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Regulation of p53: intricate loops and delicate balances

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Abstract

The p53 tumor suppressor protein provides a major anti-cancer defense mechanism, as underscored by the fact that the *p53* gene is the most frequent target for genetic alterations in human cancer. Recent work has led to the realization that p53 lies at the hub of a very complex network of signaling pathways, which integrate a variety of intracellular and extracellular inputs. Part of this network consists of an array of autoregulatory feedback loops, where p53 exhibits very intricate interactions with other proteins known to play important roles in the determination of cell fate. We discuss two such loops, one involving the beta catenin protein and the other centering on the Akt/protein kinase B. In both cases, the central module is the interplay between p53 and the murine double minute 2 (Mdm2) protein, which inactivates p53 and targets it for rapid proteolysis. Whereas deregulated beta catenin can lead to Mdm2 inactivation and p53 accumulation, active p53 can promote the degradation and downregulation of beta catenin. Similarly, Akt can block p53 activation by potentiating Mdm2, whereas activated p53 can tune down Akt in several different ways. In each case, the actual output of the loop is determined by the delicate balance between the opposing effects of its different components. Often, this balance is dictated by additional signaling processes that occur simultaneously within the same cell. Genetic alterations characteristic of cancer are capable of severely distorting this balance, thereby overriding the tumor suppressor effects of p53 in a manner that facilitates neoplastic conversion.

Keywords: p53; Mdm2; Apoptosis; Beta catenin; ARF; Akt; Ubiquitination

Extensive research over the last 12 years has identified the p53 tumor suppressor as a key player in our body's built-in scheme of cancer prevention. Consequently, direct mutational inactivation of the *p53* gene was found to be the most frequent single genetic alteration associated with human cancer, occurring in about half of all individual tumors. The great interest in p53, spurred by the realization of its pivotal relevance to human cancer, has generated a flood of information addressing almost any possible aspect of p53 biochemistry and biology [1–6]. Among the main findings was the fact that the p53 protein is by and large a sequence-specific transcription factor: upon binding to defined consensus sites within the DNA, it is capable of activating the transcription of adjacent genes. The number of confirmed and proposed *p53* target genes is constantly growing, and the identities of the proteins encoded by those genes have offered invaluable insights into the mode of action of p53. In addition, p53 can also repress the expression of many genes, by mechanisms that still remain to be fully elucidated. On the biological end, p53 was found to be capable of imposing dramatic changes in cell fate, ranging all the way from a transient growth arrest, through permanent cell cycle exit, replicative senescence, terminal differentiation, to apoptotic cell death. A central feature in the life history of p53 is that in normal, unperturbed cells it is essentially latent, at least to the extent that it does not interfere with cell fate. However, when cells are exposed to various types of stress, typically associated in one way or another with conditions conducive to cancer, p53 snaps rapidly into an active mode, exerting its potent phenotypic

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Abbreviations: Mdm2, murine double minute 2; ARF, alternative reading frame; PKB, protein kinase B; PI3 kinase, phosphatidylinositide 3′-OH kinase.

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effects. This activation is key to the ability of p53 to serve as an effective tumor suppressor. In fact, research into the biochemistry underlying the switch of p53 from latent to active form has revealed a plethora of molecular interactions which position p53 at the hub of an extensive network of signal transduction and quality control pathways [7].

Despite the extensive information that has been gathered about p53, many critical questions remain. Attempts to obtain definitive answers to these questions form the focus of much of the current p53 research. Among the most prominent questions are:

- How does p53 ''sense'' that it should become active and intervene with cell fate?
- In which ways is activated p53 different from ''latent'' p53?
- How is the decision between the different biological outcomes of p53 activation made? In other words, why does activated p53 lead to a viable cell cycle exit in some cases while triggering apoptotic cell death in others?
- Why do some individual tumors retain a wild type *p53* gene, at the same time that other tumors with similar clinical features undergo mutational inactivation of both *p53* gene alleles?
- Do mutant forms of p53, which accumulate to high levels in many tumors, contribute to the properties of the tumor?
- Can the p53 status of a given tumor be used as a guideline for better therapy decisions?

