An Investigation of the p53 Ubiquitin-Proteasome System Using a Novel Non-Steady-State Enzyme Kinetic Model

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Overzealous MDM2-mediated ubiquitination of p53 characterizes and sustains over 50% of all human cancers. Targeted cancer therapy hinges on a thorough understanding of the ubiquitination process. Unfortunately, existing mathematical models inaccurately describe the ubiquitin-proteasome system, due to the underlying assumptions of steady-state and constant cellular concentrations of the ubiquitin-conjugating and ubiquitin ligase enzymes. This project derives a novel non-steady-state mathematical model of reversible sequential bi-substrate enzyme kinetics, which can be used to simulate the behavioral response of the p53 ubiquitin-proteasome system to specific variations in the cellular concentrations of targeted p53, MDM2, and ubiquitin-conjugated E2D3. From computer simulations of the derived model it was observed that the ubiquitin-ligase MDM2 accelerates the carcinogenic ubiquitination process, while ubiquitin-conjugated E2D3 inhibits it. In particular, it was shown that E2D3-Ub is a more effective inhibitor of p53 ubiquitination when present at higher concentrations. However, it was also observed that high concentrations of p53 can hinder the ability of E2D3-Ub to decelerate the carcinogenic reaction. The mathematical model was also shown to successfully reproduce the experimentally observed p53-MDM2 interaction. The derived model therefore suggests MDM2 as a prospective target for cancer therapy. In addition, the findings of this project propose recombinant E2D3-Ub as a new promising protein-based anticancer drug for targeting overzealous p53 ubiquitination. Finally, the derived model can also suggest new therapeutic strategies for targeting various neurodegenerative diseases characterized by an overzealous ubiquitin-proteasome system.

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