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Beyond the knock-out: float through the cytosol, sting like p53

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p53, a cellular damage response regulator, is mutated in 50% of all cancers. We have constructed a mathematical model showing how different p53 dynamics after UV radiation and γ-irradiation exposure allows cells to respond properly to both slowly and quickly detected damage. We extend this model with an apoptosis module accounting for the transcription-dependent and -independent activities of p53, which is then used to analyze and classify contrasting apoptosis evasion strategies in commonly used tumour cell lines. In particular, we predict that lower levels of basal p53 contribute to the radiosensitivity observed in many cancers, and that self-overregulation of p53 is only one of many ways in which gain-of-function p53 mutations can be advantageous to tumour cell survival. Moreover, the downregulation of p53 by its canonical antagonist, Mdm2, has been well-studied in the nucleus, but this same interaction in the cytosol may be responsible for weakening the transcription-independent p53 pathway in humans. These models provide a unified framework for studying the broad and surprising array of effects of p53, far beyond the loss-of-function mutations well-known across cancers.

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