

A Mathematical Vision of TNF Receptor Interaction

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ABSTRACT

Tumor necrosis factor (TNF) induces a broad spectrum of cellular responses like differentiation, immune response or programmed cell death (apoptosis) via a highly complex signaling network. For example, TNF induced signal transduction is controlled by two distinct membrane receptors, TNFR1 and TNFR2, and a variety of intracellular signaling molecules. TNF induced apoptosis is largely attributed to TNFR1. The role of TNFR2 in TNF mediated apoptosis remains less well understood, although a positive cooperation has been demonstrated. Using in this work an integrated approach of mathematical modeling in combination with experimental data, we have investigated the mechanisms by which TNFR2 might cooperate with TNFR1 induced apoptosis in HeLa cells.

In the case of the antiapoptotic pathway the intracellular adapter molecule TRAF2 is believed to play a key role in receptor crosstalk. In order to gain a better understanding of the dynamics of TNF signaling and the TNFR1/TNFR2 crosstalk we have developed several mathematical models of the signaling pathways which enabled us to test hypotheses. We find that the apoptotic crosstalk of TNFR1 and TNFR2 does in fact depend on TRAF2 depletion, but must also rely on additional TNFR2 dependent, TRAF2 independent, mechanisms. With the help of mathematical modeling we propose a new regulatory principle of TNF receptor crosstalk based on the adaptor molecule RIP. RIP might play a key role in the TNFR1/TNFR2 crosstalk by regulating the balance between the apoptotic and gene inductive pathway. RIP concentration therefore influences NF- κ B activation and thus NF- κ B induced antiapoptotic gene products. Among these, c-FLIP and XIAP are of special interest, as these are major regulators of caspase activation.

As it has been shown that mitochondria are involved in the apoptotic pathway in HeLa cells [1], we have included this pathway into our model. With the help of computational simulation, we investigate the possible role of the mitochondrial pathway for caspase activation. Our simulation results indicate that the mitochondrial pathway delays caspase activation of up to 30 min although the maximum level is significantly increased.

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