Network-Based Analysis of Pharmacodynamic Heterogeneity in Multiple Myeloma Cells

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Objectives: The purpose of this study is to develop a Boolean logic-based network representing important intracellular signaling pathways regulating cell growth, proliferation, and apoptosis in multiple myeloma (MM) to explain differences in pharmacodynamic sensitivities of MM cell lines to bortezomib exposure.

Methods: A genetically diverse panel of four MM cell lines were chosen: U266, RPMI8226, MM.1S, and NCI-H929. Concentration-effect (CE) and cell proliferation dynamics (CPD) were obtained by treating cells with bortezomib (0.01–100 nM for CE study; 2, 4, 10, and 20 nM for CPD study) and measuring viable cells using the WST-1 assay. Data from the CE study were modeled using a standard inhibitory Emax function. A network model, built by extensive literature review, was implemented using Odefy (MATLAB® compatible toolbox), and used to simulate dynamic profiles. A model reduction algorithm identified critical system proteins, and the expression time-course of these proteins were measured in control (untreated) and bortezomib (2 and 20 nM) treated MM.1S, RPMI8226, and NCI-H929 cells using the MAGPIX® multiplex platform. Finally, a cellular pharmacodynamic model of bortezomib in RPMI8226 cells was developed.

Results: The CE study identified MM.1S as most sensitive to bortezomib, with estimated IC_{50} values of 2.28, 3.60, 4.71, and 4.75 nM for MM.1S, NCI-H929, RPMI8226, and U266 cells at 24 h. The CPD study also classified cell lines as more sensitive (MM.1S, NCI-H929) and less sensitive (RPMI8226, U266) to bortezomib based on time to complete cell death. The more sensitive cell lines exhibited protein dynamic profiles with relatively greater expression and earlier onset of intracellular signaling activation. The final cellular pharmacodynamic model, driven by RPMI8226 intracellular protein dynamics, adequately described in vitro cell death.

Conclusions: Selected cell lines were significantly different in their responses to bortezomib. The magnitude of relative expression of intracellular proteins was associated with bortezomib sensitivity in these MM cells. The cellular pharmacodynamic model for RPMI8226 will be extended to describe xenograft tumor dynamics using intracellular signaling as a tool to translate across experimental systems.