only when cancer cells carry mutant P53". However, this effect of Spautin-1 is not dependent on MDM2 and the ubiquitin-proteasome pathway; instead, it is dependent on nuclear export of mutant P53 and the presence of Hsc70 (a member of the heat shock protein 70 families).	[197, 198]
4	MCB-613	R175H	"MCB-613 preferentially targets mutant P53-R175H for lysosomal degradation by destabilizing the deubiquitinase USP15-mediated mutant P53 stabilization."	[199]
5	Statins	V157F, R172H, R175H, Y220C, R248W, R273H, R280K	"Statins induce CHIP-dependent degradation of P53 with conformational alterations".	[200]
6	Gambogic acid	R175H, G266E, R273H, R280K	"Gambogic acid targets and inhibits the mutant P53-Hsp90 complex and induces CHIP-dependent degradation or induce autophagy". "Gambogic acid (GA) induces apoptosis and inhibits tumour growth *in vitro* by upregulating protein expression of wild-type P53".	[201–203]
7	YK-3-237	V157F, M237I, R249S, R273H, R280K	"YK-3-237 reduces mutant P53 levels via deacetylation at lysine 382 by activating SIRT1". "YK-3-237 induces cell cycle arrest and apoptosis in triple-negative breast cancer cell lines with enhanced expression of *PUMA* and *NOXA*."	[204]

inhibition of tumour cell growth both *in vitro* and *in vitro*" [205]. "Romidepsin (Istodax®) is another selective inhibitor of HDACs, was approved for the treatment of cutaneous T-cell lymphoma in November 2009 by the U.S. FDA" [208]. "It is a natural product discovered from the cultures of *Chromobacterium violaceum*, a Gram-negative bacterium isolated from a Japanese soil sample" [208].

Spautin-1

"Spautin-1 is a derivative of MBCQ (4-((3, 4-methylenedioxybenzyl) amino)-6-chloroquinazoline), which identifies as a small molecule designed for inhibition of macroautophagy" [197]. "Spautin-1inhibits ubiquitin-specific peptidase 10 (USP10) and USP13, and promotes degradation of Vps34-PI3 kinase complexes (Phosphatidylinositol 3-kinase) (a key regulator of autophagy) resulting in inhibition of autophagy" [209]. "Spautin-1 also inhibits EGFR (Epidermal growth factor receptor) phosphorylation and the activation of its downstream signalling leading to cell cycle arrest and apoptosis of PCa (Prostate cancer) in a USP10/USP13 independent manner" [210].

MCB-613

"MCB-613 causes rapid ubiquitination, nuclear export, and degradation of mutant P53R175H via a lysosome-mediated pathway, resulting in cancer cell death" [199]. "Steroid receptor coactivators (SRC-1, SRC-2, and SRC-3) are emerging as targets in cancer therapy. MCB-613 acts as a potent SRC small molecule stimulator (SMS) and super-stimulate SRC's transcriptional activity" [211]. "MCB-613 increases SRC's interactions with various other coactivators and significantly induces E.R. (endoplasmic reticulum) stress that results in the generation of ROS and ultimately kills cancer cells" [211].

Statins

"Various mechanistic studies showed that lovastatin treatment inhibits the mevalonate-5-phosphate pathway and consequently induces CHIP (carboxyl terminus of Hsp70-interacting protein) ubiquitin ligase-mediated nuclear export, ubiquitylation, and mutant P53 degradation by inhibiting the interaction of mutant P53 with DNAJA1 (DnaJ Heat Shock Protein Family (Hsp40) member A1)" [200]. "Treatment with lovastatin diminishes *in vitro* and *in vitro* tumour growth only in P53 mutant cancer cells, but not in P53-wildtype cancer cells" [200]. "Thus, statins induced inhibition of the mevalonate pathway may signify a new and practical approach to kill P53 mutant cancer cells" [200].

