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The p53 tumor suppressor: A master regulator of diverse cellular processes and therapeutic target in cancer

Marianne Farnebo, Vladimir J.N. Bykov, Klas G. Wiman *

Dept. of Oncology-Pathology, Cancer Center Karolinska (CCK), Karolinska Institutet, Stockholm, Sweden

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ABSTRACT

The tumor suppressor p53 has been implicated in a growing number of biological processes, including cell cycle arrest, senescence, apoptosis, autophagy, metabolism, and aging. Activation of p53 in response to oncogenic stress eliminates nascent tumor cells by apoptosis or senescence. p53 is regulated at the protein level by posttranslational modifications such as phosphorylation and acetylation. A p53 antisense gene, Wrap53, enhances p53 mRNA levels via the 5′UTR. Lack of Wrap53 transcripts that overlap with p53 abrogates the p53 DNA damage response. Around half of all human tumors carry p53 mutation that disrupt p53 specific DNA binding, and transcriptional transactivation of target genes. Reactivation of mutant p53 is a promising strategy for novel cancer therapy. The small molecule PRIMA-1 restores wild type conformation and DNA binding to mutant p53, induces mutant p53-dependent apoptosis, and inhibits tumor growth in vivo. The PRIMA-1 analog APR-246 is currently tested in a phase I clinical trial. Improved understanding of the p53 pathway should lead to better diagnosis and treatment of cancer in the future.

1. Introduction

The discovery of p53 as a cellular SV40 large T antigen-binding protein in 1979 marks the beginning of a dynamic era in cancer research that is expected to have a major impact in the clinic. p53 has established itself as a key tumor suppressor, potent apoptosis-inducer, and prognostic marker in cancer. The p53 gene is mutated in around 50% of human tumors (reviewed by Soussi and Wiman [1]). This emphasizes the central role of the p53 pathway in regulation of cell growth and survival. Moreover, the p53 status of a tumor may have a strong influence on sensitivity to commonly used anticancer drugs and radiotherapy. p53 is therefore both an important clinical marker and novel therapeutic target.

p53 is a nuclear transcription factor that accumulates in response to cellular stress, including DNA damage and oncogene activation. This triggers transcriptional transactivation of p53 target genes such as p21, GADD45, Bax, Puma, and Noxa, leading to cell cycle arrest, senescence and/or apoptosis (reviewed by Vousden and Prives [2]). Another p53 transcriptional target is the MDM2 gene whose protein product ubiquitinates p53 and targets it for proteasome-mediated degradation. Therefore, p53 and MDM2 form a negative regulatory loop that downregulates p53 expression. p53 can also perform various functions in the cytoplasm (see [3]). Translocation of p53 to mitochondria promotes apoptosis through transcription-independent mechanisms [4]. Like the p53 family members p63 and p73, p53 is expressed as several different isoforms that either contain or lack the N-terminal transactivation domain and therefore have different biological activities [5].

Oncogene activation leads to aberrant DNA replication with stalled replication forks, which triggers a DNA damage response (DDR) involving activation of ATM and Chk2 kinases and accumulation of p53 [6,7]. Oncogene activation may also induce expression of the p14Arf protein (p19Arf in the mouse) that inhibits MDM2, leading to p53 accumulation [8]. Accumulation and activation of p53 triggers cellular senescence or cell death by apoptosis. Thus, activation of p53 upon oncogenic stress serves to eliminate nascent tumor cells by apoptosis and/or senescence, forming a critical barrier against tumor development (Fig. 1).

A vast majority of p53 mutations in human tumors are single missense mutations that cluster in the p53 core domain (residues 100–300) that recognizes p53 binding motifs in DNA (see www.p53.iarc.fr; www.p53.free.fr; [9]). In general, mutant p53 proteins are deficient for specific DNA binding, arguing that DNA binding and transcriptional regulation of target genes are crucial for p53-mediated tumor suppression [1]. Moreover, it is becoming increasingly clear that the mutations may endow p53 with various gain-of-function activities (reviewed by Brosh and Rotter [10]). These include for instance enhanced NF-κB activation [11] and promotion of tumor invasion by affecting integrin and epidermal growth factor receptor (EGFR) trafficking [12].

