Unraveling Cell Fate Control by Differential Pathway Dynamics at the Single Cell Level

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Jue Shi

Department of Physics, Hong Kong Baptist University, Hong Kong

***Email of Presenting Author: jshi@hkbu.edu.hk**

The cellular machinery, consisting of multiple networks/pathways, is highly robust with respect to genetic and environmental changes, enabling a living cell to efficiently adjust to different cellular states. Increasing evidence indicates that the dynamics of key components of signaling pathways play a crucial role in regulating proper cellular responses; however, there is still a large gap in our understanding of how complex dynamical responses are modulated and how they vary between individual cells. One research interest of our lab is to elucidate the quantitative mechanism by which cell fate is regulated by differential pathway dynamics at the single cell level. By combining live-cell imaging with computational modeling, we recently investigate the DNA damage response mediated by the p53 pathway, as the p53 pathway, consisting of mainly the tumor suppressor protein p53, its upstream regulators and downstream transcriptional targets, plays a central role in mediating the critical stress response to common chromosomal damage in mammalian cells. The p53 pathway is known to be differentially activated in response to distinct DNA damage, leading to alternative cell fate outcomes, but questions remain how p53 pathway dynamics are modulated by variable DNA damage. Our study revealed a novel, bimodal switch of p53 dynamics modulated by DNA damage strength that is crucial for cell fate control. At low DNA damage, p53 underwent periodic pulsing and cells entered cell-cycle arrest. At high DNA damage, p53 underwent a strong monotonic increase and cells activated apoptosis. We found that the damage dose-dependent bimodal switch was due to differential Mdm2 up-regulation, which controlled the alternative cell fates mainly by modulating p53's induction level and pro-apoptotic activities. Our findings not only uncover a new mode of regulation for p53 dynamics and cell fate but also suggest that p53 oscillation may function as a suppressor, maintaining a low level of p53 induction and pro-apoptotic activities so as to render cell-cycle arrest that allows damage repair at time of low DNA damage.