Gambogic acid

"Gambogic acid (GA) is a xanthone extracted from the resin of Garcinia hanburyi tree. GA induces nuclear exports of mutant P53 for ubiquitination and subsequent degradation mediated by CHIP ubiquitin ligase" [201]. "GA prevents the mutant P53-Hsp90 complex formation but enhances the mutant P53-Hsp70 complex formation" [201]. "Furthermore, gambogic acid induces the degradation of cancer cells carrying mutant P53R280K and P53S241F proteins via autophagy" [202]. "Gambogic acid inhibits the invasion and migration of transforming growth factor β1 (TGFβ1)-induced epithelial-to-mesenchymal transition (EMT) of the orthotopic model of A549 cells *in vitro*" [212]. Gambogic acid also suppressed the EMT induced by TGFβ1 and tumour necrosis factor α by inhibiting the nuclear factor-kappa B (NF-κB) pathway [212]. "In the xenograft pancreatic cancer model, the combination of gambogic acid and gemcitabine significantly repressed tumour growth, and Immunohistochemistry results demonstrated the downregulation of p-ERK, E2F1, and RRM2 in mice receiving gambogic acid treatment and combination treatment" [213].

Reactivation of P53 by MDM2 inhibitors

"MDM2 is the negative regulator of the *TP53* gene and forms an autoregulatory feedback loop that controls the cellular levels of P53 and MDM2, as given in Fig. 4" [215]. Ubiquitination and degradation of P53 is induced by MDM2, which acts as a unique E3 ubiquitin ligase protein. Small molecules that block the MDM2-P53 interaction and reactivate the P53 function seem to be a promising strategy for cancer treatment retaining wild-type P53. Many of these small molecules have also entered clinical trials.

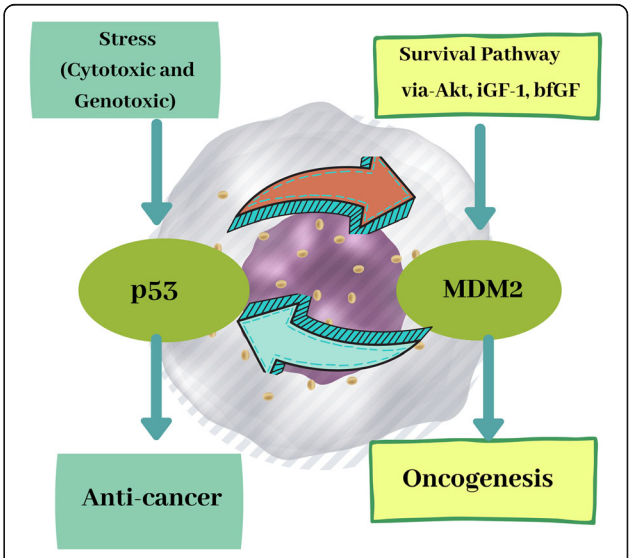

Fig. 4 The autoregulatory feedback loop of MDM2 and P53 controlling their cytological levels [214]

