Identifying Apoptosis Mechanisms in Cancer Cells

Introduction: The snap-action "all or nothing" behavior observed in apoptosis is crtically important to long term health, in that it regulates cell death to avoid "half-dead" or unstable states, thought to predispose to cancer. However, a quantitative understanding of the mechanism underlying this behavior is lacking.

Two somewhat distinct routes have been proposed as a mechanism of Trail-induced apoptosis: Type I (orange) in which caspases are the primary mediators of apoptosis, and Type II (blue) in which a feed-forward route involving the mitochondria is the primary mediator of apoptosis. Experimental evidence suggests that trail-induced apoptosis is an all or nothing phenomenon whereby caspase are either active or inactive in a given cell, and virtually no cells are observed to have only partial caspase activation.

Goal: This study was undertaken to understand the mechanistic basis of this all-or-nothing switch-like behavior of caspase activation, in the hopes of better understanding how to induce apoptosis in the treatment of cancer.

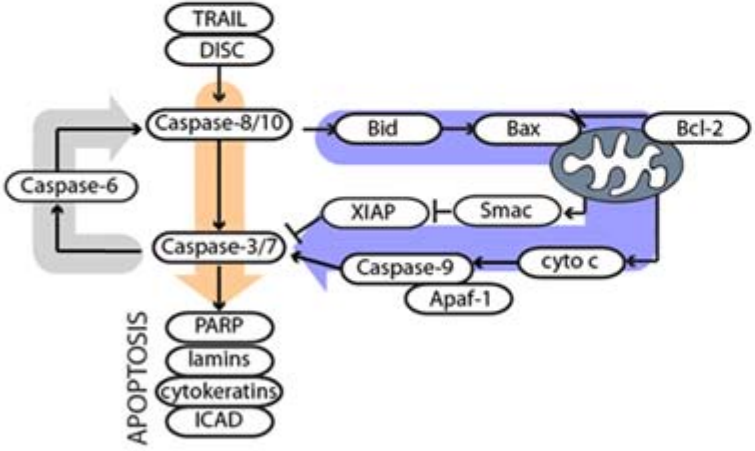

Figure 2. Schematic illustration of the two main apoptotic pathways (caspase & mitochondrial) including all relevant participating proteins.

Model: The two main apoptotic mechanisms are represented in the model as depicted in Figure 2, consisting of ~60 variables, ~70 parameters, and ~30 reactions.

Sensitivity Analysis & Calibration: To determine the minimal set of parameters required for model calibration (fitting the model to experimental data), Global Sensitivity Analysis was performed. Following identification of key model parameters, a series of algorithms were applied to calibrate the model and identify a global optimum including deterministic, stochastic, and/or hybrid approaches.

Results: The trained model accurately reproduces the behavior of normal and perturbed cells exposed to TRAIL, making it possible to study switching mechanisms in detail.

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Kim et al. (2010) BMC Bioinformatics: 11:202.