The following sections will attempt to address some of these questions, *albeit* in a limited and selective manner.

1. The basal p53-Mdm2 loop

In non-stressed cells, p53 activity is subject to effective repression, maintaining it in a biologically latent state. The repression of p53 activation is largely due to the action of the Mdm2 protein, product of a proto-oncogene. Mdm2 displays a very peculiar relationship with p53 (Fig. 1). On the one hand, the Mdm2 protein binds to p53 and acts as its major cellular antagonist. This is achieved partly through direct interference of the bound Mdm2 with the transcriptional activities of p53, and largely through the ability of Mdm2 to target p53 for rapid proteolytic demise. The latter feature is due to the ability of Mdm2 to function as a p53-specific E3 ubiquitin ligase, which attaches ubiquitin residues onto p53 and sends it for degradation by the 26S proteasome. On the other hand, the *mdm2* gene is a direct target for positive transcriptional activation by p53. This interplay between p53 and Mdm2 defines the basal p53-Mdm2 loop, which serves as the ''heart'' of the p53 network. As long as the loop is fully closed, the balance between p53 and Mdm2 seems to be in favor of the latter, resulting in continuous repression of p53 activity and its maintenance in a biologically inert state. Any shift in this delicate balance, particularly changes that reduce the interaction between the two proteins and render p53 relatively immune to Mdm2, will enable a surge in cellular p53 activity and potentially give rise to a phenotypic p53 response. It is therefore no wonder that a multitude of stress signals impinge on that basal loop in a variety of ways, their common denominator being attenuation of the restrictive effect of Mdm2 and a consequent induction of p53 activity.