Table 3 Compounds that block MDM2-P53 interaction and reactivate *TP53* gene

S. No.	Name of the Compound	Chemical name or class	Mechanism	References
1	Nutlin-3 (MDM2 antagonist)	Cis-imidazoline	Nutlin-3 is one of the compounds belonging to the class of Nutulins. It is an MDM2 antagonist that induces cell cycle arrest in rapidly proliferating cancer cells on G1 and G2 phases of the cell cycle. "In various cancer cell lines, nutlin-3 induces apoptosis and enhanced cisplatin-induced apoptosis through Fas death receptor pathway in cisplatin-resistant cells."	[216]
2	MI-219 (MDM2-P53 interaction inhibitor)	Spiro-oxindole	"MI-219 is a potent, highly selective, and orally active small-molecule inhibitor of the MDM2-P53 interaction". "In cancer cells with wild-type P53, MI-219 disrupts MDM2-P53 interaction and activates the P53 pathway leading to cell cycle arrest and apoptosis *in vitro* and *in vivo*". A similar effect of activating P53 in established tumour xenograft tissues resulted in cell cycle arrest and apoptosis. "Thus, MI-219 activates P53 in healthy tissues with minimal accumulation of P53. When used in combination with etoposide, MI-219-induced cytotoxicity was not affected by MDM2 knockdown or by an X-linked inhibitor of apoptosis protein (XIAP) inhibitor, suggesting MI-219 could act as a chemosensitizing agent".	[217, 218]
3	MI-319 (MDM2-P53 interaction inhibitor)	Spiro-oxindole	"MI-319 is an analogue closely related to MI-219 and Nutlin-3. Like MI-219, designed to target MDM2-P53 interaction, and it binds to MDM2 protein with a high affinity that is over 500-fold more potent than a natural P53 peptide". Various studies have shown that MI-319, when used in combination with anticancer drug cisplatin, synergistically inhibited cell cycle growth and induced apoptosis in pancreatic cancer.	[219]
4	HLI98 compounds	5-Deazaflavin	"HLI98 family includes compounds that are strictly related to 7-nitro-5-deazaflavin and identified via high throughput screening of MDM2 autoubiquitinylation as inhibitors of MDM2 E3 ubiquitin ligase activity". "5-Deazaflavin is a highly potent, water-soluble inhibitor of MDM2-mediated P53 ubiquitinylation with low micromolar cellular potency". "It results in increased MDM2 and P53 protein levels, leading to selective P53-dependent apoptosis in various cancer cell lines with wild-type P53".	[220, 221]

In Table 3, we have provided an overview of small molecules that block MDM2-P53 interaction and reactivate the *TP53* gene.

Role of P53 in diseases

P53 influences the onset of various lifestyle-related diseases like type 2 diabetes and obesity by altering the regulation of metabolism at the individual level [26]. "Minamino and his colleagues first reported the evidence of linking P53 to the development of type 2 diabetes. They reported that diet-induced insulin resistance in A^y transgenic mice, which are vulnerable to diabetes, is mediated by P53" [222]. "This group showed that inhibition of P53 activity, either by siRNA knockdown in cells or by *TP53* gene knockout in mice, reduced senescence and instigated decreased inflammatory cytokine expression in the adipose tissue of mice, eventually preventing them from developing insulin resistance" [222]. "The P53 codon 72 single-nucleotide polymorphism (Arg 72 Pro) has been associated with the onset of type 2 diabetes" [223]. "In a study using a murine model of Arg 72 Pro, obesity, non-alcoholic fatty liver disease (NAFLD), and diabetes were reported in Arg-genotype mice administered with a high-fat diet" [224]. "Furthermore, relationships between P53 downstream regulatory genes observed among *CDKN1A*, *TNF*, and Niemann-Pick C1-Like 1 (*NPC1L1*) (plays a role in cholesterol metabolism)" [224]. Proper regulation of the MDM2-P53 axis is essential to prevent tumorigenesis and various metabolic diseases. "Using a lipodystrophy mouse model, Liu and his colleagues showed that chronic activation of P53 by deleting MDM2 not only causes adipocyte senescence but also apoptosis, leading to progressive lipodystrophy" [225]. "This model exhibited various metabolic defects, reduced exercise capacity, multiorgan senescence, and shorter life span" [225].

The genome sequencing of cancer has revealed that 42% of cases across 12 tumour types bear mutant *TP53* [163] but taken note that the *TP53* mutation rate also varies across tumour types. "Indeed, P53 is the most commonly mutated gene in some of the most difficult-to-treat cancers such as lung cancer (squamous and small-cell types) [226], triple-negative breast cancer [227], high-grade serous ovarian cancer [228] and esophageal (squamous type) cancer" [229]. "In these cancer types. P53 is mutated in atleast 80% of cases" [163, 226–229]. "Li-Fraumeni syndrome (LFS) is a rare autosomal dominant cancer predisposition syndrome caused by germline *TP53* mutations, first described by Li and Fraumeni in the year 1969" [230]. "Patients who develop this syndrome are at increased risk of multiple primary tumours, including breast cancer, soft tissue sarcoma, brain tumours, osteosarcoma, and adrenocortical carcinoma" [231]. Furthermore, "patients with this syndrome can also develop other cancers, including ovarian, gastrointestinal, pancreatic, genitourinary, skin, thyroid, prostate, and lung, as well as leukaemia, lymphoma, and neuroblastoma" [232].