* Corresponding author. Fax: +46 8 32 10 47.
E-mail address: Klas.Wiman@ki.se (K.G. Wiman).

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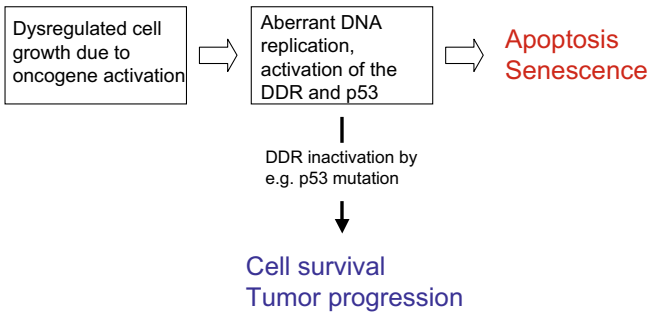

Fig. 1. p53 as a barrier against tumor development. Oncogene activation or dysregulated cell cycle progression leads to stalled DNA replication forks and activation of the DNA damage response (DDR). This response involves p53 accumulation and serves to eliminate nascent tumor cells by apoptosis or senescence. p53 mutation which occurs in a large fraction of human tumors allows evasion of this response and further tumor progression.

2. Downstream of p53: target genes and diverse biological responses

An important role of p53 in processes such as cell cycle arrest, senescence and apoptosis is firmly established. This makes perfect sense in view of p53's well-known tumor suppressor activity. However, recent studies have painted a more complex picture of p53 as regulator of diverse biological processes, such as autophagy, metabolism, and aging [2]. It has been known for decades that cancer cells have changes in multiple metabolic pathways, including the usage of glycolysis also under conditions of normoxia. Such changes seem to support dysregulated cell growth, allow synthesis of macromolecules, and protect cancer cells from oxidative stress. Interestingly, p53 has been shown to have a direct impact on metabolism. Lack of nutrients or "metabolic stress" can induce a p53 response via activation of AMP-activated protein kinase (AMPK) and inhibition of the kinase AKT that promotes MDM2-mediated p53 degradation in the proteasome. This leads to upregulation of p53 target genes, among which TSC2 inhibits the mTOR protein that stimulates protein synthesis and inhibits autophagy, a process that leads to digestion of cellular components in lysosomes. As a consequence, cell growth is suppressed (reviewed by Vousden and Ryan [13]). Moreover, p53 has been shown to directly regulate autophagy by inducing the lysosomal protein DRAM [14]. p53 may also regulate cell metabolism in other ways, for example via induction of TIGAR that inhibits glycolysis [15].

Related to the involvement of p53 in metabolism is p53's ability to regulate cellular redox status. Low levels of p53 provide an antioxidant function through upregulation of genes such as sestrins, glutathione peroxidase, TP53INPI, and TIGAR [13], while high levels of p53 instead have a pro-oxidative effect via induction of Bax, Puma, PIG3, and other genes, resulting in the production of reactive oxygen species (ROS) [16]. In addition, p53 is itself regulated in a redox-dependent manner. Efficient p53 DNA binding requires a reducing environment. The p53 core domain holds a Zn atom that stabilizes folding of the core and protects it from oxidation that might otherwise lead to intermolecular disulfide bonds and p53 aggregation. Strikingly, several mutant p53-reactivating small molecules share the ability to target thiol groups, suggesting the possibility that such compounds exploit redox-dependent pathways that regulate wild type p53 activity (see below).

