Department of Biomathematics Seminar Series:
Frontiers in Systems and Integrative Biology

Modeling cancer stem cell state transitions and extinction

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ABSTRACT:

Targeted therapy dramatically improves survival in breast cancer patients whose tumor overexpresses HER2. A subpopulation of cells in human breast tumors has been identified with characteristics of cancer stem cells. Microenvironmental signaling guiding epithelial-to-mesenchymal transition (EMT) and the reverse process (MET) is thought to play a role in the plasticity of these breast cancer stem-like cells (BCSCs). BCSCs rely on HER2 signaling for self-renewal, suggesting that HER2-targeted therapy targets BCSCs even when the bulk of the tumor does not overexpress HER2. In order to guide clinical trials examining HER2-targeted therapy in the adjuvant setting, we propose a mathematical model to examine BCSC population dynamics and predict optimal duration of therapy. Varying the susceptibility of BCSCs to HER2-targeted therapy, we quantify the average time to extinction of BCSCs. We expand our model using stochastic simulation to include the partially differentiated tumor cells (TCs) that represent bulk tumor population and examine effects of plasticity on required duration of therapy. Lower susceptibility of BCSCs and increased rates of dedifferentiation entail longer extinction times, indicating a need for prolonged administration of HER2-targeted therapy. We predict that even when therapy does not appreciably reduce tumor size in the advanced cancer setting, it will eventually eradicate the tumor in the adjuvant setting as long as there is at least a modest effect on BCSCs. We anticipate that our results will inform clinical trials of targeted therapies in planning the duration of therapy needed to eradicate BCSCs. Our predictions also address safety, as longer duration of therapy entails a greater potential impact on normal stem cells that may also be susceptible to stem cell-targeted therapies. We expand our model to study the complex regulatory feedback involved in stem cell niche regulation and EMT/MET transitions.

Host: Ph.D.: Elliot Landaw, M.D., Ph.D.

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