"Numerous studies have shown that there is a substantial increase in P53 level and activity in neurodegenerative diseases, and it seems to be a common finding" [214]. "In Alzheimer's disease (AD), increased levels of P53 were seen in various parts of the patient's brain [233] when compared with healthy patient's brains. Different animal models of AD also showed an elevation in P53 levels in affected neurons" [234]. Increased P53 levels resulted in increased sensitivity of neurons to various stressors and underwent apoptotic death [235]. "In Parkinson's disease (PD), the same phenomenon of increased P53 level and activity was observed in PD patient's brains as well as in PD animal models" [236]. This increased levels, and activity of P53 was associated with neuronal death and enhanced inflammatory cytokine levels [236]. "A substantially higher level of P53 was also detected in the affected brain areas of Huntington disease (HD) patients and HD animal models [237] as well as in cells overexpressing mutated huntingtin" [238]. A similar phenomenon observed in AD and PD that increased P53 levels was associated with DNA damage, activated cellular stress response, and apoptosis [238]. "Various series of experiments on P53+/+, P53+/- and P53-/- mice transgenic for mutant huntingtin (mHtt) proved a causal role of P53 in HD" [237, 239]. "In this experiment, the genetic deletion of P53 not only reduced the cellular marks of mHtt expression but also protected against neuronal degeneration and improved some of the neurobehavioral defects caused by HD" [237, 239]. "An interesting observation was that even though P53 ablation did not prevent the formation of mHtt containing inclusions, P53-/- mice had lower mHtt level and increased aggregate load resulting in a milder disease phenotype" [239].

"Various experimental studies support the crucial role of P53 in the pathological process of acute kidney injury (AKI) and post-AKI repair of the kidney. Dagher and colleagues in 2003 first described the role of P53 in renal-ischemic-reperfusion injury (IRI) in a rat model" [240]. "They showed that renal ischemic reperfusion-induced P53 expression in renal medulla over 24 hours postal ischemic reperfusion and pifithrin-α induced chemical inhibition of P53 activity at the time of renal ischemia inhibited tubular cell apoptosis and simultaneously resulted in renal functional protection from IRI" [240]. "Molitoris et al. demonstrated that inhibition of P53 by short interfering RNA (siRNA), which was administered at 4 hours intravenously after renal ischemia and primarily uptaken by renal proximal tubule epithelial cells (RPTECs) within the kidney, protected against apoptosis and renal function impairment" [241]. "Zhang and colleagues demonstrated that definite removal of the *TP53* gene from proximal renal tubules protected against IRI in the kidney" [242]. An important observation was that the deletion of P53 from other renal tubules segments was ineffective [242]. The above studies altogether suggest a pathological role of renal tubular cell P53 in IRI.

Various studies indicate that P53 plays a protective role against various systemic autoimmune diseases by inhibiting the production of cytokine and reducing the number of pathogenic cells. "In a meta-analysis report, they have shown that *TP53* codon 72 polymorphism may confer susceptibility to systemic lupus erythematosus (SLE) in Asians but not in Europeans. In contrast, there was no association between *TP53* codon 72 polymorphism and rheumatoid arthritis (RA) in all study subjects" [243]. Conversely, Macchioni et al. reported an association between the *TP53* codon 72 polymorphism and joint erosion in RA [244]. Also, Chen et al. have shown that patients with Hashimoto's thyroiditis displayed a higher ratio of arginine homozygosity at *TP53* codon 72 than healthy subjects [245]. The precise mechanisms of how P53 protects against the development of autoimmune diseases remains unclear.

Conclusion

In this review, we have attempted to present a comprehensive overview of some of the P53 functions by discussing the various mechanism of P53, focusing on P53-mediated DNA damage response, and P53 role in different cellular processes like DNA repair mechanism, apoptosis, autophagy, and metabolism. We have also put some light on various P53-reactivation strategies that hold great importance in cancer therapy in the future as many small molecules are under investigation. We have also discussed how P53 levels change in various diseases. In addition to its function as guardian of the genome under various cellular stress, numerous studies suggest that P53 is allied with many other physiological processes and also different pathological processes. Following several decades of research, the complete role of P53 remains unclear. Owing to a vast and variety of P53 regulatory mechanisms and their collaboration in triggering specific responses remains an open area for research.