Another exciting aspect of p53 is its emerging role in aging and longevity. In vivo studies have indicated that overactive p53 can suppress tumor formation but also induce an early aging phenotype [17]. Lack of p53 extends the life span of lower organisms such as *Caenorhabditis elegans* and *Drosophila melanogaster* [18,19]. Genetically manipulated mice carrying an extra copy of p53 and p19Arf show significant resistance to cancer and reduced aging-associated damage [20]. These results demonstrate that the Arf/p53 pathway has an important role as an anti-aging mechanism, and indicates co-evolution of longevity and resistance against cancer. Thus, it appears that p53 can both promote and limit longevity. This dualism is possibly related to the anti-oxidant pro-survival function of low levels of p53 [21] and the ability of higher levels of p53 to induce ROS and cell death.

In this context it is interesting to note that p53 has been shown to block the reprogramming of normal differentiated fibroblasts into induced pluripotent stem cells (iPS) by a combination of the c-Myc, Klf4, Oct4, and Sox2 genes. p53, which is induced by Arf, inhibits this process by inducing apoptosis or cellular senescence via upregulation of p21. The cell cycle inhibitor p16 also limits reprogramming by inducing senescence [22]. Thus, the INK4a locus that encodes both p16 and Arf acts as a barrier against iPS cell reprogramming. This has implications for the therapeutic use of iPS, since inactivation of p53 to facilitate the generation of iPS also increases the risk of malignant transformation.

3. Wrap53, a novel mechanism for regulation of p53

Considering the multiple roles of p53 in a wide range of biological processes and its ability to control life and death of cells, it is not surprising that p53 is tightly regulated. Posttranslational modifications such as phosphorylation and acetylation are clearly important for regulating p53 protein levels and activity (see [2]). Nonetheless, recent studies have revealed critical regulatory circuits that target p53 at the RNA level via both RNA-binding proteins and regulatory RNAs. Proteins such as HuR, L26, RPL26, nucleolin, and Wig-1 [23,24] can bind to the 5′ or 3′ untranslated regions (UTR) of p53 mRNA and control its stability or translation through various mechanisms. Wig-1 is induced by p53 and enhances p53 mRNA stability, thus forming a positive feedback loop [24]. The microRNAs miR-125a and miR-125b [25,26] downregulate p53 expression by recognizing response element in the 3′UTR of p53 mRNA.

We recently discovered a natural antisense transcript, Wrap53, that plays a key role in regulating the steady-state level of p53 mRNA by interacting with p53 5′UTR [27,28]. The *Wrap53* gene (*W*D40 encoding *R*NA *a*ntisense to *p53*) overlaps with the *p53* gene on chromosome 17p13 in a head-to-head fashion [27] (Fig. 2). As a result, their RNAs show perfect sequence complementarity in the first exons, suggesting that they interact and influence each other's expression. Indeed, we found that Wrap53 regulates p53 RNA at the posttranscriptional level. The complementary regions mediate this effect, and the interaction between Wrap53 and p53 mRNA is necessary for Wrap53's ability to regulate p53. It is conceivable that the Wrap53/p53 RNA interaction masks target sequences in p53 mRNA and thus protects it from degradation. In line with this notion, an element within exon 1 of p53 has previously been shown to mediate destabilization of p53 mRNA in chicken and mouse cells. Moreover, p53 constructs lacking exon 1 were significantly more stabile compared to full length p53 constructs [29].

We also demonstrated that Wrap53-mediated regulation of p53 is critical for the p53 response to DNA damage. Knockdown of Wrap53 or inhibition of the RNA–RNA interaction between Wrap53 and p53 mRNAs prevents p53 protein induction and transactivation of p53 target genes in cells treated with DNA damaging agents. Steady-state levels of both p53 and Wrap53 mRNAs increase upon DNA damage, indicating that Wrap53 not only maintains basal p53 mRNA levels but also plays a role in stabilizing p53 mRNA in response to cellular stress. In addition, overexpression of Wrap53 antisense transcripts sensitizes cells to p53-induced apoptosis [27]. Taken together, these data show that

