Targeting the MDM2-p53 Protein Interaction as a Novel Therapeutic Strategy in Cancer
The MDM2–p53 interaction plays a key role in the prevention of malignant transformation

The p53 and MDM2 (murine double minute 2) proteins interact to modulate critical functions involved in regulation of normal cell growth, and the development and progression of cancer. p53 is an important tumor suppressor that acts as a genomic watchdog, providing a surveillance system to maintain cellular integrity and protect cells from malignant transformation.1–3 p53 functions as a primary anticancer defense mechanism and is activated by cellular damage or other stressors.1 Activation of p53 induces prolonged cell-cycle arrest and prevents the replication of damaged cells or promotes apoptosis. Disruptions or abnormalities in p53 abrogate the effectiveness of the molecule to protect the genome, leading to uncontrolled cell proliferation and cancer tumors.1

In unstressed, normal cells, both p53 and MDM2 move between the nucleus and the cytosol. MDM2 binds with p53 to form a complex in the nucleus where MDM2 ubiquitinates p53, causing p53 to exit the nucleus. Once in the cytosol, p53 degradation is mediated and completed by MDM2.

While mutations in the p53 gene are present in approximately half of all cancers, in cancers with unmutated p53, the protective effects of normally functioning wild-type p53 (p53WT) can be diminished by exuberant negative regulation by MDM2.3,4 MDM2 tightly controls p53 levels via a negative feedback loop. MDM2 must maintain a delicate and sustained balance with p53 in order to prevent proliferation of compromised cells.2,4 As such, the inhibition of MDM2 may promote restoration of critical p53 functions in patients with p53WT tumors and may represent a promising strategy for the development of anticancer drug development.

p53 and MDM2 form a negative feedback loop—p53 stimulates the expression of MDM2; in turn, MDM2 targets p53 for degradation.
The p53 protein plays a critical role in maintaining genome integrity

The p53 protein is often referred to as the guardian of the genome and provides continuous surveillance of host cells.\textsuperscript{2,5} p53 plays a vital role in the prevention of malignant transformation. It also works to recognize cells that, if propagated, might transfer mutations or other harmful alterations to the organism; by identifying these cells, p53 contributes to genetic stability.

Activation of normally functioning p53, in response to unfavorable cellular conditions such as ribonucleotide depletion, oncogene activation, oxidative stress or hypoxia, DNA damage, or telomere erosion, induces cell cycle arrest or apoptosis, and serves to mitigate the potential damage from cellular insults.\textsuperscript{2,5}

Cellular insults trigger phosphorylation of the N-terminal domain of p53.\textsuperscript{2} Upon phosphorylation, conformational changes in p53 enable the protein to function as a regulator of transcription. In addition, the change in conformation acts to prevent p53 degradation, prolong molecular half-life, and allow the protein to accumulate to high levels.\textsuperscript{1} In contrast, cells without normal functioning p53 fail to recognize and address cellular stressors or abnormalities, and replication of affected cells is not constrained. In this way, loss of functioning p53 promotes the oncogenic phenotype.\textsuperscript{3} When p53 is functioning properly, oncogenic mutations are not propagated, as DNA repair activities are intact and cell cycling is tightly controlled.\textsuperscript{2}
p53 serves as a major mainstay in the body’s anticancer defense mechanisms

Inactivation of the p53 pathway in tumors confers a strong selective advantage in the carcinogenic process. In fact, it has been proposed that eliminating p53 function may be a prerequisite for tumor survival. Preclinical work in mice has shown that the absence of p53 function is a continuous requirement for the maintenance of established tumors. When p53 function in these tumors was restored, tumor regression was observed.

p53 is the most frequently altered gene in human cancer. Somatic mutations in p53 have been seen in several human tumors types—p53 mutations or deletions are observed in approximately 50% of all solid tumors. Ovarian cancers, colorectal carcinomas, lung cancers, and head and neck carcinomas are among the types of solid tumors that most commonly exhibit the mutated p53 gene. Missense mutations in p53 are frequent, and can result in gain of function changes that enhance metastatic potential and invasiveness.