Abbreviations

TP53: Tumour protein 53; MDM2: Mouse double minute 2 homologue protein; DBD: DNA-binding domain; NES: Nuclear export signal; PTMs: Post-translational modifications; ARF: Alternative reading frame; *DDB2*: Damage specific DNA-binding protein 2; *XPC*: *XPC* complex subunit, DNA damage recognition and repair factor; *CDKN1A*: Cyclin-dependent kinase inhibitor 1; *GADD45A*: Growth arrest and DNA damage inducible alpha; *BBC3*: *BCL2* binding component 3; *PUMA*: P53 upregulated modulator of apoptosis; *BCL-2*: B-cell Lymphoma 2; *BAX*: *BCL-2*-associated X, Apoptosis regulator; TIGAR: *TP53*-induced glycolysis regulatory phosphatase; *ALDH1A3*: Aldehyde dehydrogenase 1 family, member A3; *PPM1D*: Protein phosphatase, Mg2+/Mn2+ dependent 1D; WIP1: Wild-type P53-induced phosphatase 1; PP1: Protein phosphatase 1; *APAF1*: Apoptotic peptidase activating factor 1; PML: PML nuclear body scaffold; *YPEL3*: Yippee-like 3; ATM: ATM serine/threonine kinase; ATR: ATR serine/threonine kinase; CHEK1 or CHEK2: Checkpoint kinase 1 or 2; NBN: Nibrin; CDK: Cyclin-dependent kinase;