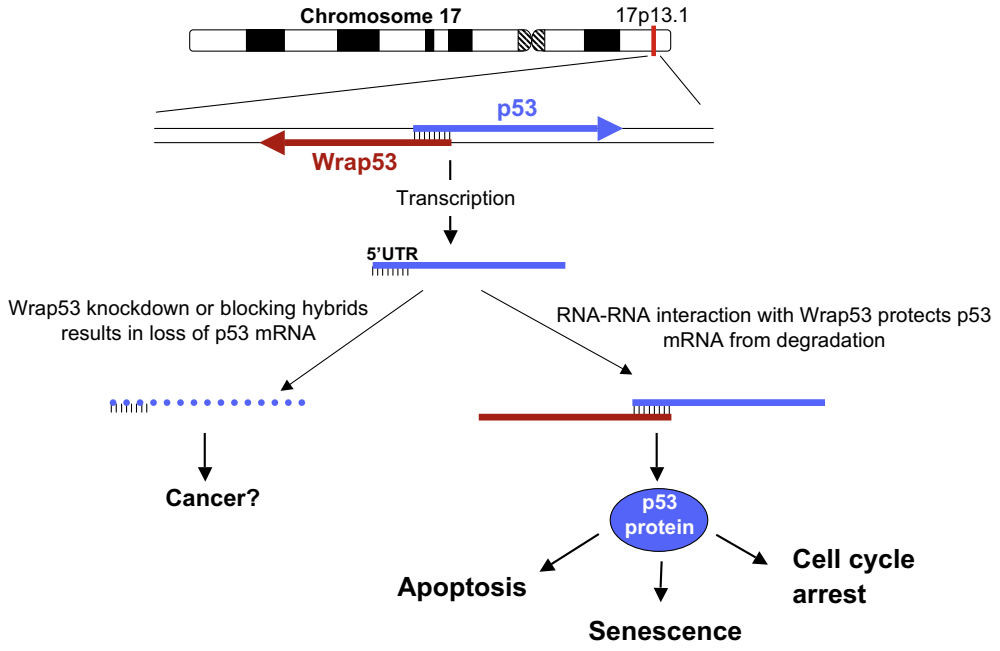

Fig. 2. Model for Wrap53-mediated regulation of p53. Wrap53α and p53 are co-expressed in cells. Interaction between the two transcripts via their complementary regions (IIIIII) protects p53 mRNA from degradation. Knockdown of Wrap53α or blocking Wrap53/p53 hybrid formation leads to reduced p53 mRNA levels. Conversely, overexpression of Wrap53α increases p53 mRNA levels and p53 protein expression. Thus, Wrap53α will potentiate p53-induced cell cycle arrest and/or apoptosis in response to cellular stress.

Wrap53 has a considerable impact on p53 function in response to stress, which highlights the importance of p53 RNA regulation as a way of controlling p53 action.

Inactivation of p53 function allows evasion of apoptosis and/or senescence, a key step in tumor evolution (Fig. 1). The identification of Wrap53 raises the possibility that dysfunction of Wrap53 itself may contribute to cancer. Conceivably, lack of Wrap53α RNA or insufficient levels of expression could represent a novel mechanism for p53 inactivation in wild type p53-carrying tumors. This could be addressed by examining Wrap53 expression in primary tumors of various origins. If it turns out that Wrap53 dysfunction contributes to loss of p53 function in tumors that carry wild type p53, analyzing Wrap53 status could provide a more accurate picture of p53 inactivation in such tumors. Moreover, manipulation of Wrap53 expression could offer a novel therapeutic strategy for cancer treatment, to either increase wild type p53 expression in tumors or to suppress expression of mutant p53 and putative gain-of-function activities.

4. Mutant p53 reactivation by small molecules: towards improved cancer treatment

The high frequency of p53 mutations in human tumors and the often observed increased resistance of mutant p53-expressing tumors to conventional chemotherapy and radiotherapy makes mutant p53 an appealing target for novel cancer therapy [30]. The concept of cancer treatment by mutant p53 reactivation is supported by in vivo studies demonstrating that restoration of wild type p53 expression in p53-deficient mouse tumors triggers efficient elimination of the tumor through cell cycle arrest, senescence and/or apoptosis [31–33]. However, mutant p53 is a challenging target for several reasons. Whereas novel targeted drugs such as imatinib (Gleevec) and gefitinib (Iressa) inhibit overactive kinases in tumors, mutant p53 must be reactivated, not inhibited. Also, since a broad range of p53 mutations in human tumors may give rise to unique structural alterations in the protein, mutant p53 is a heterogeneous target.

