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Understanding the complexity of p53 in a new era of tumor suppression

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SUMMARY

p53 was discovered 45 years ago as a SV40 large T antigen binding protein, coded by the most frequently mutated *TP53* gene in human cancers. As a transcription factor, p53 is tightly regulated by a rich network of post-translational modifications to execute its diverse functions in tumor suppression. Although early studies established p53-mediated cell-cycle arrest, apoptosis, and senescence as the classic barriers in cancer development, a growing number of new functions of p53 have been discovered and the scope of p53-mediated anti-tumor activity is largely expanded. Here, we review the complexity of different layers of p53 regulation, and the recent advance of the p53 pathway in metabolism, ferroptosis, immunity, and others that contribute to tumor suppression. We also discuss the challenge regarding how to activate p53 function specifically effective in inhibiting tumor growth without harming normal homeostasis for cancer therapy.

Keywords

p53; tumor suppression; p63; p73; MDM2; MDMX; apoptosis; cell-cycle arrest; senescence; genome stability; metabolism; ferroptosis; stem cell dynamics; cell competition; metastasis; immunity; p53 mutation; targeting p53; cancer treatment

INTRODUCTION

Discovered in 1979, the p53 protein, encoded by the tumor protein p53 (*TP53*, or p53) gene, has captivated the attention of both the cancer research community and the pharmaceutical industry, positioning it the most extensively studied gene.[1] Over the past 45 years of research, p53 has consistently yielded both surprise and excitement, albeit accompanied

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DECLARATION OF INTERESTS

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by persistent confusions. Numerous efforts have been dedicated to understanding p53. In return for this, we now have a better picture of this gene (Figure 1). However, there are still certain aspects of p53 that remain unclear. In this review, we first introduce the basic information about p53 and its regulatory mechanisms. We then summarize the functions of p53 and its roles in both normal physiological conditions and various pathological disorders, particularly cancers. Finally, we discuss the therapeutic applications of targeting p53 and the unaddressed issues in the p53 field. Due to space constraints, many original research papers and important reviews on p53 could not be cited.

DISCOVERY, EVOLUTION, AND STRUCTURE OF p53

The study of p53 has experienced several pivotal twists and turns over the past decades, mirroring the tortuous development of oncology, characterized by significant paradigm shifts.[2–5] In 1979, the p53 protein was independently discovered by several laboratories during research on cells transformed by simian virus 40 (SV40) or through other methods.[6–9] Initially, p53 was believed to be an oncogene involved in cell transformation. However, in 1989, a series of papers revealed that wild-type (WT) p53 is, in fact, a tumor suppressor (Figure 1).[2–5,10–14]

The human p53 gene family comprises three members p53, p63, and p73. This family originated at least 800 million years ago and followed by gene duplication and structural diversification.[15,16] An intriguing discovery is that the p53 family gene is present in some unicellular eukaryotes, such as the choanoflagellate Monosiga brevicollis, suggesting its important role in the evolution of multicellular organisms. The p53 family gene in unicellular eukaryotes is believed to maintain genome stability in response to various stresses. The p53 gene emerged in the earliest vertebrates and has since been evolutionarily conserved.[15,16] The presence of p53 family in lower organisms is remarkable, given their minimal risk of cancer. This raises a question about the primitive role of p53 family in evolution. It is possible that this family was initially involved in maintaining the integrity of germline cells, with its well-known tumor suppression capability emerging much later.

The p53 protein primarily functions as a transcription factor (TF), although TF-independent activity has also been implicated (Figure 2).[15,17,18] The full-length p53 protein (FLp53) in human comprises 393 amino acids, which are organized into five different domains: the N-terminal transactivation domain (TAD), the proline-rich domain (PRD), the central DNA-binding domain (DBD), the tetramerization domain (TD), and the C-terminal regulatory domain (CTD). The TAD of p53 is divided into two subdomains TAD1 and TAD2.[15,19] In unstressed cells, p53 protein adopts a mixture of monomeric, dimeric, and tetrameric states, with dimer predominating.[20] Upon diverse types of stress signals (including DNA damage, oncogene activation, ribosomal stress, telomere erosion, nutrient deprivation, and hypoxia), the majority of p53 proteins rapidly assemble into a functional tetramer (a dimer of dimers) via its TD. By using the DBD, this tetramer recognizes the p53 binding sites located at either the promoters or enhancers of target genes to modulate transcription. Unlike the well-folded DBD, whose structure has been solved, the TAD and CTD of p53 are intrinsically disordered, facilitating their interaction with cofactors for transcription mediation.[15] These two domains are also the major regions to undergo post-translational

modifications (PTMs).[21] The PRD also contributes to the activity of p53.[22] p53 is recruited to DNA via a specific response element (RE) composed by two decameric repeats: RRRCWWGYYY (R, purine; W, A or T; and Y, pyrimidine).[23] p53 directly regulates the transcription of more than 300 target genes. In view of the indirect targets, p53 is believed to mediate the expression of several thousands of genes.[24] Majority of the reported targets are protein-coding genes, but p53 also regulates various non-coding RNAs.[25]

REGULATION OF p53: PTM IS THE KEY

To accurately execute its multifaceted functions, the expression and activity of p53 are subject to elaborate and multilayered regulation at the protein, DNA, and RNA levels (Figure 2).[23,26]

Regulation of p53 at the protein level

The p53 protein can undergo many types of PTMs, including ubiquitination, phosphorylation, acetylation, methylation, SUMOylation, NEDDylation, O-GlcNAcylation, ADP-ribosylation, UFMylation, hydroxylation, β-hydroxybutyrylation, sulfation, and isoLG adduction.[21,27–29] Different stress signals determine the site and type of PTMs. Many PTMs of p53 are reversible. The overall effect of PTMs on p53 include altering its protein level, cellular localization, cofactor recruitment, target selectivity, and even protein aggregation.[21,29,30] Among these, ubiquitination, phosphorylation, and acetylation are the most common and influential in affecting p53 activity.

Ubiquitination typically occurs at the C-terminal lysine residues of p53. Mouse double minute 2 homolog (MDM2) is the most well-known regulator of p53, ubiquitinating p53 to maintain low protein levels in unstressed cells or to export nuclear p53 to the cytoplasm.[21] Many stimuli and regulators activate p53 through alleviating repression by MDM2.[21] For instance, the $p14^{ARF}$ protein can stabilize p53 via inhibiting MDM2-mediated degradation of p53. Convincing evidence supporting the importance of MDM2-mediated p53 inhibition comes from mouse models, where the MDM2 deficiency-caused embryonic lethality can be rescued by deleting p53.[31,32] Interestingly, MDM2 is itself a target gene of p53.[33] The MDM2-p53 feedback loop forms the core in p53-associated pathways. MDMX (or MDM4), a family member of MDM2, although lacking E3 ubiquitin ligase activity itself, can form a heterodimer with MDM2 to enhance the degradation of p53. Other E3 ubiquitin ligases that can degrade p53 include ARF-BP1/HUWE1, COP1, CHIP, and Pirh2.[21]

Serine and threonine phosphorylation sites span across the p53 protein. The phosphorylation of p53 by ATM represents the earliest mechanism demonstrating how p53 responds to DNA damage.[34,35] Phosphorylation at S15, T18, and S20 disrupts the binding and inhibition of p53 by MDM2, while enhancing interaction with transcription cofactors such as CBP. As a result, p53-mediated transcription is activated to induce cell-cycle arrest and apoptosis.[36–38] Severe DNA damage further phosphorylates p53 at S46, strengthening apoptosis.[39]

Acetylation of several lysine residues in the DBD is critical for p53's ability to activate key targets responsible for cell-cycle arrest, apoptosis, senescence, ferroptosis, and mTOR inhibition in a promoter-specific manner. The impact of p53 acetylation in tumor

suppression is best illustrated by a series of acetylation-defective knock-in mouse models.[40–46] For example, although the p53–3KR mutant, retaining its DNA binding activity, fails to activate the major targets such as p21 and PUMA critical for cell-cycle arrest, apoptosis, and senescence, the p53–3KR mutant mice are not tumor prone.[41] However, further elimination of its ability to regulate ferroptosis and the mTOR pathway by p53–4KR and p53–5KR mutants recapitulates the loss of its tumor suppressor function as observed in p53-null mice.[43] Notably, the role of acetylation in the CTD is complexed by the fact that the same lysine residues are also modified by methylation, ubiquitination, SUMOylation, and NEDDylation, in addition to acetylation. Thus, the CTD acetylation-defective mutant (p53–6KR and p53–7KR) mice fail to show dramatic impact in tumor suppression as these mutants eliminate both positive and negative effects on p53 function by different types of PTMs.[45,46] Indeed, the acetylation–mimicking (p53-KQ) mutant mice show substantial p53 activation in transcription and tumor suppression without increasing p53 protein levels, underscoring the role of the CTD acetylation *in vivo*.[42,44]

Taken together, a gamut of the various PTMs cooperatively orchestrate the activity of p53. A serious caveat is that, albeit many PTMs are proven crucial for regulating p53 *in vitro*, the *in vivo* functions might be more complex.[21] Knock-in mouse models serve as valuable tools for elucidating the functions of specific PTMs in modulating p53 activity.