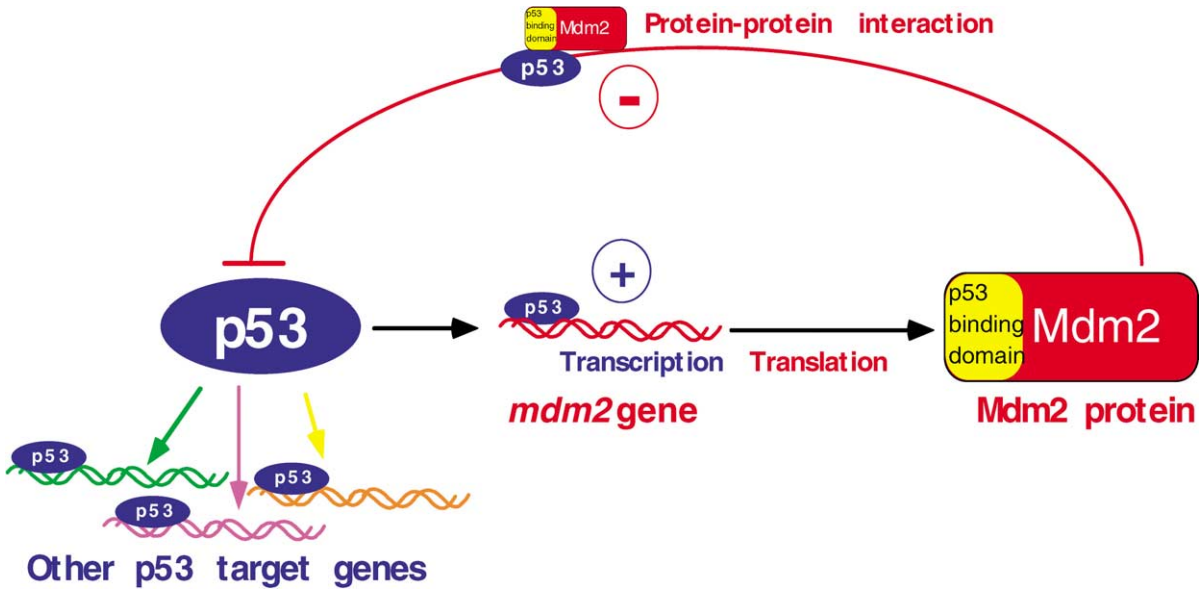

Fig. 1. The basal p53-Mdm2 loop. This module is the hub of the p53 network. The Mdm2 protein binds to p53, and abrogates p53 function by physically interfering with the biochemical activities of p53, and primarily by promoting the ubiquitination and proteasomal degradation of p53. This inhibitory interaction is believed to be largely responsible for maintaining p53 in a biologically latent state in non-stressed cells. On the other hand, the *mdm2* gene is a direct target for binding and transcriptional activation by p53, which is a sequence-specific transcription factor. Thus, the balance between p53 and Mdm2 dictates, to a large extent, the state of activity of p53 within a living cell.

2. The beta catenin-p53 loop and cancer

One of the conditions that often gives rise to a surge in p53 activity is the illegitimate constitutive activation of growth-stimulatory signaling pathways, as is the case when particular proto-oncogenes undergo mutational activation and turn into active oncogenes. At first glance, the activation of p53 by oncogenes seems counter-intuitive. However, this is most probably designed to act as a sophisticated built-in protective mechanism against cancer. Thus, when an oncogene is aberrantly activated in an otherwise normal cell, p53 will be alarmed and will trigger a phenotypic response that will prevent such a potentially pre-neoplastic cell from continuing down the path to cancer. However, in cells in which the coupling between oncogene activation and p53 induction is severed, the activated oncogene will be free to exert its aberrant effects and drive further neoplastic conversion. The coupling between oncogene activation and p53 induction, therefore, defines a pivotal component of the tumor suppressor capability of p53.

Although activated oncogenes probably elicit a p53 response in more than a single way, the best understood and probably the most important mechanism involves the ARF tumor suppressor protein [8,9]. ARF ($p19^{ARF}$ in the mouse, $p14^{ARF}$ in human cells) is encoded by an Alternative Reading Frame of the Ink4A tumor suppressor locus. It binds to Mdm2 and inhibits its activity, thereby allowing p53 to escape Mdm2-mediated repression and accumulate to levels that are sufficient to trigger a p53 response. Earlier studies have identified a number of oncogenes whose activation is coupled with p53 induction via ARF; these include myc, Ras, adenovirus E1A and E2F1 [8,9].

Recent work indicates that a similar coupling pertains also for another oncogene, beta catenin. The importance of beta catenin in human cancer has become well recognized in recent years, owing to the analysis of colorectal cancer and several other types of tumors, such as hepatocellular carcinoma and melanoma [10–12]. Whereas beta catenin is normally a structural component of cell-to-cell adhesion sites (adherens junctions), it can sometimes also double as a transcription factor in the nucleus. This occurs normally in particular developmental contexts, and abnormally in cancer cells where beta catenin becomes deregulated owing to mutational events. As it turns out, deregulated beta catenin not only drives processes that promote cancer, but in fact it can also lead in parallel to p53 induction [13]. As with several other oncogenes, this relies on the ability of deregulated beta catenin to stimulate the transcription of ARF mRNA, leading to inhibition of Mdm2 and a consequent accumulation of active p53 (Fig. 2; [14]). In keeping with the notion that the coupling between beta catenin and p53 serves as an anti-cancer mechanism,

