Switching from life to death: The Miz-ing link between Myc and p53

Cells can respond to the activation of the tumor suppressor protein p53 by undergoing cell cycle arrest or apoptosis, and Myc has now been shown to help switch the response to apoptosis by repressing the expression of $p21^{CIP1}$, a cyclin-dependent kinase inhibitor with antiapoptotic activity.

As in any well-ordered society, individual cells in complex multicellular organisms must obey the laws and live within the confines of their normal environment. Malignant progression is the consequence of cellular anarchy, where developing tumor cells acquire alterations that allow them to flout the rules governing where and when proliferation and survival can take place. A series of checkpoints operate to ensure that order is maintained, and an integral part of this team is p53—an efficient hitman that can take out cells attempting to proliferate beyond their defined limits. Under some circumstances, p53 achieves this end by inducing cell death, thereby completely eliminating the errant cell. But on other occasions, p53 shows some leniency, inducing a cell cycle arrest that might potentially be reversible should the cell be rehabilitated (Vousden and Lu, 2002). Clearly, these are very different responses, and the issue of why some cells die while others arrest in response to p53 activation is of considerable interest.

Particularly provocative is the observation that activation of proteins that can drive cell proliferation—like Myc—also tilts the response to p53 activation toward apoptosis. Deregulated proliferation is one of the linchpins underlying malignant progression—a mission-critical event that is required for any cancer to develop (Evan and Vousden, 2001). The concomitant sensitization of cells with proliferative abnormalities to death means that successful cancer cells must acquire additional alterations—like loss of p53—to allow them to survive. The assumption is that cancer cells are more likely than normal cells to undergo apoptosis following repair of these lesions—for example, following reactivation of p53. Understanding what determines the choice of response to p53, how deregulated proliferative events also promote apoptosis, and how these pathways are derailed in tumors have therefore become key questions in the field.

Two models—which are not mutually exclusive—have emerged to explain the choice of response to p53. The first suggests that in the process of malignant progression, cells are exposed to death signals that cooperate with p53 to reach an apoptotic threshold. In this model, the activity of p53 remains the same regardless of the outcome, which is determined by the presence or absence of additional signals. In the second model, the response is determined by changes in the function of p53 itself—more specifically, the differential regulation of p53's DNA binding and transcriptional activity. Phosphorylation of p53 and the availability of apoptotic cofactors have been shown to be required for transcriptional activation of some apoptotic target genes, but dispensable for the induction of genes mediating the cell cycle arrest (Figures 1A and 1B). These studies raise the possibility that the switch to an apoptotic response may reflect expression or activation of critical kinases or cofactors required for p53 to induce apoptotic target genes, and that cancer cells may survive because these factors are lost or mutated (Vousden and Lu, 2002).

Now Seoane et al. (2002) have uncovered a new mechanism through which Myc can switch the p53 response to apoptosis—not by affecting whether p53 can induce activators of apoptosis,

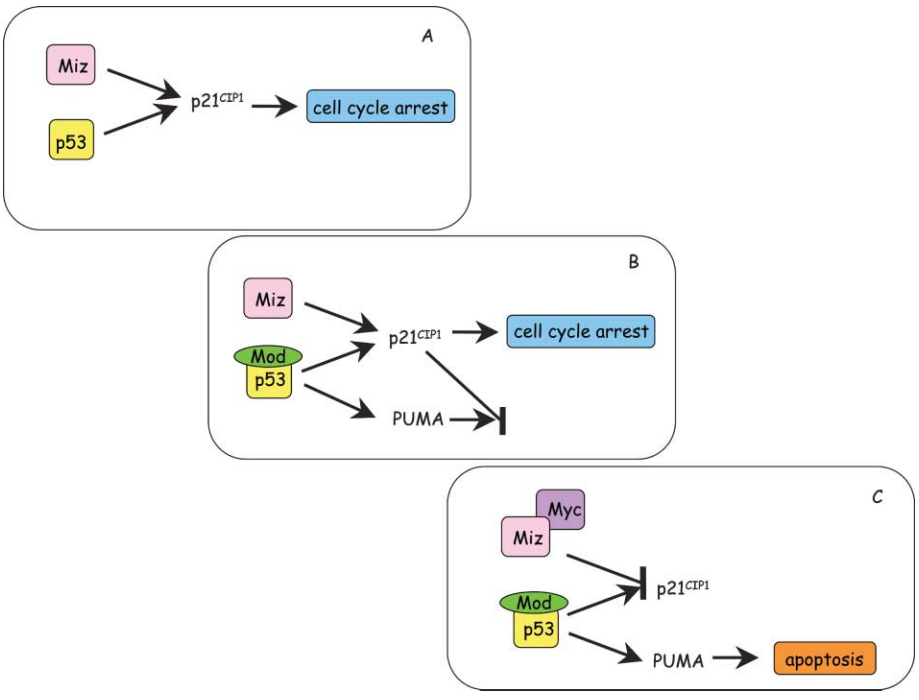

Figure 1. Simplified model of the mechanisms that can help determine the choice of response to p53

A: Activation of p53 in normal cells results in selective ex pression of a group of p53 target genes that mediate cell cycle arrest, but not the apoptotic targets. The expression of $p21^{CIP1}$—the principal mediator of cell cycle arrest—depends on the activity of both p53 and Miz-1.

B: In response to some oncogenic changes, modification or coactivator binding to p53 (mod) allows for the activation of apoptotic targets, like PUMA. However, the expression of p53-inducible genes like $p21^{CIP1}$ can block implementation of the apoptotic response.