At the protein level, recruitment of cofactors is another important parameter influencing p53 activity. p53 protein can bind to a plethora of interacting partners, including both activators and repressors, which profoundly affect its folding, stability, cellular localization, DNA binding, transactivation ability, and target selection.[23,47] For example, a group of chaperone proteins regulate p53's folding and stability.[48–50] MDM2 and MDMX bind the TAD of p53 to restrict its transactivation activity, independently of MDM2's role as an E3 ubiquitin ligase.[51] Several transcription regulators such as PBRM1, SET, and Dicer are able to interact with p53 in an acetylation-dependent manner.[40] The components of the m6A methyltransferase complex, METTL3 and RBM15, interact with p53 to selectively modify the mRNAs of a group of p53 target genes.[52,53]

The local chromatin structure and epigenetic state also play a crucial role in dictating p53's DNA binding and effective transcriptional induction. In glioblastoma, BRD8 maintains a repressive chromatin state by retaining histone variant H2AZ at p53 target loci, thus blocking p53 recruitment.[54] TRIM24 simultaneously binds p53 and unmethylated H3K4, impeding chromatin opening by p53.[55] p53 can cooperate with other locally bound TFs to establish an accessible chromatin state and boost transcription.[56]

Regulation of p53 at the DNA and RNA levels

The modulation at the DNA and RNA levels substantially influences the protein level of p53.[26] p53 gene possesses two promoters, which leads to alternative transcriptional initiation.[57] The promoter region of the p53 gene can undergo DNA methylation and histone methylation, thereby impacting its transcription.[58,59] Multiple TFs control the transcription of the p53 gene.[26] The pre-mRNA of p53 may undergo alternative splicing.[60] Besides, the stability, localization, and translation of p53 mRNA are all tightly regulated.[61–63]

p53 activation is not a simple all-or-none mode, but a dynamic process. The heterogeneity of cells, the characteristic of stresses, the diversified regulatory factors above, and the stability of target genes together determine the dynamics of p53 activity.[23,64,65]

VARIANTS, ISOFORMS, AND FAMILY MEMBERS OF p53

Besides the diverse regulatory means acting on WT FLp53, the field is further complicated by the presence of p53 variants (including single nucleotide polymorphisms (SNPs) and mutants), isoforms, and other family members (Figure 2).

p53 SNPs: twins are different

The P72R polymorphism is the most extensively studied SNP of p53. The P72 variant has a weaker ability to induce apoptosis compared to the R72 variant,[66] and thus is associated with a longer lifespan but a higher cancer mortality than the latter.[67,68] However, there is also report that people bearing the P72 variant are less susceptible to HPV-associated carcinogenesis.[69] Mice carrying the R72 variant of p53 show a higher propensity for metabolic dysfunction,[70] yet they also exhibit increased rates of embryo implantation in females[71]. There are also several ethnic-specific SNPs in the p53 gene that have implications for disease susceptibility and treatment.[72]

p53 mutants: guardian has a dark side

Beyond SNPs, the p53 gene undergoes other types of genetic variation, such as deletions, and more commonly, mutations. p53 is among the most frequently mutated genes in cancers, with over half of all cancers possessing a mutated p53 allele. Missense mutation is the predominant mutation type of p53. There are six notable hotspots for missense mutations: R175, G245, R248, R249, R273, and R282, that all locate in the DBD, accounting for nearly 30% of all missense mutations of p53. Other sites with relatively higher incidences of missense mutations include H179 and Y220.[15,73,74] All missense mutations affect the thermal stability of p53 to varying degrees. Generally, missense mutations can be classified into contact mutations, which maintain the overall conformation of p53 but impair DNA binding (e.g., R248W and R273H), and structural/conformational mutations, which significantly alter the conformation and stability of the DBD (e.g., R175H, G245S, and R249S), all disrupting p53's TF activity. R196, R213, R306, and R342 are major sites for nonsense mutations.[15,73,74] While most cancer patients acquire p53 mutations in their somatic cells, a notable exception is seen in patients with Li-Fraumeni syndrome (LFS), who carry a germline mutant p53 and have up to a 90% lifetime risk of developing one or more cancers and 50% of them get cancer before 30 years old.[75,76] Notably, normal somatic cells may also harbor p53 mutations and other oncogenic mutations,[77,78] raising the question of whether these cells are predisposed to oncogenesis under certain conditions.

The functional outcome of mutant p53 can be attributed to three different effects: (1) Loss-of-function (LOF): mutant p53 loses the activity of WT p53. For example, p53 mutants are often impaired in their ability to induce cell-cycle arrest and apoptosis.[79] (2) Dominant-negative effect (DNE): mutant p53 interferes with the function of any remaining WT p53. In human pluripotent stem cells, mutant p53 confers an advantage in accelerating

self-renewal.[80] However, this DNE in normal tissues may not be as common as in cancer cells, as the levels of mutant p53 in normal cells are often kept low, similar to WT p53. (3) Gain-of-function (GOF): mutant p53 acquires additional activities not observed by loss of WT p53, typically through interaction with specific cofactors. The GOF of mutant p53 is largely attributed to its accumulation to high levels in cancer cells. For instance, mutant p53 can co-aggregate with WT p53 and other tumor suppressors (such as p63 and p73).[81,82] The p53 hotspot mutants gain anti-ferroptosis activity to promote tumor growth.[83,84] By modulating the expression of pro-metastatic targets, the p53 mutants are able to enhance the metastatic potential of cancer cells in different mouse models.[83,85–88] Depsite the overwhelming evidence indicating the importance of the GOF of p53 mutants,[89] one recent study showed that the LOF but not the GOF of p53 mutants is more critical under different experimental settings[90]. Nevertheless, categorizing p53 mutations into only one of these three effects is over-simplistic and whether the GOF or the LOF plays a more dominant role *in vivo* is likely context-dependent. It is clear that the overall outcome induced by p53 mutations results from the combination of all the three effects described above.

p53 isoforms: one root, many branches

Beyond FLp53, the p53 gene can produce other protein isoforms, resulting from promoter selection, alternative splicing, alternative translation, and even post-translational cleavage of FLp53.[57] Attributable to combinations of four distinct N-termini (ATG1, Δ40, Δ133, and Δ160) and three different C-termini (α, β, and γ), there are twelve canonical isoforms of the p53 protein. The expression of these isoforms depends on the isoform type, developmental stage, tissue type, and is also subject to various regulatory mechanisms. These isoforms may possess unique activities, with the N-terminal isoforms being better investigated than the C-terminal ones. Particularly, they are often dysregulated in different cancers.[57] For example, Δ40p53 suppresses tumor cell growth,[91] while Δ160p53 can cooperate with mutant p53 to facilitate tumorigenesis[92].

p63 and p73: siblings stand together

p53 shares high structural similarity with p63 and p73, especially in the DBD. Yet they also show differences in structure.[15] These structural features result in both shared and distinct functions among the three proteins. Both p63 and p73 are able to regulate a number of well-known p53 targets,[93] and exhibit tumor suppression activity[94]. Compared to p53, p63 and p73 have more roles in germ cell protection, fertility maintenance, and development regulation.[16,95] For instance, p63 knockout (KO) mice exhibit defects in limb, craniofacial, and epithelial development, while p73 KO mice display neurological abnormalities.[95]

FUNCTIONS OF p53: DIVERSITY AND COMPLEXITY

p53 regulates a vast range of functions, constituting the complex p53 network (Figure 3).[96]

Cell-cycle arrest, apoptosis, senescence, and genome stability

The inductions of cell-cycle arrest, apoptosis, and senescence are among the earliest discovered functions of p53.[2] Various stress signals can induce p53 to exert these functions, with DNA damage being the most potent trigger. Upon DNA damage, p53 is stabilized and

activated to arrest the cell cycle, providing cells with a time window and adequate material and energy spared from cell cycle progression to repair damaged DNA. If the damage is too severe to repair, apoptosis and senescence will be elicited by p53 to eliminate the compromised cells. Notably, the outcome of p53 activation is also determined by the type of cell and DNA damage. These three activities are well accepted as the major barriers to prevent tumorigenesis.

On the other hand, failure to eliminate the damage cells leads to genomic instability. The loss of p53, including loss of heterozygosity (LOH) and biallelic inactivation or deletion, promotes genomic instability and drives the evolution of the tumor cell genome.[97–99] p53 is well known as "guardian of the genome",[100] thus a highly relevant activity of p53 is to directly promote DNA damage repair. Indeed, a number of p53 targets have been identified to contribute to the DNA repair process.[101,102] Nevertheless, it remains unclear whether p53-mediated activation of those DNA repair-related targets is sufficient to suppress tumorigenesis independent of other p53 activities.