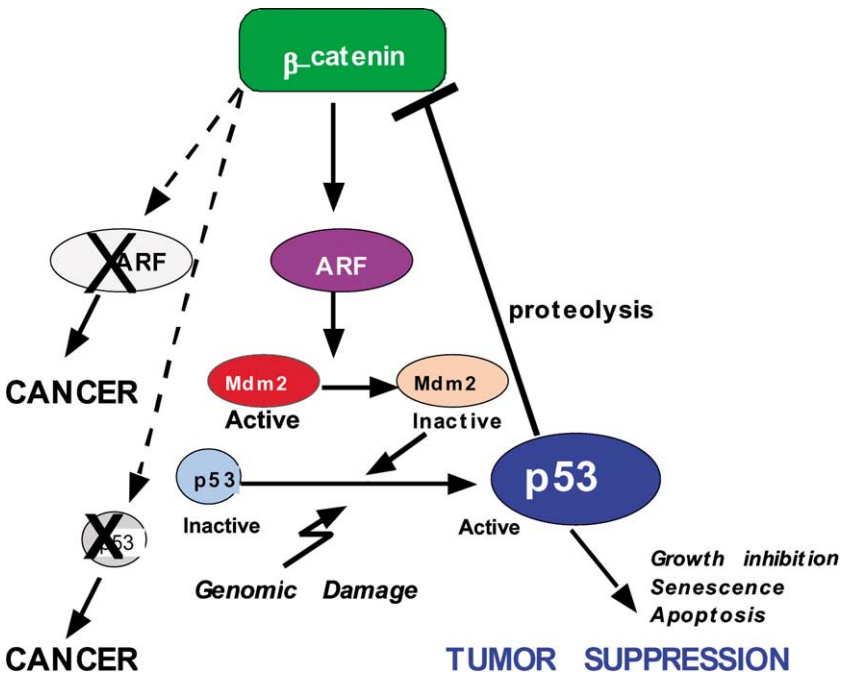

Fig. 2. The p53-beta catenin loop. Deregulated, transcriptionally active beta catenin induces the expression of the ARF tumor suppressor protein, which binds and inactivates Mdm2. The inactivation of Mdm2 results in constitutive activation of p53, leading to the triggering of a cellular p53 response. This response, which may take the form of cell cycle exit, replicative senescence or apoptosis, serves to curtail the potential oncogenic effects of deregulated beta catenin, thereby constituting an anti-oncogenic tumor suppressor activity of p53. In cells where this inhibitory pathway is defective, owing to dysfunction of either ARF or p53 itself, beta catenin is free to exert its oncogenic effects and to promote cancer. p53 can also be activated by genomic damage, in a manner that is at least partially independent of ARF. The activated p53, when present in sufficiently high levels, can drive the proteasomal degradation of beta catenin, further counteracting its potential oncogenic effects. This inhibitory arm of the loop is abrogated when p53 undergoes direct mutational inactivation.

excess beta catenin indeed elicits inhibitory effects in cells with intact p53 function; in primary mouse fibroblasts, this takes the form of growth inhibition accompanied by features of replicative senescence [14]. So how does beta catenin promote cancer after all? One way this may happen is by mutational inactivation of p53. Such inactivation is in fact observed in many tumors harboring deregulated beta catenin [15]. However, the model in Fig. 2 predicts that ARF inactivation may also suffice to relieve cancer cells of this unwelcome coupling with a protective p53 response. Indeed, analysis of colorectal tumors reveals a significant proportion that fail to express ARF, owing to transcriptional silencing by promoter methylation [16]. Importantly, ARF silencing appears to occur early in the course of tumor progression [16], positioning it close to the deregulation of beta catenin, which is believed to serve as an initiating event in this type of cancer [15].