RB1: RB transcriptional corepressor 1; H2AX: H2A.X variant histone; 14-3-3σ: 14-3-3 Phospho-serine/phospho-threonine binding proteins; CDC2: Cell division control protein 2 homologue; $P21^{CIP1}$: Cyclin-dependent kinase inhibitor 1; P16 INK4A: A protein encoded by the gene *CDKN2A* (Cyclin-dependent kinase inhibitor 2A); SA-β-gal: Senescence-associated beta-galactosidase; *SERPINE1*: Serpin family E member 1; *PAI-1*: Plasminogen activator inhibitor-1; TRIM: Tripartite motif-containing protein superfamily; SASP: Senescence-associated secretory phenotype; TNF-α: Tumour necrosis factor alpha; SSBs: Single-strand breaks; DSBs: Double-stranded breaks; NER: Nucleotide-excision repair; BER: Base-excision repair; NHEJ: Non-homologous end-joining; HRR: Homologous recombination repair; SSA: Single-strand annealing; CPDs: Cyclobutane pyrimidine dimers; 6-4PPs: (6-4) Pyrimidine-pyrimidone photoproducts; POLII: RNA polymerase II; GG: Global-genome; RRM2B: Ribonucleotide Reductase Regulatory *TP53* Inducible Subunit M2B; RR: Ribonucleotide Reductase; PCNA: Proliferating Cell Nuclear Antigen; POLH: DNA polymerase eta; XPV: Xeroderma pigmentosum variant; TLS: Translesion synthesis polymerases; XP: Xeroderma pigmentosum; CS: Cockayne syndrome; CASPASES: Cysteine-aspartic proteases; FAS: FS-7-associated surface antigen; TNFSF10: TNF superfamily member 10; TRAIL: TNF-related apoptosis-inducing ligand; DR: Death receptors; TNFRSF10A: Tumour necrosis factor (TNF)-receptor superfamily member 10a; TNFRSF10B: Tumour necrosis factor (TNF)-receptor superfamily member 10b; TNFRSF1A: TNF receptor superfamily member 1A; MOMP: Mitochondrial outer membrane permeabilization; *BAK*1: *BCL2* antagonist/killer 1; *PMAIP1*: Phorbol-12-myristate-13-acetate-induced protein 1; *BBC3*: *BCL-2*-binding component 3; *BCL2L1*: *BCL2* like 1; *AEN*: Apoptosis-enhancing nuclease; *CERS5*: Ceramide Synthase 5; *CERS6*: Ceramide Synthase 6; *TRIAP1*: *TP53* Regulated Inhibitor of Apoptosis 1; *DRAM1*: DNA damage-regulated autophagy modulator 1; *ULK1*: UNC-51-like autophagy-activating kinase 1; *TSC2*: Tuberous Sclerosis Complex subunit 2; *PTEN*: Phosphatase and tensin homologue; *PRKAA2*: Protein kinase AMP-activated catalytic subunit alpha 2; mTOR: Mechanistic target of rapamycin kinase; *BNIP3*: *BCL2* Interacting Protein 3; *DAPK-1*: Death-associated protein kinase 1; MAP 1 LC3A: Microtubule-associated protein 1A/1B-light chain 3 alpha; MAP1 B: Microtubule-associated protein 1B; SLC2A1: Solute carrier family 2 member 1; GLUT1: Glucose transporter type 1; SLC2A4: Solute carrier family 2 member 4; GLUT4: Glucose transporter type 4; SLC2A3: Solute carrier family 2 member 3; GLUT3: Glucose transporter type 3; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; TIGAR: *TP53*-inducible glycolysis and apoptosis regulator; PFK1: Phosphofructokinase 1; PGM: Phosphoglycerate mutase; miR-34a: MicroRNA-34a; *RRAD*: Ras-related glycolysis inhibitor and calcium channel regulator; *PDK2*: Pyruvate dehydrogenase kinase 2; *PDH*: Pyruvate dehydrogenase; *PRKN*: Parkin RBR E3 ubiquitin-protein ligase; *PDH*1A: Pyruvate dehydrogenase E1 subunit alpha 1; GLS2: Glutaminase 2; MCAT: Malonyl-CoA-acyl carrier protein transacylase; SCO2: Synthesis of cytochrome *c* oxidase 2; ETC: Electron transport chain; *AIFM1*: Apoptosis-inducing factor mitochondria associated 1; MIEAP: Mitochondria-eating protein; PPP: Pentose phosphate pathway; AKT1: AKT serine/threonine kinase 1; G6PD: Glucose-6-phosphate dehydrogenase; *PANK1*: Pantothenate kinase-1; *G6PC*: Glucose-6-phosphatase catalytic subunit; *PCK1*: Phosphoenolpyruvate carboxykinase-1; GK: Glycerol kinase; *SIRT6*: Sirtuin 6; FOXO1: Forkhead box protein O1; FAO: Fatty acid oxidation; *CROT*: Carnitine O-Octanoyltransferase; *CPTA1*: Carnitine palmitoyltransferase 1A; *CPT1C*: Carnitine palmitoyltransferase 1C; *LPIN1*: Lipin1; FAS: Fatty acid synthesis; SREBP: Sterol regulatory element-binding proteins; SCD1: Stearoyl-CoA-desaturase 1; MUFAs: Mono-unsaturated fatty acids; *SLC7A3*: Solute carrier family 7 member 3; PHGDH: Phosphoglycerate dehydrogenase; *ATF4*: Activating transcription factor 4

Acknowledgements
We thank Dr. Y. Srinivasa Rao and Mr. Vinod Kumar Mugada for their continuous support and help to carry out the article review process.

Authors' contributions
W.F. contributed towards the concept of the article. A.M.A.S. designed the framework of the article and contributed towards drawing the figures. Supervision—A.M.A.S. W.F. was a major contributor for the literature research and writing of the manuscript. Critical reviews—all authors read and approved the final manuscript.

Funding
None

Availability of data and materials
This article is a review article and does not need any data and materials.

Ethics approval and consent to participate
This is a review article; thus, it does not involve studies with human beings as participants performed by any of the authors.

Consent for publication
All authors provided the consent to publish the review article.

Competing interests
All the authors declared that there are no competing interests (none).

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Received: 5 June 2020 Accepted: 11 August 2020
Published online: 16 November 2020

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