Metabolism and ferroptosis

p53 is a master regulator in modulating metabolism of glucose, lipids, amino acids, nucleotides, iron, and redox processes. It also regulates autophagy and has broad crosstalks with key metabolic regulators such as AMPK, AKT, and mTOR.[103] This function of p53 links it to several metabolic disorders, especially cancers. In general, p53 represses anabolic processes (such as *de novo* lipogenesis and nucleotide synthesis), while promotes catabolisms (including oxidative phosphorylation, lipolysis, and fatty acid oxidation). The enhanced glycolysis generates multiple molecular materials for biosynthesis in cancer cells and thus is inhibited by p53, as well.[103] These activities of p53 counteract the rapid proliferation requirements of cancer cells, thus leading to tumor suppression.

However, p53 manifests bidirectional roles in many metabolic processes. This paradoxical activity lies in the context-dependent nature of p53 function.[96,104] The role of p53 in ROS control provides a good example. When there is a low intensity of ROS (indicating mild, transient, tolerable, and mitigable stresses), p53 plays an anti-oxidative role to reduce it to safeguard the cell from damage (pro-survival). On the contrary, when ROS levels are excessively high and potentially cause uncontrollable damage (representing severe, prolonged, detrimental, and unrelievable stresses), p53 further intensifies the ROS, leading to cell death and limiting harm in the damaged cells, thus protecting nearby undamaged cells (pro-death).[47,103,105]

Ferroptosis is an iron-dependent form of regulated cell death that occurs upon excess levels of lipid peroxidation, tightly linked with metabolic pathways. Several metabolic targets of p53 including SLC7A11, VKORC1L1, GLS2, and PLTP are directly involved in modulating ferroptosis.[106–111] Similar to apoptosis during the DNA damage response, ferroptosis is able to eliminate the severe damaged cells during metabolic stress.[112] By using acetylation-defective p53 mouse models, p53-mediated ferroptosis is implicated as an important arsenal in tumor suppression[41,43] and interestingly, the defect in p53-mediated ferroptosis caused by an African-specific p53 SNP impairs its tumor suppressive function.[113] Unlike apoptosis, initiation of canonical ferroptosis often relies on the treatment of cells with ferroptosis

inducers, such as GPX4 inhibitors. It remains unclear whether ferroptosis-dependent tumor suppression requires ferroptosis inducers *in vivo*. Notably, a recent study showed that PHLDA2-mediated phosphatidic acid peroxidation triggers a non-canonical ferroptotic response in the absence of common ferroptosis inducers.[114] Since p53 is able to promote both canonical and non-canonical ferroptotic processes, it will be interesting to examine which ferroptotic pathway plays a more dominant role in p53-mediated tumor suppression.

Stem cell dynamics and cell competition

Stem cells share many similarities with cancer cells, including sustained proliferative ability, reprogrammed metabolism, and the core transcription network. Therefore, it is not surprising that p53 restricts the cell stemness and modulates cell fate in various types of stem cells.[115,116] In embryonic stem cells (ESCs), p53 inhibits genes that maintain stemness while activating those related to differentiation.[117,118] In diverse types of adult stem cells (ASCs), p53 represses self-renewal, promotes depletion, maintains quiescence, or stimulates the differentiation.[116] The ability of p53 to limit stemness is critical to its tumor suppression function, as it impedes the formation of cancer stem cells.[119,120] Specific differentiation route guided by p53 contributes to tumor suppression in lung cancer.[121] Loss or mutation of p53 may cause dedifferentiation, cell reprogramming, and increased cellular plasticity in cancers.[122,123] The course of generating induced pluripotent stem cells (iPSCs) resembles dedifferentiation and cell transformation. p53 serves as a major brake in this process, and silencing p53 greatly improves the efficiency of iPSC generation.[124,125]

Cell competition is vital in development, tissue injury repair, tumor evolution, and metastasis. Generally, as p53 inhibits anabolism and proliferation while promoting cell death, which are not beneficial for cell to outcompete neighboring cells, a high level of p53 activity often marks a “loser” cell state in cell competition.[126] However, there is a study that reports p53 activity is required for supercompetitor cells to eliminate nearby normal cells in Drosophila.[127] The regulation of cell competition by p53 has significant physiological implications.[128–131] Cells harboring mutant p53 may undergo clonal expansion, potentially driving tumor initiation and evolution.[80,132,133] However, these p53 mutant cells are not always retained, as they may experience necroptosis by competing with nearby normal cells, or be outcompeted by cells with mutations in other genes that confer higher fitness.[134,135]

Metastasis

p53 suppresses metastasis at its multiple stages and in both cell-autonomous and non-cell-autonomous manners.[136] In tumor cells, p53 restricts their mobility and epithelial-mesenchymal transition (EMT) process.[136] Metastatic cancer cells in circulatory system may undergo anoikis and ferroptosis, both of which are promoted by p53 to prevent cancer cell migration to new sites.[106,136] At each step of metastatic spread, cancer cells adopt specialized metabolic programs to meet their energy and biomolecular requirements, which can be counteracted by p53.[103,137] On the other hand, p53 shapes a tumor microenvironment (TME) that is unfavorable for metastasis. For example, p53 restrains the angiogenesis and lymphangiogenesis, blocking the main metastatic routes via blood and lymphatic systems.[138,139] It also maintains the integrity of extracellular matrix and enhances tumor

cell adhesion to it, limiting tumor cell movement.[140] Moreover, p53 hinders pro-metastatic inflammation.[141]

Immunity

Another essential function of p53 is to regulate immune response. p53 functions in both innate and adaptive immunity through multiple mechanisms.[142,143] Both p53 in tumor cells and non-tumor cells synergize to construct a tumor-suppressive immune network. In tumor cells, p53 indirectly represses PD-L1 expression by upregulating miR-34, sensitizing tumor cells to anti-tumor immune response and immunotherapy.[144] p53 activates cGAS-STING pathway to induce anti-tumor activity.[145] In a mouse liver carcinoma model, restoring p53 expression induces tumor cell senescence, triggering the release of inflammatory cytokines and eliciting an innate immune response to eliminate tumor cells.[146]

In hepatic stellate cells, p53-induced senescence also exhibits a tumor-suppressive effect in liver cancer, establishing a senescence-associated secretory phenotype (SASP) that bolsters M1 macrophage polarization to maintain a tumor-inhibitory TME.[147,148] In a subtype of murine myeloid precursor cells, p53 drives their differentiation into $Ly6c^{+}CD103^{+}$ monocytic antigen-presenting cells, enhancing anti-tumor immunity.[149]

Loss of p53 in tumor cells or TME cells significantly reverses the tumor-suppressive immune microenvironment to an immunosuppressive condition, promoting the immune tolerance or escape of tumor cells, or establish an inflammatory environment conducive to tumor metastasis.[150,151] Mutant p53 may stimulate tumor cell immune evasion,[143,152] and intriguingly, p53 mutants themselves can generate neoantigens that may be novel immunotherapeutic targets.[153–155]

p53 participates in autoimmune responses and immune defenses against various pathogens as well.[142,156] Noteworthily, not all immunity-related activities of p53 promote immune cell function or are beneficial to health. p53 may inhibit the proliferation and function in certain T cell subtypes.[157,158] For instance, p53 suppresses antigen-non-specific $CD4^{+}$ T cell proliferation, a process that can be abolished by T cell receptor (TCR) signaling.[158] Some viruses rely on p53 activity for cell-cycle arrest and replication.[156]

Rethinking the multitudinous functions of p53

p53 is such a powerful regulator with an array of diverse and complex functions that summarizing its roles in just a few words is challenging. These functions are intricately orchestrated by this single protein to achieve a unified biological purpose. Simplified expressions are often used to describe the working model of p53, such as “guardian of the genome”,[100] “protector or killer”,[47] and “pro-survival or pro-death”[159]. The working mode of p53 originates from the protection of germ cells by the ancestral p53 gene in lower organisms.[160] Human p53 plays a similar protective role in somatic cells. In the majority of species expressing p53 or p53-like gene, this gene is essentially a stress-responder, but not merely a tumor suppressor. Therefore, p53 could also be called the “guardian of the cell”.[21] The tumor-suppressive role of p53 may be considered coincidental, as some of its guardian functions are inherently antagonistic to many cancer cell characteristics. Thus, p53’s normal activity incidentally represses tumor initiation and development.

p53 IN PHYSIOLOGY AND PATHOLOGY: GUARDIAN IS AN ALL-ROUNDER

Due to its myriad functions, p53 is involved in a multitude of biological processes in normal physiology. However, both normal and dysregulated p53 activity also contribute to various disorders (Figure 3).

