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Abstract

Approximately 50% of all known cancers involve a mutation of the tumor suppressor protein p53 (Baugh et al., 2018). In certain cancers, this figure is even higher; in SKOV-3 Ovarian cancer cells, for example, approximately 90% are p53-null— completely devoid of functional p53. While prior studies have shown that p53 dynamics in response to DNA-damage correlate strongly with cell fate (Purvis et al., 2012), the dynamics following p53 restoration, a bleeding-edge potential therapeutic approach, remain largely unresearched. This project investigates how early signaling dynamics of p53 influence eventual cell fate, specifically proliferation, arrest, or death, in p53-null SKOV-3 cancer cells post p53 restoration. A more developed understanding of this relationship could help shape the evolution of next-generation therapies for p53-deficient cancers. Utilizing large-scale single-cell time series datasets from the Lahav Lab at Harvard Medical School enabled the application of machine learning methods to extract interpretable features of early p53 dynamics that correlate with cellular outcomes. The two-pronged approach combined manual feature design with automated extraction (through the utilization of tools such as tsfresh) to maximize both biological relevance and model-performance. Classifiers were then trained and evaluated, with particular emphasis on transparent, non-black-box models to reflect biological decision-making pathways. After identifying the most predictive features, they were cross-referenced with known biological mechanisms and developed new hypotheses regarding the relationship between p53 dynamics and cell fate following restoration. Given the novelty of this therapeutic context, and the fact that p53 is among the most studied and fundamental proteins in cancer biology, these findings carry significant potential (Millau et al., 2010). They lay the groundwork for future research into restorative p53 therapies and point toward industrial applications with the possibility of transforming treatment for millions of patients worldwide.