A multi-scale model for investigating TRAIL resistance in multi-cellular tumor spheroids

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TRAIL is an anti-cancer drug that induces apoptosis selectively in cancer cells. Unfortunately even high doses of TRAIL do not kill all cells and subsequent TRAIL treatments are transiently less effective. Despite extensive studies, a mechanistic understanding of these phenomena is still lacking. In this talk, I will present an extension of a previously-proposed model describing TRAIL signal transduction in Hela cells (Spencer et al, Nature 2011) with simple models accounting for the turnover of the proteins involved in the pathway at the cell level and the dynamics (growth and death) of the cell population in monolayers and in 3D spheroids. This model is minimalistic in the sense that it uses default values from the literature for all but two parameters. Yet, it explains the existence of survivors (fractional killing), the increased resistance of the surviving population and its transient aspect. The analysis of model predictions calls into question the importance of survival pathways and highlights the critical role of the stochastic turnover of proteins in zymogen-based pathways in which activated forms are rapidly degraded.