Reproduction, development, regeneration, repair, and aging

p53 predominantly influences maternal reproduction.[161,162] Mechanistically, p53 transactivates leukemia inhibitory factor (LIF), a key cytokine for implantation, in the uterus. Lower LIF levels in p53-null female mice cause impaired implantation.[162] In women under 35 with infertility, the P72 variant of p53, which has a weaker transactivating effect on LIF, is overrepresented, suggesting a positive correlation between p53 activity and implantation rate.[71]

p53's regulation of development is rooted in its pivotal roles in the cell cycle, cell death, stem cell dynamics, and cell competition.[116] p53 maintains genomic integrity in stem cells of embryo, promote differentiation, and permit normal development.[116] The activity of p53 in early development must be kept in check, as evidenced by that deregulated p53 (loss, hyperactivation, and mutation) is linked to a variety of developmental defects in mice and humans.[163,164] p53 also functions in distinct types of ASCs to maintains proper tissue hierarchy by protecting their integrity, holding them in dormancy, fine-tuning differentiation route, preventing unlimited proliferation, unordered differentiation, and dedifferentiation, plus suppressing tumorigenesis.[116] p53 also plays a role in tissue regeneration.[165] A recent study reported that p53 facilitates alveolar regeneration by regulating AT1 differentiation.[121] As the wound healing course has many similarities with metastasis, p53 is supposed to impede it.[166]

Theoretically, p53's activity has both pro-aging and anti-aging effects. On one hand, p53-mediated stress (particularly the DNA damage, a key driver of aging) response supports cell survival, removes damaged cells, protects tissue integrity, and maintains organismal homeostasis, potentially delaying aging. However, excessive and persistent DNA damage response by p53 has the opposite effect on aging.[167] On the other hand, stem cell depletion by p53 accelerates aging process,[38,168] yet there are counter-examples.[169,170] Furthermore, functions of p53 in modulating senescence, metabolism, immune activity, and its interplay with sirtuins are also related to aging mediation.[171,172] The relationship between p53 activity, tumor suppression, and aging has been investigated in different mouse models and little consensus has reached, which may stem from the highly context-dependent nature of p53's function.[170,173–177] Insights into the relationship between p53, cancers, and aging may be gleaned from studying animals other than mice.[178] A notable example is the elephant, which has twenty copies of the p53 gene and exhibits a low tumor incidence along with a long lifespan.[179] More efforts are required to dig out the role of p53 in aging, hoping to develop interventions that could better balance tumor suppression with aging, or possibly achieve longevity with a reduced incidence of tumors.

Neurodegenerative disease (NDD)

p53's role in aging regulation is closely related to its function in various NDDs.[180–183] The p53 protein level is often elevated in these disorders. Primarily, p53 contributes to NDD pathology by inducing apoptosis. Recently, ferroptosis has been recognized as playing a significant role in NDDs.[184] As a master regulator of ferroptosis,[106] it is logical to speculate that p53 participates in NDD progression via regulating ferroptosis. Additionally, p53 protein aggregation is implicated in Alzheimer's disease.[185] When developing drugs targeting p53 pathway for cancer treatment or slowing aging in elder people, the impact of p53 on NDDs should be considered.

Radiation sickness, chemotherapeutic toxicity, and ischemic injury

Exposure to radiation and genotoxic reagents, whether accidental or as part of cancer treatment, activates p53-dependent apoptosis and ferroptosis, causing pathologies in various organs.[106,186] Particularly, this mechanism underlies major side effects in tumor radiotherapy and chemotherapy.[187,188] Upon genotoxic stresses, the presence of p53 is not always harmful. The response of p53 to radiation is tissue-specific; while it stimulates radiation-related cell death in hematopoietic system, hair follicle, and spinal cord, it offers a radioprotective effect on gastrointestinal tract.[186,189] Similarly, apoptosis and ferroptosis promoted by p53 lead to ischemic injuries in organs such as brain (e.g. stroke), kidney (e.g. kidney transplantation), and heart (e.g. myocardial infarction).[106,186]

Metabolic disease

p53 plays a complicated role in diverse metabolic diseases, including obesity, diabetes, alcoholic and non-alcoholic fatty liver diseases (AFLD and NAFLD), and cardiovascular diseases.[103,190,191] Its multifaceted activities, particularly in metabolic regulation, affect these disorders in different cells, tissues, and organs, such as pancreatic β-cell, liver, muscle, and adipose tissue. Contradictory results are often reported about functions of p53 in these diseases. For example, while p53 in skeletal muscle progenitor cells and agouti-related peptide neurons protects against obesity,[192,193] the liver R72 variant of p53, with enhanced transactivation ability, promotes fat accumulation and NAFLD.[70] Besides, in endothelial cells p53 exacerbates dietary obesity-related metabolic abnormalities.[194] Hence, when discussing the function of p53 in systemic metabolism and associated metabolic diseases, it must be put into a specific setting. Care must be taken when targeting p53 to treat certain metabolic diseases to avoid disrupting other metabolic processes and minimize the risk of predisposing recipient cells to cancer.

Cancer

As previously mentioned, p53 possesses an arsenal of functions to combat all the hallmarks of cancer,[195] which may be lost or reversed due to its mutation, deletion, or repression in cancer cells (Figure 4).

While a mutation in one p53 allele may be sufficient for cellular transformation when the other WT p53 allele remains intact,[196,197] LOH of p53 gene is often observed. The mechanisms behind p53 mutations are not entirely clear. Some may result from environmental and chemical carcinogens such as ultraviolet radiation, aflatoxin, and tobacco

smoke, which leave characteristic fingerprints on the p53 gene.[73,198] The frequency and spectrum of p53 mutations are dictated by factors such as gender, tissue type, and both cell-autonomous and non-cell-autonomous mechanisms in tumor evolution.[199–203] In addition, the timing of p53 mutations varies among different tumors.[198] Even within the same tumor type, different p53 mutants may not lead to the same phenotype.[204] As introduced before, mutant p53 promotes tumor development via LOF, DNE, and GOF, which are well-elucidated in mouse models.[79,196,197] While extensive focus has been placed on p53 hotspot mutations, other mutations should not be overlooked. For instance, missense mutations disrupting p53 oligomerization can lead to tumorigenesis.[205,206] Missense mutations in the PRD of p53 may potentially impact its tumor-suppressive functions.[207] Serum antibodies against mutant p53, immunohistochemistry of mutant p53, and DNA fragments of mutant p53 in tumor cells or body fluids and feces can be used as diagnostic and prognostic biomarkers in tumor patients.[198,208–211] p53 mutations also act as predictors for the efficacy of certain tumor treatments and are useful for patient stratification.[212]

The p53 gene is located on the short arm of chromosome 17 (17p13.1), a region frequently deleted in tumors. p53 loss promotes tumor growth and metastasis in many different ways.[97,98,123,151,213] p53 deletion is often linked with the loss of nearby genes, such as POLR2A and EIF5A, which also contributes to tumorigenesis and creates therapeutic vulnerabilities by targeting the co-deleted genes.[214,215]

As p53 mutation and deletion have significant impact on carcinogenesis, mutating or deleting p53 have been effectively applied to generate various mouse tumor models.[196,197,216,217] A tightly relevant question is, among the LOF, DNE, and GOF of p53 alteration, which is the predominant mechanism underpinning p53-related tumor initiation and progression? While GOF of p53 mutants has garnered plenty of evidence supporting its tumorigenic role,[218] there are also studies suggesting that LOF and DNE contribute more to cell transformation than GOF[90,201,219]. The moderate LOH rate (40–60%) in LFS patients has implications for this question.[220] More well-controlled and tumor type-specific studies are warranted to clarify this issue. The answer is likely highly context-dependent.

A notable percentage of tumors retain two intact WT p53 alleles. These tumors may use different methods to attenuate p53 activity and its associated pathway. A common way is to enhance inhibition of p53 protein level, nuclear import, promoter recruitment, and transactivation activity by upregulating its negative regulators.[54,63,221] The amplification of the MDM2 gene in sarcoma and glioblastoma is a notable example.[221,222] Besides amplification, the T309G SNP of MDM2 and deletion of $p14^{ARF}$ both enhance repression of WT p53 by MDM2 in tumors.[221,223,224] Many oncogenic viruses (such as SV40, EBV, and KHSV) transform cells partially by inactivating p53.[221] Sometimes, WT p53 is misfolded into a pseudo-mutant conformation due to multiple mechanisms.[74] In addition to inhibiting p53 directly, disruption of p53 downstream effectors also impairs the tumor-suppressive effect of WT p53.[225]

Although p53 is a well-known tumor suppressor, sporadic reports indicate that under certain circumstances, WT p53 activity may facilitate tumorigenesis and tumor survival. This can occur in the precancerous stage[226] and during tumor growth[227–230]. Activation of WT p53

may also impair the efficacy of tumor treatment, promote resistance to anti-tumor drugs, and cause tumor relapse.[231–234] These cases stem from the hijacking of one or more functions of p53 by precancerous or tumor cells to survive and develop. Correspondingly, some bona fide p53 target genes, such as MDM2 and TIGAR,[235,236] can function as oncogenes. Hence, p53 should not be seen as a stereotypical tumor suppressor, but as a context-dependent guardian of the cell.

