REGIONAL CENTRE FOR BIOTECHNOLOGY
Journal Club

Survival and Death Signals Can Predict Tumor Response to Therapy After Oncogene Inactivation.

Phuoc T. Tran et al.(2011) Sci Transl Med 3, 103ra99 .

Avinash Bajaj, PhD

Wednesday, February 20, 2013
4:00 pm
Seminar Room

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Cancers can exhibit marked tumor regression after oncogene inhibition through a phenomenon called “oncogene addiction.” The ability to predict when a tumor will exhibit oncogene addiction would be useful in the development of targeted therapeutics. Oncogene addiction is likely the consequence of many cellular programs. However, we reasoned that many of these inputs may converge on aggregate survival and death signals. To test this, we examined conditional transgenic models of K-rasG12D– or MYC-induced lung tumors and lymphoma combined with quantitative imaging and an in situ analysis of biomarkers of proliferation and apoptotic signaling. We then used computational modeling based on ordinary differential equations (ODEs) to show that oncogene addiction could be modeled as differential changes in survival and death intracellular signals. Our mathematical model could be generalized to different imaging methods (computed tomography and bioluminescence imaging), different oncogenes (K-rasG12D and MYC), and several tumor types (lung and lymphoma). Our ODE model could predict the differential dynamics of several putative prosurvival and prodeath signaling factors [phosphorylated extracellular signal–regulated kinase 1 and 2, Akt1, Stat3/5 (signal transducer and activator of transcription 3/5), and p38] that contribute to the aggregate survival and death signals after oncogene inactivation. Furthermore, we could predict the influence of specific genetic lesions (p53−/−, Stat3-d358L, and myr-Akt1) on tumor regression after oncogene inactivation. Then, using machine learning based on support vector machine, we applied quantitative imaging methods to human patients to predict both their EGFR genotype and their progression-free survival after treatment with the targeted therapeutic erlotinib. Hence, the consequences of oncogene inactivation can be accurately modeled on the basis of a relatively small number of parameters that may predict when targeted therapeutics will elicit oncogene addiction after oncogene inactivation and hence tumor regression.