As is often the case in regulatory circuits, the story is not as simple as that. Thus, there exist colorectal tumors where p53 mutation is seen in addition, rather than instead of, ARF silencing [16]. Why does p53 need to undergo direct inactivation if the coupling with deregulated beta catenin is disrupted anyway? There seem to be at least several answers to this intriguing question. Perhaps the most likely one is that such tumors often accumulate many features of genomic instability, including extensive chromosomal aberrations and aneuploidy. Since such genomic damage can induce p53 even in the absence of ARF, it will impose a pressure for direct inactivation of p53 irrespective of ARF status. Typically, one may expect that ARF silencing may occur early and will suffice to override the undesirable inhibitory effects of deregulated beta catenin, whereas p53 mutations will be selected at a later stage, concomitant with a gradual increase in overall genomic instability. In this regard, it is of note that loss of function of the APC tumor suppressor—the most common cause for the presence of deregulated beta catenin in colorectal cancer—can directly promote genomic instability through aneuploidy [17]. Another attractive explanation for the emergence of mutations in p53 during later stages of tumor progression is provided by the discovery of the second arm of the p53-beta catenin loop. High levels of activated wild type p53, which can be elicited in response to excessive DNA damage, can promote the proteolysis of beta catenin, perhaps through more than a single molecular mechanism and by multiple E3 ubiquitin ligases [18–20]. Hence, when the endogenous p53 in emerging tumors becomes activated in response to accumulated genomic damage, it may eventually down-regulate the hyperactive beta catenin and abrogate the signal that initiated the entire neoplastic process. Such situation will obviously impose a strong selective pressure for inactivation of p53, allowing beta catenin to maintain maximal levels and activity even in DNA-damaged cells. Finally, and perhaps not less importantly, the mutant p53 proteins that accumulate in tumor cells may be much more than just ‘‘dead’’ p53. In fact, there is growing evidence that beyond abrogation of the tumor suppressor functions of wild type p53, the p53 mutations that occur frequently in cancer actually confer new, oncogenic properties upon the mutant proteins [21]. This ‘‘gain of function’’ may be a strong additional driving force for the acquisition of p53 mutations at later stages of tumor progression.

Unlike the apoptotic response which often follows the induction of ARF and the activation of p53 by other oncogenes, deregulated beta catenin appears to favor a viable cell cycle exit [14]. This suggests that, in parallel with the upregulation of p53, beta catenin may also exert an anti-apoptotic effect that precludes a lethal outcome. Strong support for this notion was provided by the recent discovery that one of the proteins whose expression is elevated by deregulated beta catenin, WISP-1, possesses potent anti-apoptotic features [22]. Interestingly, WISP-1 does so by driving the activation of the Akt protein kinase, which is a component of yet another p53-related autoregulatory loop (see below).

And even that is not the end of the story. Beyond the changes in p53 and beta catenin, a typical cancer cell contains a substantial number of additional genetic alterations. Many of those may also impinge on the beta catenin-p53 loop, changing the balance between its different and opposing components. One relevant example is the Ras oncogene, which is frequently activated in human tumors. It was found that Ras can trigger the transcription of the *mdm2* gene, thereby elevating Mdm2 levels and counteracting the activity of p53 [23]. Importantly, Ras also induces ARF expression. The data suggest that in cells lacking ARF, Ras will suppress p53 function by upregulating Mdm2; on the other hand, if ARF is functional and well expressed, it may win over Mdm2 and enable a protective p53 response [23].

Overall, the emerging picture is that the eventual output of the beta catenin-p53 loop is dependent not only on the integrity of the various components, but also on the precise nature of the additional events that have occurred in a given cancer cell. Thus, the balance of signals that feed into this loop will determine whether or not it will be able to function effectively in cancer prevention.

3. The p53-Akt-Mdm2 loop: new insights into apoptosis?

Studies on the regulation of p53-mediated apoptosis have identified yet another control loop that may play an important role in dictating the cellular outcome of p53-related events (Fig. 3). This loop involves the Akt/PKB protein kinase, long known to be important in eliciting anti-apoptotic effects and mediating survival signals [24]. The activation of Akt by survival signals is achieved mainly through a kinase cascade involving PI3-kinase and downstream protein kinases. Recent work has revealed that