The list of disorders influenced by p53 extends to some other diseases. Taken together, beyond its most famous function in cancer, p53 is a highly health-relevant gene in both normal physiology and pathology (Figure 3). Health is achieved by maintaining the body's homeostasis, which is a dynamic and balanced process. As a major stress-responder, p53 guards cellular homeostasis against various stresses. However, its activity can have both positive and negative effects on health and should be kept in equilibrium. Both insufficient and excessive p53 activities can disrupt a healthy state. Hence, the double-edged power of p53 should be seriously and carefully considered in health promotion and disease treatment strategies targeting p53.

TARGETING p53 FOR DISEASE TREATMENT: ALL ROADS LEAD TO HEALTH

Targeting p53 in cancer

Its "tumor-suppressive TF" nature makes p53 seemingly undruggable. Nevertheless, a multitude of methods have been developed to enhance or recover the WT function of p53 depending on its status in cancer cells (whether repressed, mutated, or lost) (Figure 5). For more information, readers are referred to recent reviews.[74,237]

In cancer cells retaining WT p53, an intuitive idea is to abrogate p53's inhibition. This can be achieved by reducing the protein level (using siRNA, proteolysis-targeting chimera (PROTAC), or molecular glue) or activity of negative regulators of p53. However, these methods often lack specificity, as many p53 inhibitory factors have additional targets.[238] Hence, lots of efforts have been made to identify molecules that specifically disrupt the protein-protein interactions (PPIs) between p53 and its negative regulators. MDM2 is the major target for elevating WT p53's protein level and activity. Nutlin, the first small molecule to interfere with MDM2's binding and degradation of p53 was proposed in 2004.[239] Based on it, several derivatives including RG7112 and a more potent RG7388 (idasanutlin) have been developed and tested in clinical trials.[74,237,240] However, in the phase 3 MDM2 antagonist Idasanutlin in Relapsed or Refractory acute myeloid leukemia for Overall Survival (MIRROS) trial, although an encouraging overall response rate was observed in cytarabine plus idasanutlin group over cytarabine plus placebo group, the primary endpoint (overall survival) was not reached.[241] What's more, idasanutlin treatment may cause hematological and gastrointestinal toxicities, highlighting the potential side effects of p53-activating drugs.[240] Other small molecular inhibitors of the MDM2-p53 interaction include APG-115[242] and AMG 232 (KRT-232)[243], both undergoing clinical trials. ALRN-6924, a stapled α-helical peptide, simultaneously relieves the inhibition of MDM2 and MDMX on p53.[244] Other negative regulators of p53, such as USP7,[245] HPV

E6,[246] SIRT1/2,[247] VPRBP,[248] and SETD8,[249] are promising targets for p53 activation. Given that PTMs are crucial for regulating p53 activity, targeting these cofactors holds attractive potential. Again, how to specifically affect the PTM status of p53 is a big challenge. Cofactors adjusting WT p53's protein folding, cellular localization, DNA recruitment, and activity dynamics should be considered for targeting as well. Other aspects related to p53 expression and activity, including alternative splicing and translation, mRNA stability, and SNPs, can be targeted, too.

In cancer cells with p53 missense mutations, primary efforts are focused on restoring WT p53 activity. The existence of pseudo-mutant p53,[74] second-site reversion of mutant p53,[250] and temperature-sensitive mutant p53[251] imply that the conformations of WT and mutant p53 might be interchangeable. This possibility opens the door to restoring the tumor-suppressive conformation of mutant p53 using specially designed small molecules (correctors). CP-31398, discovered in 1999, was the first compound found to enable mutant p53 to activate transcription and suppress tumor growth.[252] After that, many more correctors are identified, for instance PRIMA-1.[253] The degradation metabolite of PRIMA-1, methylene quinuclidinone (MQ), covalently binds to the thiol group of cysteine in mutant p53, restoring the WT conformation. Nevertheless, it also alters the redox state of the cell independently of p53 by reacting with other proteins. Its derivatives PRIMA-1MET (APR-246, or eprenetapopt) and APR-548 are undergoing multiple clinical trials.[237] A thiosemicarbazone drug COTI-2, is also in a clinical trial.[254] Arsenic trioxide (ATO), a drug to treat acute promyelocytic leukemia, has been found to rescue many p53 mutants, with varying efficiencies depending on the solvent accessibility and temperature sensitivity of the mutants.[255,256] The antiparasitic drug potassium antimony tartrate (PAT) also rescues temperature-sensitive p53 mutants, like p53-V272M.[257] These correctors above are responsible for rescuing multiple p53 mutants, but their broad-spectrum nature may limit efficiency for specific mutations. Targeted correctors for particular mutations would be more suitable for personalized treatment. For example, PhiKan083,[258] PK7088,[259] PC14586,[260] and KG13[261] are designed to correct the p53-Y220C mutant, because of its special conformation. Additionally, MS78, an acetylation targeting chimera (AceTAC), promotes the K382 acetylation of p53-Y220C, thereby specially rescuing its tumor suppressive activity.[262] For a more common p53-R175H mutant, the thiosemicarbazone drug ZMC1 (NSC319726) is discovered, facilitating zinc binding and forcing the mutant into a WT conformation.[263] The aggregation of mutant p53 can be relieved by ReACp53[264] and ADH-6[265]. The dissociated mutant p53 partly recovers tumor-suppressive activity. Some GOF aspects of mutant p53 are targetable, too. NSC59984, for example, promotes mutant p53 degradation,[266] releasing sequestered p73 to inhibit tumor growth. Other drugs, such as ganetespib,[267] MCB-613,[268] and biomimetic nanoreceptor,[269] also promote mutant p53 degradation.

To treat nonsense mutations of p53, chemicals inducing translational readthrough or inhibiting nonsense-mediated mRNA decay (NMD), such as G418, 2,6-DAP, CC-90009, and NMDI14 can be utilized.[74,237] For p53-mutated cancer cells, an alternative approach is oncolytic virus therapy. ONYX-015, a modified adenovirus, replicates only in p53-inactivated cells, thus selectively targeting cancer cells with p53 mutations while sparing normal cells.[270]

To treat p53-null tumors, one approach is to introduce p53 protein or use gene therapy to deliver p53 mRNA or DNA into tumor cells, thereby reinstating the expression of WT p53 protein.[271–273] Advances in adeno-associated virus (AAV) and nanoparticle techniques may enhance the development and application of p53 gene therapy. The potential of CRISPR-Cas9 base editing technology for correcting p53 mutations in tumors is intriguing.

Targeting p53 can involve diverse cell types in the TME to achieve a tumor-suppressive outcome. For example, p53 activation induces the expression of endogenous retroviruses, which can potentiate immunotherapy.[274] As previously introduced, mutant p53 can generate neoantigens targetable by immunotherapy.[153–155] The engineered antibody P1C1TM, for instance, can distinguish between different p53-derived peptide-MHCs on WT and p53 mutant cells, mediating cytotoxicity or serving as an antibody-drug conjugate (ADC) to specifically eliminate p53 mutated tumor cells.[154] The bispecific antibody H2-scDb, which bridges cancer cells presenting a p53-R175H neoantigen with T cells, effectively facilitates the destruction of cancer cells by T cells.[153] Identifying mutant p53-derived neoantigens can also enhance adoptive cell therapies (such as CAR-T and TCR-T)[155] and the development of p53 vaccines[275,276]. The success of mRNA vaccine technology encourages further exploration in the p53 vaccine direction. Targeting p53 in immune cells and tumor stroma cells (e.g. cancer-associated fibroblasts) could enhance anti-tumor effects as well.[147,277,278]

The status of p53 can significantly impact the sensitivity to certain cancer treatments.[279,280] Often, p53-targeted therapies are combined with other treatments for two primary purposes: to enhance the efficacy of activating or restoring p53,[281] and to exploit synthetic lethal effects created by simultaneously activating p53 and intervening in other pathways[282–284]. For instance, in acute myeloid leukemia, the activation of p53 coupled with Bcl-2 inhibition helps overcome resistance to individual treatments and stimulates apoptosis in cancer cells.[282]

Beyond directly targeting the p53 protein, key downstream components, especially those effectors critical for p53-mediated tumor suppression, can also be targeted to partially reactivate the p53 signaling pathway. This approach, while potentially less effective than activating WT p53, may be more feasible and serve as a complement to p53-targeting strategies.[122,225,285] Besides the therapeutic and prophylactic applications, the diagnostic and prognostic values of p53 should not be overlooked either.[198,208–212,286]

Although there never lacks ideas to target p53, only a minority of them can enter clinical trial, not to mention the successful approval into clinical application. There are several obstacles to overcome before a p53-targeted drug can truly benefit the cancer patients. Firstly, the absorption, distribution, metabolism, and excretion (ADME) of the drug need to be optimized. Secondly, the efficiency of the p53-targeted therapy is influenced by various factors. Although p53 has potent tumor-suppressive capabilities, its activation does not always guarantee efficient tumor cell eradication.[287,288] Strategies such as patient stratification and combination treatments may enhance efficacy. Thirdly, the low specificity of some drugs may result in off-target effects. Fourthly, the side effects caused by the on-target or off-target drug toxicity are among the major safety concerns. This is particularly evident in normal cells when activating WT p53 by blocking MDM2-p53 interaction.

