Modeling Cancer Cell Fate Decisions Under Targeted Therapy

Austin Oleskie\textsuperscript{1}, Halina Halina\textsuperscript{1}, Jie Zhao\textsuperscript{1}, Darren Tyson\textsuperscript{2}, Vito Quaranta\textsuperscript{2} and Erin C. Rericha\textsuperscript{1}

Short Abstract — The growth rate of a cancer cell population depends on the timing and outcome of individual cell decisions such as whether to initiate the cell cycle or whether to undergo cell death. Building on prior work, we develop a synthesis model of tumor cell fate as a function of experimentally measurable inputs including: local drug concentration, cell type, and substrate stiffness. We compare the model predictions to \textit{in vitro} and \textit{in vivo} growth of a non-small cell lung cancer line in the presence and absence of targeted drug therapy.

Keywords — Mathematical models, cancer, drug efficacy

I. PURPOSE

The parameters governing simple macroscopic tumor models, such as growth rate and carrying capacity vary among and within tumors [1]. We consider whether a microscopic model, built from current understanding of the protein interaction networks that govern cell proliferation and cell death, could be used to develop a look up table for macroscopic parameters based on measurable, patient specific values. To keep the initial model simple, we work in the non-small cell lung cancer line, PC9, which proliferates in the presence of EGFR signaling and is commonly treated with the EGFR inhibitor erlotinb.

II. EXPERIMENTS

Building on the work of Tyson \textit{et al} [2] we follow the fate of individual PC9 cells over time as a function of erlotinb concentration and environmental factors. We record the total cell number, the time between cell divisions (intermitotic time, IMT), and the time when apoptotic cells are removed from the population. Previous work found that PC9 cell populations in the absence of therapy have indistinguishable IMT distributions and each population doubles at the same growth (DIP) rate. Erlotinb treatment revealed a prior heterogeneity in the cell line with stable sublines of PC9 growing with a range of DIP rates [-.002hr\textsuperscript{-1},-.0015hr\textsuperscript{-1}] under the same erlotinb concentrations. We find that the untreated cell expression of the receptor tyrosine kinase cMET linearly correlates with DIP rate under erlotinb. In addition, we find that the measured DIP rate for a given subtype decreases as the log of the environment stiffness decreases. These experimental findings map to an inverted pyramid structure of cell decision making where multiple inputs (EGFR, cMET, integrins) feed into a small number of downstream targets. Western blots of PC9 cells under different growth conditions locate the relative phosphorylation of AKT to the funnel neck governing the balance of cell proliferation and cell death under erlotinb therapy.

III. MODELING

Gerard and Goldbeter proposed a mammalian cell cycle model based on the negative feedback loops of the cyclins A-E [3]. In this model the concentration of a single input factor (EGFR) governs the transition of cyclin concentrations from stable to oscillatory, where the period of oscillation is the IMT. We modify the input to the model to be based on AKT phosphorylation and match the output of a stochastic simulation to the measured IMT distributions of PC9 in the absence of therapy. To account for the negative DIP rates under erlotinb, we modify the apoptotic cell death model proposed by Zhang [4] where phosphorylated AKT acts as an inhibitor to BCL2 driven apoptosis. We match a stochastic simulation of the combined model in the absence of AKT phosphorylation to the most negative measured DIP rate. In this combined model, increasing AKT phosphorylation shifts the cell fate bias from apoptosis to proliferation. At intermediate AKT phosphorylation levels, neither state is favored, matching the experimentally observed quiescence states. We test the predictive power of the synthesis model against \textit{in vitro} measurements of IMT and DIP rates with changing combination therapies (both cMET inhibitors and erlotinb) as well as against experiments \textit{in vivo} in the presence and absence of erlotinb therapy.

REFERENCES


\textsuperscript{1}Department of Cancer Biology, Vanderbilt University, Nashville, TN, USA.

\textsuperscript{2}Department of Physics and Astronomy, Vanderbilt University, Nashville, TN 37235. E-mail: erin.rericha@vanderbilt.edu

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\textsuperscript{1}Department of Physics and Astronomy, Vanderbilt University, Nashville, TN 37235. E-mail: erin.rericha@vanderbilt.edu
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