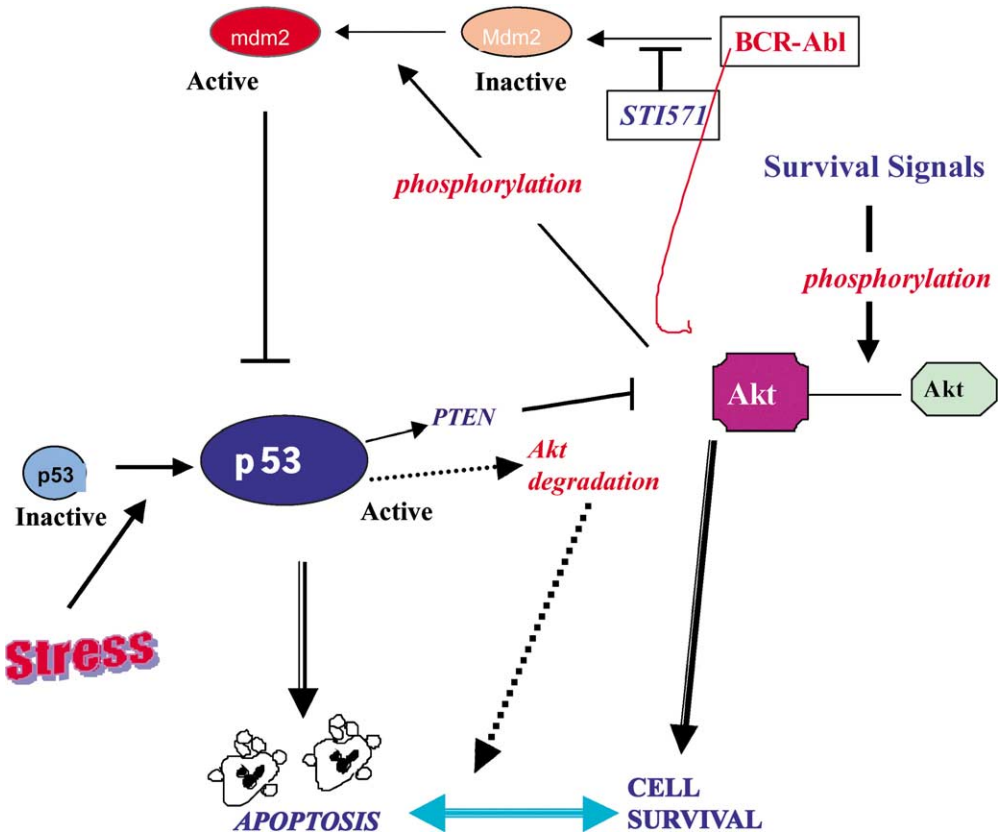

Fig. 3. The p53-Mdm2-Akt loop. The Akt/PKB kinase is induced by a variety of growth factors and other survival signals, and is also constitutively active in many tumors. Akt phosphorylates Mdm2, which enables Mdm2 to translocate into the nucleus and exert there its p53-inhibitory activity. Thus, Akt contributes to p53 inactivation and thereby to the inhibition of apoptosis. On the other hand, when p53 is activated by appropriate stress signals, it can downregulate Akt function by at least 2 mechanisms: promotion of caspase-mediated proteolysis of Akt, and transcriptional activation of the *PTEN* gene whose product—a phosphatidylinositide phosphatase—prevents Akt activation. The down-regulation of Akt function by p53 thereby facilitates apoptosis.

Akt also has intricate dealings with the p53 pathway. In that case, as in the case of ARF, the direct target is not p53 itself but rather Mdm2. Akt can bind to Mdm2, and phosphorylate it on at least two sites within the central domain of Mdm2 [25–27]. This enables Mdm2 to translocate from the cytoplasm into the nucleus, where it is required in order to bind p53 and target it for inactivation, ubiquitination and degradation. Thus, Akt is actually required for full Mdm2 activity. Survival signals that increase Akt activity will therefore potentiate the inhibitory effect of Mdm2 and attenuate the p53 response, providing one attractive explanation for the ability of Akt to interfere with p53-mediated apoptosis [28].

