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Alternative cell fate in response to DNA damage regulated by differential p53 pathway dynamics

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Alternative Cell Fate in Response to DNA Damage Regulated by Differential p53 Pathway Dynamics

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Abstract

The tumor suppressor protein, p53, and its downstream effectors play a crucial role in mediating proper cellular process of repair or death in response to a wide variety of stress stimuli. Cell fate varies, depending on the type of stress, its level and the genetic background of individual cell types. In this study we quantify the phenotypic response to DNA damage, and investigate how the response process is differentially regulated by the p53 pathway dynamics. We induced DNA damage in selected cultured mammalian cell lines by using a DNA-damaging drug, etoposide. By using quantitative time-lapse microscopy, we tracked dynamics of individual cells in real time, acquiring information with respect to protein kinetics and cellular processes that are beyond ensemble approaches. Our results showed that when being treated with low dosage of etoposide, the majority of cells exhibited continuous oscillation of p53 followed by cell-cycle arrest , while at high dosage cells tended to die rapidly with monotonic elevation of p53. In constrast to common hypothesis, we found the bimodal p53 dynamics did not control phenotypic response by modulating p53's transcriptional activation as DNA damage increased. Our data so far showed that the differential p53 dynamics regulate the alternative cell fate of arrest vs. death mainly by modulating p53's direct pro-death activity in the cytoplasm in a damage-dose dependent manner.

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