Given that the induction of cell-cycle arrest, apoptosis, and senescence is dispensable in p53-triggered tumor suppression,[289] developing methods to retain p53's anti-tumor effect without harming normal cells is a realistic goal. Another concern arises from the possibility that in normal cells harboring p53 mutations, MDM2 inhibitors could potentially activate the oncogenic function of these p53 mutants by stabilizing them. This consideration warrants serious attention in clinical practice. Specific drug delivery to tumor cells could reduce toxicity. It's worth noting, as previously discussed, that p53-mediated cell death contributes significantly to the side effects experienced during tumor radiotherapy and chemotherapy.[187,188] Consequently, suppressing p53 activity might be beneficial in reducing these treatment-related side effects.[290] Interestingly, if controlled well, the mild activation of p53 could be employed in cyclotherapy, serving to protect normal cells.[291] Fifthly, p53-targeted therapy poses the risk of driving tumor evolution, and selection of new mutations of p53 or alterations in the p53 pathway, leading to treatment resistance and tumor relapse.[74,292,293] Appropriate combination treatments may help to mitigate this risk. Sixthly, p53 rarely promotes tumor survival, progression, drug resistance, and relapse, as mentioned before. In such scenarios, careful consideration is necessary to determine whether activating p53 is advisable. With progress in fields like artificial intelligence,[294] structural biology, and multi-omics, these problems will be eventually addressed.

Targeting p53 in other physiological and pathological settings

The exploration of targeting p53 in normal physiological processes and non-cancerous diseases is not as extensive as in cancers. However, given p53's broad impact, strategically modulating its activity could potentially enhance health by improving normal physiological functions and alleviating p53-associated disorders. For example, activating p53 in the uterus might increase the success rate of embryo implantation, while inhibiting p53 might prevent NDDs and reduce ischemic organ injury. In the context of metabolic disorders and aging, the role of p53 remains debatable and warrants further investigation. To suppress p53 activity, various methods can be employed, such as using p53 inhibitors,[186,290] disrupting the PPIs between p53 and its activators,[295] or augmenting the function of negative regulators of p53. These approaches essentially mirror those used for activating p53 but in reverse. A word of caution is that suppressing p53 might inadvertently increase the risk of tumorigenesis. Strategies like short-term intervention and cell type-specific delivery of p53-inhibitory drugs could decrease this risk. Looking ahead, it is full of hope that targeting p53 can improve health outcomes beyond just cancer treatment.

INTRIGUING QUESTIONS IN THE p53 FIELD: OPEN QUESTIONS, BRIGHT FUTURE

Great progress has been made over the past 45 years in p53 research. Basic regulations, functions, and therapeutic potentials of p53 have been elucidated. Nevertheless, there are still some fundamental questions awaiting to answer.

Firstly, what is the function of basal p53? In resting cell, both the expression and activity of p53 protein are kept low, until various stimuli stabilize and activate it. However, obvious stress is not always required for p53 to carry out some of its functions, such as regulating

stem cell dynamics, cell competition, ROS level, and immune activity.[105,142,296] So how does basal p53 work in unstressed cells? Does the basal activity of p53 contribute to tumor suppression? Basal p53 can bind to the promoters or enhancers of its target genes, establishing a primed state for rapid responses to stresses.[23] Importantly, it also maintains a specific expression profile of target genes.[297] Particularly, basal p53 is responsible for the baseline level of some tumor suppressor genes like PTEN.[298] There may be differences in the target gene lists between basal and activated p53. Evidence also suggests that robust stabilization,[44] full transactivation ability,[297] and tetrameric conformation[205] of p53 are not absolutely necessary for its tumor suppression effect. Therefore, leveraging the basal activity of p53 may help minimize side effects on normal cells and reduce the risk of selecting p53 mutations resulting from its activation. Studying the function of basal p53 requires an appropriate model. While knocking out p53 in a tumor cell line might provide some insights, transferring cells to tissue culture can be a p53-inducing stress. p53 levels in cultured cells may not reflect a truly unstressed basal state, which presents a caveat when interpreting *in vitro* results. More importantly, cultured cells lack the diverse environmental cues present *in vivo* and thus cannot fully simulate the actual tumorigenic process. Moreover, the phenotype observed in p53 KO mice should not be solely attributed to the loss of basal p53 activity, as the functions of stress-activated p53 are eliminated, too.

Secondly, what is the contribution of p53's repressive target genes to its function? p53's role is not limited to activating transcription. It has also been found to repress the expression of many genes,[299] with the notable examples such as SLC7A11,[107] NANOG,[117] and VKORC1L1[109]. In most cases, p53 suppresses gene expression indirectly, either through transcriptional or post-transcriptional mechanisms. It competes with other TFs for DNA binding,[120,300] activates negative regulators of gene expression,[301–304] and suppresses the expression of transcription activators.[305] Otherwise, direct repression of transcription by p53, through binding to special REs,[117,119,306,307] interfering with enhancer function,[118,305] and remolding chromatin structure[305] are reported as well. Although the direct transcriptional repression by p53 is a subject of ongoing debate[308] and requires further investigation, it is clear that hundreds of genes are downregulated upon p53 activation or upregulated in its absence. Future studies are expected to shed more light on whether and how p53 functions as a direct transcription repressor, and the roles these repressive target genes play within the p53 network.

Thirdly, are genetically engineered mouse models (GEMMs) sufficiently effective for p53 research? While GEMMs have significantly advanced our understanding of p53,[289,309] they also present inherent limitations. The most notable is the species gap between humans and mice, as many human p53 targets are not shared by mouse p53,[310] not to mention the differences in immune system or other biological systems. The knowledge about p53 got from *in vitro* studies is often tested in mouse models. Nonetheless, most reproducible results in mice could not be directly translated to applications in humans. Currently, humanized mouse models[311,312] and human organoids[313] serve as useful supplements to GEMMs. However, these alternatives have their limitations as well. Consequently, there is a pressing need to develop more practical and human physiopathologically relevant systems for p53 research.

Fourthly, what are the underpinning mechanisms and biological relevance of the context-dependent activity of p53? A reiterated feature of p53 activity in above sections is its context-dependency. The target profile of p53 exhibits significant organ specificity and spatiotemporal variations.[314] Heterogeneity in p53 expression is also evident within a single tumor.[315] Even within the same cell, the target selectivity and functional outcome of p53 activation are determined by a variety of variables.[23] In addition, gender can dictate p53-regulated human behavior.[316] When interpreting experimental results related to p53, placing them within a specific context is essential.[104] Further effort is still warranted for a deeper understanding of p53 activity and the development of context-specific treatment regimens that target p53.

Fifthly, is targeting p53 truly a practical approach for treating cancers? The differential alterations of p53 in cancers and the extensive variety of p53 missense mutations complicate the design of specific drugs for each type of p53 alteration. The context-dependency of p53 activity adds another layer of complexity to this issue. However, targeting p53 as a treatment for cancers remains an enticing approach to pursue. Considering the frequent side effects, are there other elements in the p53 pathway that could serve as safer targets than MDM2, without compromising anti-tumor efficacy? Is it possible to achieve a “two-drugs-cure-all” goal by activating or inhibiting p53 to treat all p53-associated diseases, and improve overall health, particularly in extending longevity? This ambition may seem lofty, but it is certainly worth exploring.

Likewise, several other important questions remain unanswered. New targets of p53 are continuously being identified. A notable example is zinc finger matrin-type 3 (ZMAT3), which plays a critical role in p53-dependent tumor suppression.[317–320] What are the unidentified targets and functions of p53? What targets or functions are indispensable for p53 to mediate tumor suppression? What is the functional diversity and evolutionary significance of p53’s two TADs? How do they cooperate in executing p53’s tumor-suppressive function? Some progress has been made in this area,[19,297] but it has not been fully addressed. Are the non-cell-autonomous activities of p53 viable targets for cancer treatment? Under what circumstances does p53 shift to support tumor development? Can we leverage p63 and p73 to synergize with p53 targeting in the treatment of cancers or other diseases? The list of the questions could be longer. New questions will emerge in the future. It is on the way to find answers to these questions, our understanding of p53 is refreshed and deepened.

