Targeting Ribosome Assembly Factors Selectively Protects p53 Positive Cells from Chemotherapeutic Agents

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Targeting Ribosome Assembly Factors Selectively Protects p53 Positive Cells from Chemotherapeutic Agents.

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Many chemotherapeutic agents act in a nondiscriminatory fashion, targeting both cancerous and noncancerous cells in S phase and M phase. One approach to reduce the toxic side effects in normal tissue is to exploit the differences in p53 functionality between cancerous and noncancerous cells. For example, activating p53 signaling by nongenotoxic means can transiently arrest noncancerous p53 positive cells in G1 phase and protect them from the cytotoxic effects of chemotherapeutic drugs. However, since most cancerous cells have faulty p53 signaling, they will proceed to cycle, and continue to be affected by the drug. In this study we asked if this G1-phase arrest and cytoprotection can be achieved by targeting ribosome biogenesis. Through the expression of a dominant negative mutant ribosome assembly factor Bop1, we were able to transiently inhibit rRNA maturation. Using this genetic model, we have shown that inhibition of rRNA maturation protects 3T3 cells from chemotherapeutic agents camptothecin and methotrexate. This cytoprotection is associated with a transient arrest of cells in G1 phase, and is p53 dependent. We have also shown that the depletion of ribosomal protein Rps19 via shRNA arrests cells in G1 phase and protects them from camptothecin. However, this G1 arrest and cytoprotection was not achieved in shRNA-mediated depletion of several other tested ribosomal proteins, indicating distinct cellular responses to different targets in ribosome biogenesis. Using a mixed population of isogenic p53 positive and p53 negative cell lines, we have further shown that camptothecin in combination with the inhibition of ribosome biogenesis selectively kills p53 negative cells. We propose that the inhibition of select post-transcriptional ribosome assembly steps can enhance the efficiency of existing chemotherapeutic treatments.