At the opposing arm of the loop stands the observation that activated p53 can lead to down-regulation of cellular Akt levels [25]. In this scenario, induction of high p53 activity, as occurs in cells exposed to extensive DNA damage, triggers rapid and effective caspase-mediated proteolytic cleavage of Akt, resulting in a dramatic drop in the overall levels of Akt [25]. Caspase-mediated Akt cleavage is frequently seen during late stages of the apoptotic process, and is believed to be a secondary consequence of the massive caspase activation that is inherent to this process. However, in the case of activated p53 this cleavage occurs much earlier [25], supporting the notion that it plays a critical role in the facilitation of p53-dependent apoptosis. The exact manner by which activated p53 leads to rapid caspase-mediated Akt cleavage remains to be figured out. However, it is noteworthy that a similar picture was also observed with the pRb tumor suppressor protein, whose p53-dependent rapid cleavage by caspase(s) is also likely to facilitate apoptosis in some cell types [29].

Once again, the story does not end here, and the next player in this loop is PTEN. PTEN, also a tumor suppressor, encodes a phosphatidylinositide phosphatase which counteracts the action of PI3-kinase [30]. Thus, PTEN serves to prevent the activation of Akt, thereby facilitating apoptosis. Recent work has revealed that p53 can transactivate the *PTEN* gene [31]. This implies that, when p53 becomes activated, it may cause an elevation in cellular PTEN levels, thereby attenuating Akt and further enabling apoptosis. In fact, it could be shown that PTEN can effectively protect p53 from the inhibitory effects of Mdm2 and augment p53-dependent cell killing by chemotherapy [32].

Further highlighting the complexity of this network, there exists an unexpected twist to the story: under some circumstances, p53 can actually activate Akt rather than

repress it. This is achieved through the ability of p53 to induce transcription of the heparin-binding EGF-like growth factor gene, whose protein product turns on a PI3-kinase/Akt signaling pathway [33]. Obviously, this option must be used sparingly, or else p53 would never be able to act as an effective inducer of apoptosis. However, when it is used successfully, it may affect profoundly the consequences of p53 activation.

The p53-Mdm2-Akt loop may serve as a site of integration of opposing inputs emanating from survival signals, on the one hand, and pro-apoptotic stress signals on the other hand (Fig. 3). This loop defines another setting where the cellular outcome may vary dramatically, depending on the cellular context. In the absence of survival factors, extensive stress will lead to successful p53 activation, inactivation and proteolytic degradation of Akt, and eventually apoptosis. On the other hand, potent survival signals will activate Akt, potentiate Mdm2, and eventually attenuate p53 and alleviate its biological effects. Hence, the balance between the different components of the loop can determine the choice between the life and death of a cell.

4. Conclusions

It is now clear that p53 is positioned in the heart of a complex array of regulatory networks. Parts of this array are represented by the autoregulatory loops discussed above. However, as complex as these loops may seem, they are probably still a gross oversimplification. It is most likely that these loops intercalate with additional ones, as illustrated by the WISP-1 protein, which is induced by deregulated beta catenin and feeds into the Akt pathway, eventually inhibiting p53-mediated apoptosis. Hence, it is almost impossible to predict the eventual biological outcome of a p53 response by simply looking at one or a few components only. The better one can assemble the picture in its entirety, the more likely it is that correct predictions can be made.

The presently available information would suggest that, in normal cells, the overall balance of opposing forces is set such that p53 will usually ‘‘win.’’ This enables p53 to serve as an effective integrator of stress signals and a very successful tumor suppressor. Even in such normal cells, this delicate balance may be upset by a variety of factors, including developmental cues and inputs from the extracellular environment. In these cases, the inhibition of p53 activation presumably serves a beneficial purpose, such as allowing necessary cell proliferation or sparing cells from undesirable death. However, the balance can in some cases be permanently shifted, as occurs for instance when ARF is silenced, or PTEN is deleted, or p53 itself is mutated. In such cases, the cell is deprived of the protective action of p53, leaving the road wide open to the emergence of cancer.

Acknowledgments

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