CONCLUSIONS

The past 45 years of p53 research represent a remarkable journey. As discussed above, countless discoveries result in a much better understanding of the complexity of p53 functions under different physiological settings. The diverse tumor suppression mechanisms including both classical activities and a growing number of other p53 functions raise a more interesting issue about which pathway is more critical for suppressing tumor growth in different types of human cancers. Moreover, although p53 is well accepted as a tumor suppressor, not all p53-induced activities are necessary for tumor suppression. For example, p53-mediated pro-survival activity seems at odds with its growth-suppressive function in

tumors; however, this activity is potentially important for normal cell homeostasis, allowing normal cell survival during stress responses. The challenge remains how to activate p53 function for cancer therapy. The difficulties associated with translating the MDM2-targeting approach into clinical application raises a serious issue about how to kill cancer cells without harming normal tissues. It remains unclear whether the toxicity induced by MDM2 inhibitors (particularly in the bone marrow) is unique for the MDM2 pathway or for p53 activation in general. If the former is the case, targeting different pathways for p53 activation should be seriously considered.[248] Notably, in contrast to the classic activities such as apoptosis, many p53 targets involved in metabolism, ferroptosis, and immunity do not directly cause severe harm to cell viability.[321] It will be interesting to examine whether the specific activation of those pathways effectively suppresses tumor growth without causing severe toxicity.

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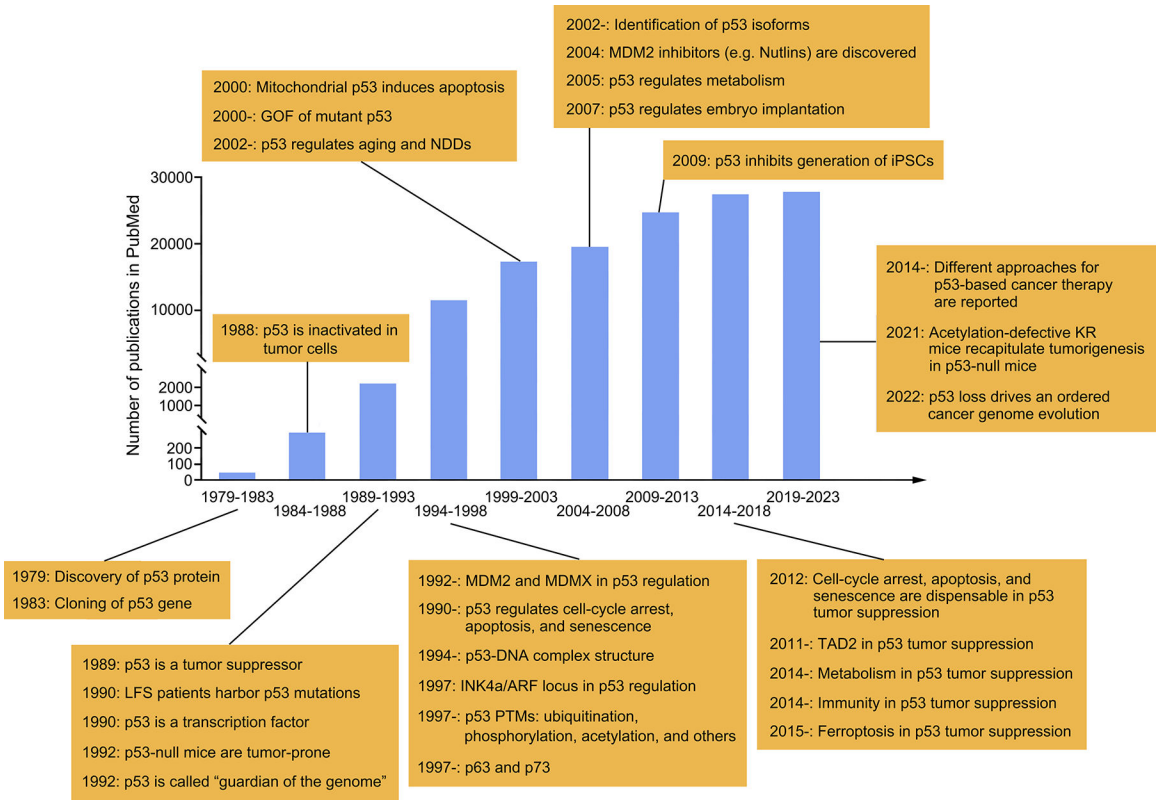

Figure 1. Timeline of research in the p53 field over the past 45 years.

This figure shows the number of publications recorded in PubMed every five years since 1979, along with key discoveries about p53. Due to space constraints, many excellent studies cannot be included here. LFS, Li-Fraumeni syndrome; PTM, post-translational modification; GOF, gain-of-function; NDD, neurodegenerative disease; iPSC, induced pluripotent stem cell; TAD2, transactivation domain 2; KR, lysine-to-arginine mutation.

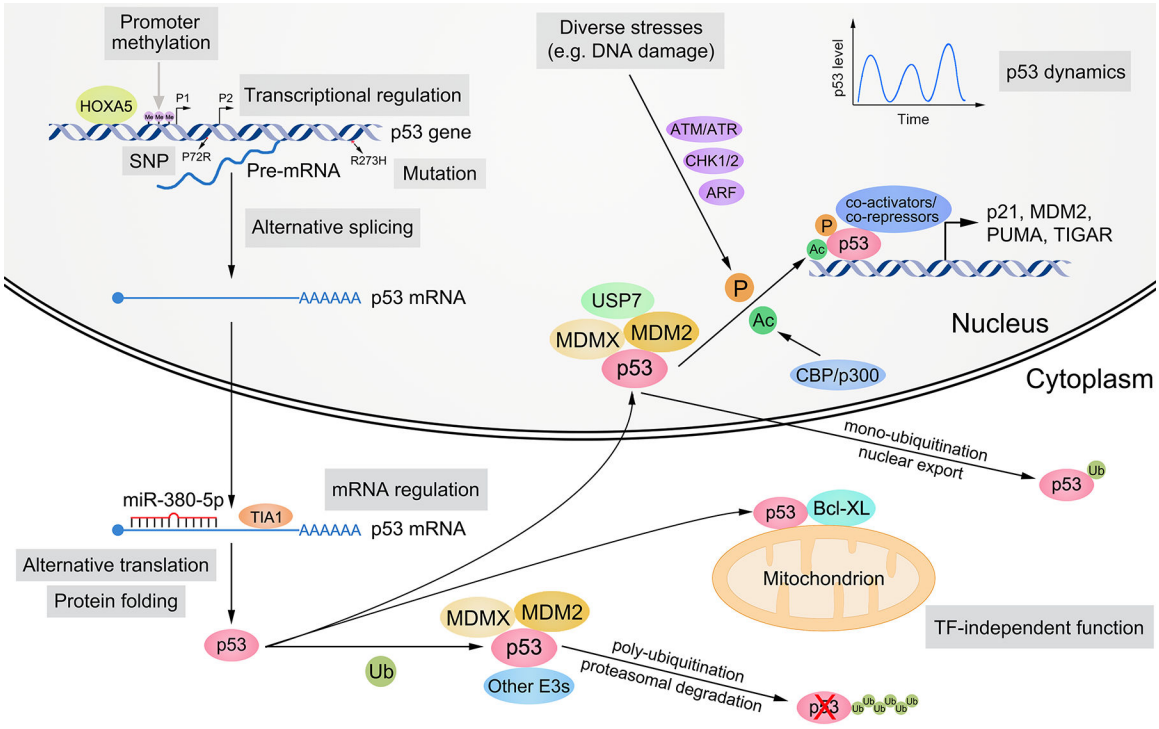

Figure 2. Regulation of p53.

The expression and activity of p53 are controlled by multilayered regulation at the DNA, RNA, and protein levels. At the DNA level, SNPs (e.g. P72R) and mutations (e.g. R273H) may occur in the p53 gene. p53 possesses two promoters, which can be methylated and silenced. The transcription of p53 gene is activated or suppressed by various TFs (e.g. HOXA5). At the RNA level, the cellular localization, stability, and translation of p53 mRNA are modulated by RNA-binding proteins (e.g. TIA1) and ncRNAs (e.g. miR-380–5p). p53 pre-mRNA and mRNA can undergo alternative splicing and alternative translation, respectively. At the protein level, p53 folding, stability, cellular localization, DNA binding, transactivation ability, and target selection are primarily mediated by post-translational modifications (e.g. ubiquitination, phosphorylation, and acetylation) and cofactors (e.g. MDM2, MDMX, and CBP). Diverse stress signals (e.g. DNA damage) can activate p53, and its activity as a TF is highly dynamic. p53 also exhibits TF-independent function in cytoplasm (e.g. promoting apoptosis via interacting with Bcl-XL). P1 and P2, promoter 1 and 2; SNP, single nucleotide polymorphism; E3, E3 ubiquitin ligase; TF, transcription factor; Me, methylation; Ub, ubiquitination; P, phosphorylation; Ac, acetylation.