Various strategies can be adopted for discovery of mutant p53-reactivating compounds (Fig. 3). The reverse chemical genetics approach is based on screening of chemical libraries for substances that directly affect a target protein. It requires knowledge of the target, but does not address questions of toxicity and bioavailability. By contrast, the forward chemical genetics approach involves screens for certain phenotypic traits, for instance growth suppression or induction of apoptosis in tumor cells in a manner that depends on the target. The main advantage is that such screens are focused on a desired biological outcome regardless of mechanism, and that only compounds that are able to enter cells and lack general toxicity are identified.

The reverse chemical genetics approach was used by Rastinejad et al. [34] to identify CP-31398, a substance that prevents unfolding of wild type p53 under denaturing conditions [34]. CP-31398 refolds newly synthesized mutant p53 [35], and has anti-tumor activity in vivo [34,36]. However, CP-31398 does not bind directly to p53 [35]. Molecular modeling is another reverse chemical genetics approach. The observation that the Y220C substitution in p53 results in a crevice on the protein surface prompted Fersht and colleagues to perform a molecular docking-based screen for a molecule that fits into this cavity. The rationale is that high affinity binding of a drug would stabilize the Y220C mutant protein and thus restore wild type function. Indeed, the identified compound PhiKan083 increases p53 melting temperature, a measure of structural stability [37].

Using a forward genetics approach, we identified PRIMA-1 and the structural analog PRIMA-1Met, also named APR-246 [38,39]. These compounds restore wild type conformation to mutant p53 and inhibit growth of a wide range of tumor cell lines in a mutant p53-dependent manner [40]. Systemic administration of PRIMA-1 or APR-246 suppresses growth of tumor xenografts in SCID mice [38,41–43] and tumor growth in syngeneic mice [44]. PRIMA-1 and PRIMA-1Met/APR-246 induce p53 targets such as p21, MDM2, Bax, Noxa, Puma, 14-3-3, GADD45, and PIDD according to several studies [38,45–47]. It has also been shown that PRIMA-1 activates transcription of miRNA34a [48], a known transcription

