Live-cell microscopy and kinetic modeling of TRAIL-mediated apoptosis

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I will discuss our attempts to understand why some aspects of receptor-mediated apoptosis in tumor cells are highly variable from one cell to the next whereas others are remarkably constant.
Variability in the timing and probability of death in a clonal cell population, or among recently born sister cells, has its origin in cell-to-cell differences in the concentrations of key regulatory proteins.This in turn, arises from the stochastic nature of gene expression, translation and protein partitioning at mitosis. In contrast, constancy in the time required to die, or in the efficiency of caspase activation, involves a complex and robust regulatory circuit that controls mitochondrial outer membrane permeablization. We observe variability in the responses of cells to virtually all ligands and drugs, and such variability is likely to partly explain the "fractional kill" observed for many chemotherapeutic agents in vivo. Moreover, the existence of long-tailed response distributions is a probable explanation for many phenomena currently ascribed to "tumor stem cells."