A Novel Mathematical Model of Targeted Cancer Therapy along p53 Proteasomal Degradation Pathways

Prem Talwai
Department of Mathematics, American River College
ptalwai98@gmail.com

Keywords: targeted cancer therapy, non-steady-state enzyme kinetic model, molecular inhibitor of p53 ubiquitination, protein-based anticancer drug

Overzealous MDM2-mediated ubiquitination of p53 characterizes and sustains over 50% of all human cancers. Successful targeted cancer therapy hinges on a thorough understanding of the ubiquitination process. Unfortunately, current steady-state enzyme kinetic models fail to accurately describe the ubiquitin-proteasome system, due to the assumption that the enzyme (E3 ligase) is expressed at infinitesimally smaller concentrations than the substrates (E2 conjugase and target protein). This limitation of the quasi-steady state assumption prohibits the use of steady-state models when analyzing the cancerous consequences of extreme ubiquitin-ligase overexpression. This paper derives a novel non-steady-state mathematical model of ternary complex enzyme kinetics, which can be used to simulate the behavioral response of the ubiquitin-proteasome system to specific variations in the cellular concentrations of targeted the E2 conjugase, E3 ligase, and target protein. Computer simulations of the model were used to study the effects of E2D3 and MDM2 concentrations on the rates of p53 ubiquitination at different temperatures. At each temperature, it was observed that the ubiquitin-ligase MDM2 accelerates the dangerous degradation process, while the ubiquitin conjugating-enzyme E2D3 inhibits it. It was also discovered that E2D3 is a more effective inhibitor of p53 ubiquitination at higher body temperatures, whereas MDM2 is then a less-effective catalyst. The derived model therefore suggests MDM2 as a prospective target for cancer therapy. In addition, the findings of this project propose recombinant E2D3 as a new promising protein-based anticancer drug and a potential tumor suppressor protein. The mathematical model successfully reproduced the experimentally observed p53-MDM2 interaction. Further *in vivo* experimentation is necessary for additional validation of the computational results. The derived model can suggest new therapeutic solutions for decreasing the harmful effects of many human cancers, bacterial infections, and inflammatory diseases (such as rheumatoid arthritis) characterized by an overzealous ubiquitin-proteasome system.