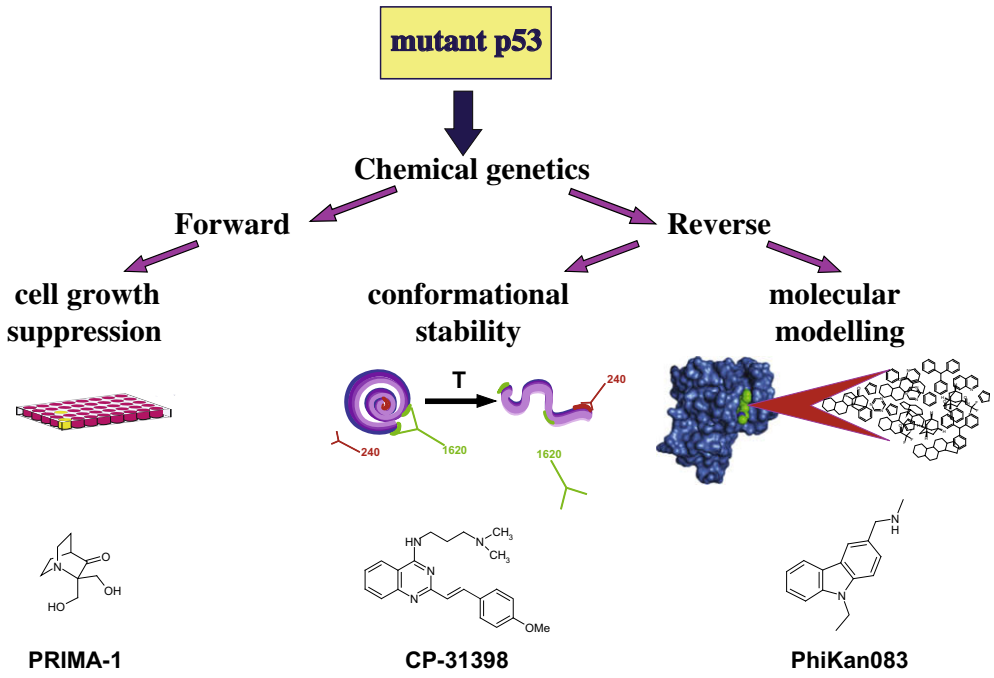

Fig. 3. Approaches for discovery of mutant p53-targeting drugs. Forward chemical genetics relies on cellular screening to identify compounds with a desired phenotypic effect, such as induction of mutant p53-dependent apoptosis in tumor cells. Reverse chemical genetics, on the other hand, is based on screening to identify compounds that have direct effects on the target protein, for example increasing conformational stability of mutant p53. Molecular modeling can be used to identify compounds that potentially bind to specific sites on the target protein and affect its conformation and/or stability.

target of wild type p53 [49], in a mutant p53-expressing cells. Interestingly, targeting of miRNA34a by siRNA makes tumor cells less amenable to apoptosis induction by PRIMA-1 [48]. Caspase 2 is activated early after PRIMA-1/APR-246 treatment, most likely due to PIDDosome-mediated cleavage of pro-caspase 2 [47]. Microarray analysis showed that PRIMA-1Met/APR-246 triggers multiple pro-apoptotic pathways and ER stress [46].

Both PRIMA-1 and PRIMA-1Met/APR-246 are converted to methylene quinuclidinone (MQ), a reactive compound with Michael acceptor activity and the ability to modify free thiol groups [45]. Despite the apparent chemical reactivity of MQ, no adverse effects were observed in animals at therapeutic doses, consistent with a high degree of target specificity. Unfolded mutant p53 is preferentially modified by PRIMA-1/APR-246 as compared to the correctly folded wild type protein [45]. Moreover, modification of most proteins by MQ might have minor consequences for cell survival. While introduction of PRIMA-1/APR-246-treated mutant p53 (thus covalently modified by MQ) into p53 null cells induces Puma, Bax, Noxa, and subsequent apoptosis [45], albumin treated in the same way has no effect. Also, it should be noted that both leptomycin B [50], which increases wild type p53 activity by binding and inactivating the CRM1 nuclear export protein, and HKI-272 [51], a follow-up compound of Iressa that targets a Cys residue in the epidermal growth factor receptor, are Michael acceptors with significant target specificity.

PRIMA-1 and PRIMA-1Met/APR-246 have been tested in primary leukemic cells from AML and CLL patients. Although p53 mutations are relatively rare in these patients, a subgroup of patients with hemizygous deletion of the *p53* gene on chromosome 17p (indicating mutation of the other *p53* allele) have worse prognosis. PRIMA-1 and PRIMA-1Met/APR-246 were particularly effective in this group of patients [52,53]. APR-246 is currently tested in a phase I clinical trial in patients with hematological malignancies or prostate cancer.

5. Conclusions

p53 continues to fascinate scientists and clinicians. Novel findings add to the complexity of this pathway every year, implicating p53 in an ever growing number of cellular processes and pathways. We now know that p53 not only acts as an inducer of cell cycle arrest, senescence and apoptosis, but also regulates for instance autophagy and metabolism, and has a major impact on overall life span and stem cell reprogramming. Recent studies indicate that regulators of p53 at the RNA level, such as Wrap53 and Wig-1, are required for the p53 stress response. Finally, the discovery of small molecules that target and reactivate mutant p53 proteins raises new hopes for more efficient cancer therapy with less severe side effects in the not so distant future. If these dreams come through, p53 has no doubt lived up to our expectations.

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