PUMA Mediates the Apoptotic Response to p53

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Technology description

Technical Details:
The p53 pathway is inactivated in the great majority of human cancers. Of the many physiologic effects of p53 that have been described, current evidence suggests that apoptosis is critical for its tumor suppressor activities. Although several genes that might mediate p53-induced apoptosis have been proposed, none have previously been shown to play an essential role in this process through a rigorous gene disruption approach. In a systematic examination of genes activated by p53 in apoptosis, investigators at Johns Hopkins identified a Bcl-2 homology domain 3 (BH3)-only protein termed PUMA (p53 up-regulated modulator of apoptosis, which is also known as Bbc3 (Bcl-2 binding component 3). Recently, these investigators used a gene-targeting approach to evaluate p53-mediated death in human colorectal cancer cells (HCT116). Expression of p53 in these cells induces growth arrest through transcriptional activation of the cyclin-dependent kinase inhibitor p21. If p21 is disrupted via gene targeting, the cells die through apoptosis. If the PUMA gene is also disrupted in such p21-deficient cells, apoptosis is prevented. These findings suggest that the balance between PUMA and p21 is pivotal in determining the responses to p53 activation.
A number of valuable reagents were generated in the course of this study for the purpose of expressing PUMA in any cell type and for addressing the role of PUMA in apoptosis. Among these are HCT116 cell lines in which the PUMA gene was disrupted either alone, or in combination with p21. Adenoviruses expressing wild-type PUMA and a PUMA gene with a deletion of the BH3 domain are also available.

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