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Heterogeneity in Tumour Necrosis Factor induced Pro- and Anti-Apoptotic Signalling from a Systems Biology Perspective

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Many immune hormones are pleiotropic, i.e. they can induce a broad, even contradictory pattern of cellular responses. This also holds true for the cytokine tumour necrosis factor (TNF), which is able to trigger apoptosis, but can also stimulate cellular growth. The final fate of a given cell after TNF stimulation is highly dependent on the balance between the implicated pathways in combination with the cellular context.

This study analyses the complex interplay of the crosstalk of TNF receptor type 1 (TNF-R1) induced pro- and anti-apoptotic signalling pathways. Both signalling pathways are regulated via feedback loops. For example, the mutual activation of caspases includes a positive feedback loop, while IkBa and NF-kB form a negative feedback loop.

A well defined model of TNF-induced apoptosis is the human cell line KYM-1, on which experimental kinetic data (life cell imaging, western blotting, cytotoxicity and caspase activity assays as well as microinjections) were obtained at various concentrations of TNF.

A useful tool integrating quantitative, dynamical data with the corresponding hypotheses is mathematical modelling, which formalises the biological knowledge and allows for generating model-based predictions.

Based on this thesis' experimental findings, in particular that the cellular response is determined by both the intensity and the duration of the TNF stimulus, a mathematical model of the intracellular signalling pathways of TNF-R1 was derived. This model describes the behaviour of a single cell and consists of a system of ordinary differential equations with 47 components and 106 parameters.

The experimental data reveals a qualitative discrepancy between single cell and cell population responses to TNF. For a specific stimulus, the qualitative response varied between individual cells of the cell population: some cells survive, some die with a time of death from 2 hours post stimulus onward. Hereby, cell death is defined as the time point of 50% cleavage of the Caspase-3 substrate PARP.

The heterogeneity described above led to the expansion of the mathematical model to a cell ensemble model, whose production rates were lognormally distributed within the cell population. The cell ensemble model reproduces experimental findings of different stimulus intensities and measurements at multiple times post stimulus, and allows for a systematic analysis of those parameters within the signal network that are crucial to the cell's destiny, i.e. cell death versus survival.

Cell ensemble modelling of a heterogeneous cell population including a global sensitivity analysis presented here illuminates the role of the different elements and parameters in apoptotic signalling. The receptors serve to transmit the external stimulus, procaspases and their inhibitors control the switching from life to death. A simulated knockout of the NF-kB-mediated anti-apoptotic signalling reveals the importance of this pathway for delaying the time of death, reducing the death rate and significantly increasing cell-to-cell variability. The global sensitivity analysis of the cell population model further reveals that heterogeneity reduces parametric sensitivity.

An important feature of TNF-R1 signalling is the complexity induced by cell heterogeneity. This was uncovered by mathematical modelling at the single cell and cell population level on the basis of quantitative and dynamical dose-response experiments. Since dose dependent dynamic responses and cell heterogeneity are key features of e.g. cancer development or the immune system, the approach presented here could have a wide applicability.