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No Way Out for Tumor Cells

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In this issue of *Cancer Cell*, Huang et al. report that preventing exit from mitosis provides a very efficient strategy for killing cells. Although this is not an unexpected finding, it nevertheless provides a novel conceptual framework for augmenting the antimitotic strategies currently under development for fighting cancer.

The mitotic spindle has long been a useful target for chemotherapy (reviewed in Jordan and Wilson, 1998). The various spindle poisons used in the clinic prevent stable attachment of spindle microtubules to kinetochores and therefore inhibit satisfaction of the mitotic checkpoint (MC). Failure to satisfy this checkpoint significantly retards the degradation of cyclin B1, which results in a sustained mitotic arrest (reviewed in Musacchio and Hardwick, 2002).

Despite what we know regarding the action of spindle poisons, it remains unclear how they kill cells. The current consensus is that prolonging mitosis spindle poisons induces some cells to die in mitosis, although others can "slip" through the checkpoint into the next G1 as tetraploid cells (reviewed in Rieder and Maiato, 2004). However, cells that undergo mitotic slippage may or may not die in the subsequent G1. p38/p53-proficient cells that escape cell death undergo a permanent G1 arrest in a tetraploid state after slippage, while cells lacking p38 or p53 can undergo additional rounds of division to produce highly aneuploid progeny (Figure 1).

Recent live-cell imaging studies have provided important new insights into how normal and cancer cells respond to various spindle poisons. First, it is now clear that mitotic slippage occurs because cyclin B is slowly degraded in the background of a fully active MC (Brito and Rieder, 2006). It is also evident that cancer cell lines are more sensitive to spindle poisons than nontransformed cells (Brito and Rieder, 2009; Gascoigne and Taylor, 2008; Orth et al., 2008; Shi et al., 2008). These studies also clearly show that the duration a cell spends in mitosis does not strictly determine whether it will live or die, challenging the longstanding idea that it is the duration of the mitotic arrest that dictates cell fate. Perhaps the most surprising conclusion from these studies was, however, that the response to a spindle poison is not necessarily predetermined by genetic background or the type of drug. In the presence of the same drug cells within a single cell line display variable cell fates, which is clearly demonstrated by the fact that the fate of one daughter cell is independent of that of the other derived from the same mother (Gascoigne and Taylor, 2008).

So if the fate of a cell after spindle disruption cannot be predicted based on its genetics, how is it determined? Gascoigne and Taylor proposed an elegant "competing-networks" model for cell fate in spindle poisons (Gascoigne and Taylor, 2008, 2009). One of these networks works to maintain the mitotic condition by preventing cyclin B degradation (via the MC), while the other works to activate the apoptotic machinery. In their model mitotic slippage occurs when cyclin B drops below a critical threshold, whereas cell death occurs when the apoptosis-activating network reaches a critical threshold. During a delay in mitosis, both networks are active and the network that eventually prevails determines cell fate. The model draws some support from data that delaying slippage by simply increasing the level of cyclin B is sufficient to enhance death in mitosis (Gascoigne and Taylor, 2008).

The information from these studies defined the starting point for the Huang et al. (2009) investigation reported in this issue of *Cancer Cell*. They reasoned that drugs that block cells in mitosis without allowing mitotic slippage should kill cells more efficiently than current antimitotic drugs. Because mitotic slippage occurs through the slow "background" degradation of cyclin B, and because normal exit from mitosis also requires cyclin B destruction, Huang and coworkers tested their idea by inhibiting the degradation of cyclin B. They did this by either expressing a nondegradable mutant of cyclin B or depleting an essential cofactor (Cdc20) required for activating the E3 ubiquitin ligase complexes (APCs) responsible for targeting cyclin B for proteolysis (reviewed in Musacchio and Hardwick, 2002). As predicted, both strategies killed cancer cells more effectively than drugs that simply perturb the mitotic spindle (Figure 1).

So why the excitement? Considering that spindle poisons have long been suspected to kill tumor cells by causing a protracted mitotic arrest, the finding that an irreversible arrest is a more efficient killer does not really come as a surprise. However, in sharp contrast to drugs that target the spindle, the MC becomes rapidly satisfied (just like in a normal mitosis) when Cdc20 is depleted or in the presence of nondegradable cyclin B, but the cell remains stuck in mitosis. Under this condition cell death occurs *independent of MC activity* (Huang et al., 2009). This strongly suggests that a proapoptotic signal slowly accumulates during mitosis that is not dependent on spindle damage or the inability to satisfy the MC, and that if this signal breaches its critical threshold before mitotic exit occurs, it will invariably trigger death in mitosis. None of the currently available drugs that target mitosis, including inhibitors for kinesin-5, Polo, or Aurora kinases, prevent the degradation of cyclin B. As a result their efficacy is limited because