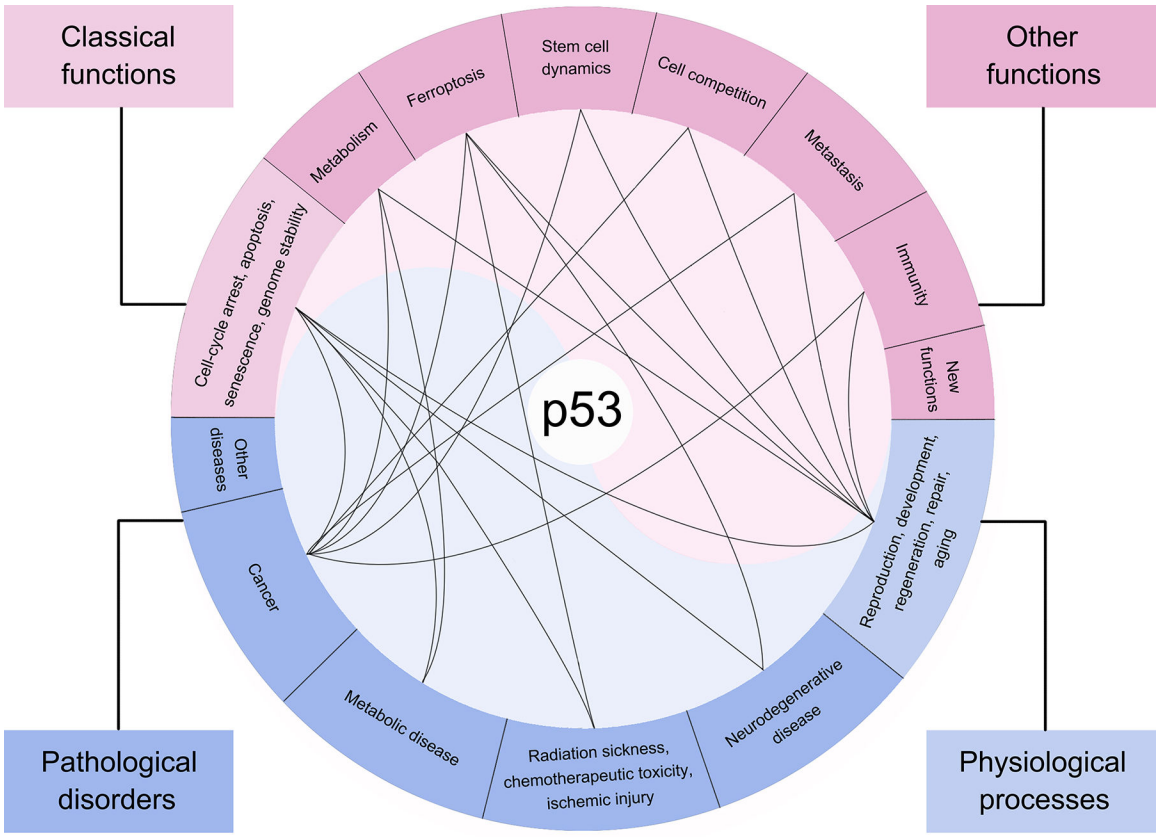

Figure 3. Functions and physiopathological roles of p53.

p53 exhibits diverse and complex functions: classical functions (including inducing cell-cycle arrest, apoptosis, and senescence, and maintaining genome stability) and other functions (such as mediating metabolism, ferroptosis, stem cell dynamics, cell competition, metastasis, and immunity). Due to its wide array of functions, p53 plays a crucial role in numerous physiological processes (e.g., reproduction, development, regeneration, repair, and aging) and pathological disorders (like neurodegenerative disease, radiation sickness, chemotherapeutic toxicity, ischemic injury, metabolic disease, and cancer). The black curves illustrate how specific functions of p53 contribute to its role in linked physiological or pathological processes.

Figure 4. p53 and cancer hallmarks.

Activity of WT p53 antagonizes all the hallmarks of cancer, as depicted in the surrounding ovals. In contrast, alterations in p53, including repression, mutation, and deletion, promote these hallmarks. It is partially adapted from reference[195].

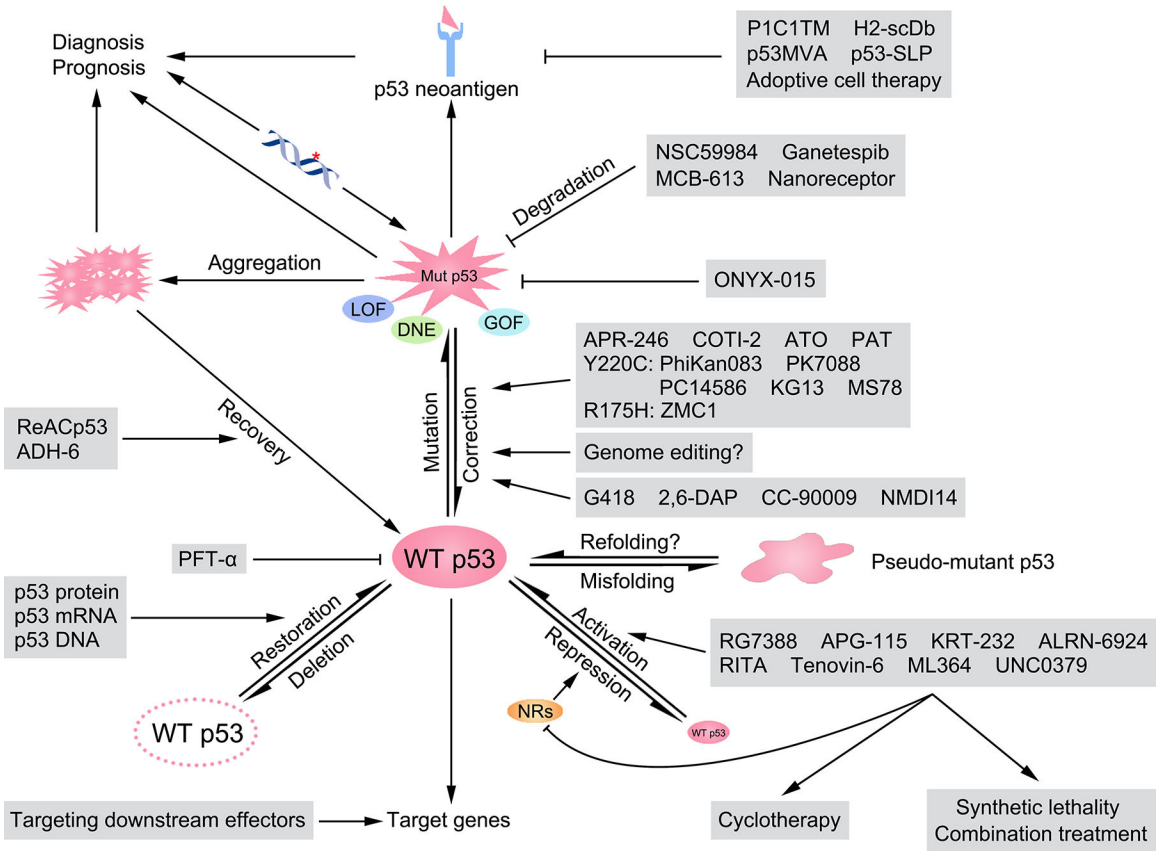

Figure 5. Targeting p53 in cancer.

Various methods have been developed to target p53 for tumor treatment. In tumors retaining WT p53, RG7388, APG-115, KRT-232, and ALRN-6924 are used to disrupt the PPIs between p53 and MDM2 or MDMX, while RITA, tenovin-6, ML364, and UNC0379 target other negative regulators of p53. Activation of p53 can be utilized in cyclotherapy to protect normal cells, or in combination with other treatments for synergistic tumor eradication. WT p53 can be misfolded into a pseudo-mutant conformation, which may be reversed with appropriate drugs. Downstream targets of p53 are also potential therapeutic targets to partially reactivate the p53 signaling pathway. In tumors containing p53 missense mutations, APR-246, COTI-2, ATO, and PAT are capable of restoring the WT conformation of many p53 mutants. Specific agents such as PhiKan083, PK7088, PC14586, KG13, and MS78 target the p53 Y220C mutation, while ZMC1 is used for the p53 R175H mutant. Additionally, genome editing may be useful in correcting p53 gene mutations. NSC59984, ganetespib, MCB-613, and nanoreceptors are able to degrade mutant p53. ONYX-015, an oncolytic virus, specifically kills tumor cells with p53 mutations. Agents like ReACp53 and ADH-6 resolve the aggregation of mutant p53, partially restoring WT p53 functions. Antibodies like P1C1TM and H2-scDb, which recognize neoantigens derived from mutant p53, mediate tumor cell elimination by immune cells. p53MVA and p53-SLP are p53 vaccines used in immunotherapy. Mutant p53 neoantigens are also useful for developing adoptive cell therapies. Mutant p53 DNA fragments and proteins (including their aggregates) can be utilized for tumor diagnosis and prognosis. In tumors with p53 nonsense mutations, G418, 2,6-DAP, CC-90009, and NMDI14 can induce the readthrough of p53 mutant

mRNAs, or inhibiting NMD. In p53-null tumors, delivery of p53 protein, mRNA, and DNA may restore p53 expression and eliminate tumor cells. LOF, loss-of-function; DNE, dominant-negative effect; GOF, gain-of-function; NR, negative regulator of p53.