C: A further signal, such as deregulated Myc, is required for the inhibition of $p21^{CIP1}$ expression by the Miz/Myc complex and induction of apoptosis.

but by blocking the expression of a p53-induced inhibitor of cell death. The p53 target gene in question is the cyclin-dependent kinase inhibitor $p21^{CIP1}$, the principal mediator of p53-induced cell cycle arrest. Although the $p21^{CIP1}$ promoter is highly responsive to p53, it is now evident that another transcription factor, Miz-1, also plays a critical role in regulating $p21^{CIP}$ expression (Herold et al., 2002; Seoane et al., 2002; van de Wetering et al., 2002) (Figure 1A). Like p53, Miz-1 can be activated in response to stress, and both transcription factors are required for the induction of $p21^{CIP1}$ expression (Herold et al., 2002). Previous studies had shown that the transactivation activity of Miz-1 could be inhibited by interaction with Myc (Seoane et al., 2001; Staller et al., 2001), and the interaction of Myc with Miz-1 also results in repression of $p21^{CIP1}$ transcription, even in the presence of activated p53. This observation therefore nicely explains how Myc expression can overcome the p53-mediated block to cell cycle progression. In addition, the regulation of $p21^{CIP1}$ activity through this Myc/Miz interaction plays an important role in regulating the switch from proliferation to differentiation (van de Wetering et al., 2002). However, $p21^{CIP1}$ has another less well-explored activity, which is the ability to protect cells from p53-induced death signals. So in removing the block to cell cycle progression, Myc also deprives the cells of this survival signal. Importantly, because the effect of Myc on $p21^{CIP1}$ expression is mediated though Miz-1, it does not directly affect p53 function. This means that the activation of expression of other p53 target genes that encode proapoptotic proteins like PUMA and PIG3 remains unaffected (Seoane et al., 2002), and suggests that ultimately the death response is engaged by virtue of the loss of the protective effect of $p21^{CIP1}$ (Figure 1C). The model is simple and elegant, but also an incomplete view of how Myc sensitizes cells to death. Herold et al. show that a mutant of Myc that selectively fails to bind Miz cannot repress expression of $p21^{CIP1}$—as expected—but retains the ability to sensitize cells to apoptosis (Herold et al., 2002). This mutant remains competent in binding Max and functions as a transcriptional activator, supporting the proposal that part of the Myc apoptotic signal is dependent on activation of gene expression.

A closer consideration of these new clues as to how Myc can switch the p53 response to apoptosis reveals some interesting twists to the current thoughts on choice of response to p53. Under some conditions, inhibition of p53-mediated apoptosis reveals an underlying cell cycle arrest, suggesting that the cell cycle arrest response remains intact in cells destined to die. The implication is that the choice of response to p53 is either induction of cell cycle arrest or induction of both cell cycle arrest and apoptosis, with death taking precedence in the latter situation. The notion that apoptosis is somehow an additional step that is superimposed onto cell cycle arrest fits well with the idea that unmodified forms of p53 that may be induced in relatively normal cells activate expression of only cell cycle arrest targets, and that further posttranscriptional modification or cofactors are required to allow activation of apoptotic targets (Figure 1A and 1B). The new studies now reveal an extra layer of complexity by showing that even when both cell cycle arrest and apoptotic target genes are induced by p53, the resultant response may still be cell cycle arrest. Under these conditions, apoptosis ensues only following selective inhibition of p53 target genes that encode a survival function, like $p21^{CIP1}$. In this case, apoptosis would not be superimposed onto an underlying cell cycle arrest, which would also be eliminated with the loss of $p21^{CIP1}$ (Figure 1C).

So what does $p21^{CIP1}$ do to protect the cells from apoptosis? The answer is not clear, although there seems to be some specificity to inhibition of the mitochrondrial apoptotic pathways, since induction of cell death by TRAIL is not affected by loss of $p21^{CIP1}$ (Javelaud and Besancon, 2002). Although it has been suggested that enhanced apoptotic sensitivity following loss of $p21^{CIP1}$ results from elevated p53 expression, and therefore an increase in p53-induced apoptotic signaling (Javelaud and Besancon, 2002), Seoane et al. show that $p21^{CIP1}$ expression can protect from apoptosis without significantly altering p53 activity. These authors showed that the presence of $p21^{CIP1}$ did not protect from apoptosis by reducing p53-mediated accumulation of apoptotic proteins like PUMA or PIG3 (Seoane et al., 2002), suggesting that $p21^{CIP1}$ can function to impede the apoptotic pathways downstream of p53. One intriguing suggestion is that this reflects the ability of $p21^{CIP1}$ to block the activation of E2F1, another transcription factor with apoptotic functions.

These studies represent an exciting step forward in our understanding of how the choice of response to p53 is regulated, and also generate a host of new questions. Can p53 induce the expression of other antiapoptotic proteins that can play a similar role to $p21^{CIP1}$ and contribute to the regulation of response even when $p21^{CIP1}$ levels remain constant? Can related cyclin-dependent kinase inhibitors, like $p27^{KIP1}$, function in the same way? Does the choice of response to p53 induced by other stress signals also depend on downregulation of $p21^{CIP1}$? Does deregulated expression of $p21^{CIP1}$ play a more general role in protecting tumor cells from apoptosis? Leading to the most practical question: could regulation of the transcription factors that control $p21^{CIP1}$ expression be beneficial in tumor therapy? These issues are unlikely to remain a Miz-tery for long.

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Selected reading

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