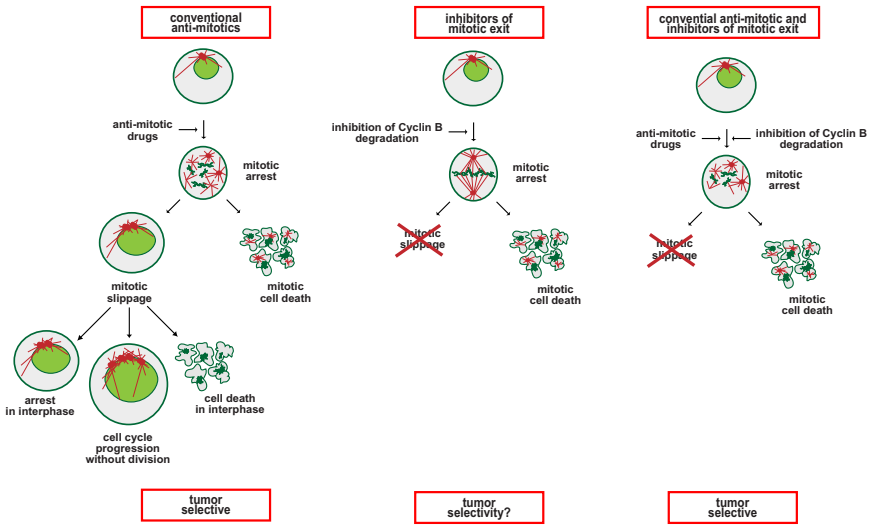

Figure 1. Blocking Mitotic Exit as an Antitumor Strategy

Conventional spindle poisons interfere with the assembly of a normal bipolar spindle. Taxanes and vinca alkaloids directly target the microtubules of the spindle and interfere with microtubule dynamics that are essential for proper attachment of chromosomes, while inhibition of Eg5, Polo, or Aurora A causes formation of a monopolar spindle. All of these drugs can cause a prolonged mitotic arrest in cultured cells and many have been shown to display tumor selectivity. However, cells can escape from this arrest by mitotic slippage, after which a cell can die in the subsequent G1, undergo a permanent arrest, or continue on through additional cell cycles. It is noteworthy that clinically effective drug concentrations are likely to be well below that needed to arrest cultured cells in mitosis. An outstanding question therefore remains whether antimitotics really "arrest" tumor cells in mitosis in situ, or if the mitotic delay induced by lower drug concentrations induces cell death during the ensuing G1. Drugs that block mitotic exit would prevent mitotic slippage, and Huang et al. demonstrate that this strategy is highly efficient in promoting mitotic cell death, even in the absence of spindle damage. Nonetheless, it is currently unclear if this type of strategy will display tumor-selective cell killing. Combining spindle poisons with drugs that block mitotic exit could potentially provide sufficient tumor selectivity (see text for details).

they allow some cells to escape death in mitosis by slipping into the next G1. With this in mind the findings of Huang and colleagues provide a novel conceptual framework for maximizing the efficiency of antimitotic drugs for killing cells. Their work suggests that drugs that target Cdc20, or other components involved in cyclin B degradation including the APCs or proteasomes, may prove more effective in killing cells. In principle, such drugs could be combined with established spindle poisons: one would prolong mitosis by preventing satisfaction of the MC while the other would prevent mitotic slippage by inhibiting the degradation of cyclin B (Figure 1).

Although this approach for killing cells in mitosis may well prove superior to other drug-based strategies, how can it be made tumor selective? Clearly, if the proapoptotic machinery becomes progressively more aggressive during a prolonged mitosis, then cell killing in response to spindle poisons will not be limited to tumor cells. Yet, compared to nontransformed cells, tumor cell lines appear more prone to dying in mitosis in response to spindle poisons (Brito and Rieder, 2009; Gascoigne and Taylor, 2008; Orth et al., 2008; Shi et al., 2008), suggesting that they more easily reach the apoptosis threshold, possibly because they are "primed for death" (Green, 2007). Thus, the necessary tumor-selectivity might be achieved by combining a drug that delays mitotic exit with a drug that promotes apoptosis. Drugs that prevent degradation of cyclin B will not produce this selectivity because cyclin B degradation is essential for normal cells to exit mitosis. Of course it is possible that simply slowing cyclin B degradation could provide enough time to breach the apoptosis barrier and selectively induce mitotic cell death in some tumors. Selectivity may also be achieved via the route by which cells are arrested in mitosis. For example, tumor cells with aberrant numbers of centrosomes depend on the microtubule motor protein HSET (Kwon et al., 2008), which clusters the extra centrosomes and allows proper bipolar spindle assembly. It is therefore possible that combining drugs that target HSET with drugs that inhibit mitotic exit will provide a highly selective treatment for tumors that display centrosome amplification.

All in all the study by Huang and coworkers provides a new antitumor strategy that is based on inhibiting mitotic slippage by preventing cyclin B degradation, while enhancing cell death in mitosis by lowering the threshold for apoptotic-induced death in mitosis. Both strategies require further study of how their corresponding and competing networks are wired to enable the eventual development of drugs that can target these networks in a highly selective manner.

REFERENCES

Brito, D.A., and Rieder, C.L. (2006). Curr. Biol. *16*, 1194–1200.

Brito, D.A., and Rieder, C.L. (2009). Cell Motil. Cytoskeleton *66*, 437–447.

Gascoigne, K.E., and Taylor, S.S. (2008). Cancer Cell *14*, 111–122.

Gascoigne, K.E., and Taylor, S.S. (2009). J. Cell Sci. *122*, 2579–2585.

Green, D.R. (2007). Cancer Cell *12*, 97–99.

Huang, H.-C., Shi, J., Orth, J.D., and Mitchison, T. (2009). Cancer Cell *16*, this issue, 347–358.

Jordan, M.A., and Wilson, L. (1998). Curr. Opin. Cell Biol. *10*, 123–130.

Kwon, M., Godinho, S.A., Chandhok, N.S., Ganem, N.J., Azioune, A., Thery, M., and Pellman, D. (2008). Genes Dev. *22*, 2189–2203.

Musacchio, A., and Hardwick, K.G. (2002). Nat. Rev. Mol. Cell Biol. *3*, 731–741.

Orth, J.D., Tang, Y., Shi, J., Loy, C.T., Amendt, C., Wilm, C., Zenke, F.T., and Mitchison, T.J. (2008). Mol. Cancer Ther. *7*, 3480–3489.

Rieder, C.L., and Maiato, H. (2004). Dev. Cell *7*, 637–651.

Shi, J., Orth, J.D., and Mitchison, T. (2008). Cancer Res. *68*, 3269–3276.