In many tumor types, p53 mutations have been associated with diminished overall survival and more aggressive tumor behavior. Thus, mutations in p53 not only abrogate tumor suppressive functions, but may also confer oncogenic properties, and contribute to a poorer overall prognosis.

It is important to note that p53 is not mutated in up to 50% of solid tumors and is generally not mutated in hematologic malignancies. In these tumors, p53WT is most likely inactivated; inactivation of p53 plays a critical role in development and progression of the cancers. Approaches that re-activate p53WT, permitting normal function, may lead to tumor regression. Therefore, with the development of novel therapies designed to re-establish function of p53WT in tumor cells, determining the mutational status of p53 in tumors may be important predictor of response to treatment.

Tumors have the ability to evade growth suppression, normal surveillance and immune defenses; they are often not susceptible to p53-mediated cell death. These qualities are among the hallmarks of cancer that enable tumors to survive, proliferate, and metastasize.
Overexpression of MDM2 promotes the development of the malignant phenotype

The MDM2 protein is an important negative regulator of p53. It inhibits p53 activity via three mechanisms: as an E3 ubiquitin ligase, MDM2 targets p53 for destruction in the cytosol, driving it to the proteasome. It also facilitates transport of p53 from the nucleus to the cytosol, in order for degradation to occur. Furthermore, MDM2 acts to block the transactivation domain of p53. These three actions in concert facilitate degradation of p53, and inhibit its ability to influence transcription of genes to block cell cycle progression and promote apoptosis, markedly impinging on the tumor suppressive actions of p53.

Some human tumors overexpress MDM2, which abrogates the protective effects of normal functioning p53. Consequently, MDM2 overexpression negatively affects prognosis. For example, solid tumors including breast, lung, esophagus, and stomach, and sarcomas, glioblastomas, and leukemias, have been associated with high levels of MDM2. High levels of MDM2 have been shown to correlate with poor prognosis, promotion of the malignant phenotype, treatment resistance, and metastatic capacity.
Inhibition of MDM2 allows for restoration of p53 tumor suppressor function

Developmental efforts on cancer therapeutics that act to remove the negative regulatory effect of excessive MDM2, and allow restoration of normal p53 activity are ongoing. One such approach is via the effective inhibition of MDM2 to diminish p53 transport to the cytosol, allowing for p53 accumulation in the nucleus, and enabling transactivating functionality—allowing p53 to interrupt propagation of abnormal or oncogenic cells. Normal functioning p53 would have the capacity to recognize replicating cells that could prove to be a threat to the organism, and would be able to promote tumor cell death. MDM2 inhibitors in development have been shown to activate p53, promoting cell cycle arrest and apoptosis; a number of such agents are currently in clinical trials.

Several different mechanisms to inhibit MDM2 have shown activity in tumor xenograft models. These approaches all act to down-regulate the p53-MDM2 loop, thus increasing levels of activated p53 and inhibiting tumor growth. An alternate mechanism of MDM2 inactivation targets the interaction of MDM2 with proteins of the proteasome that degrades p53. Disturbance of the ubiquitin-proteasome proteolysis pathway has been shown to induce apoptosis and growth inhibition in several different tumor models. Moreover, preclinical experiments have shown that molecules that inhibit MDM2-p53 protein-protein interactions can induce apoptosis, cell cycle arrest, and inhibit DNA synthesis, indicating restoration of p53 functionality in tumor cells.
The MDM2-p53 interaction represents a compelling therapeutic strategy in cancer

Activated p53 leads to transactivation of a range of genes involved in metabolic homeostasis, DNA repair, growth arrest and other critical functions, with the purpose of preventing propagation of cellular abnormalities. p53 exists in a tightly controlled feedback loop with MDM2. MDM2 also blocks the transactivating function of p53. In some human cancers, p53 is mutated or deleted, resulting in uncontrolled proliferation. In other cancers, however, p53 is intact but overexpression of MDM2 contributes markedly to the malignant phenotype, correlating with poor prognosis, treatment resistance, and metastatic capacity. Inhibition of MDM2 in p53WT tumor cells may restore p53 function, permitting cell cycle arrest and apoptosis of cancerous cells. Currently there are several approaches under investigation to exploit the anti-tumor effects of reactivating p53 by MDM2 inhibition.
References
