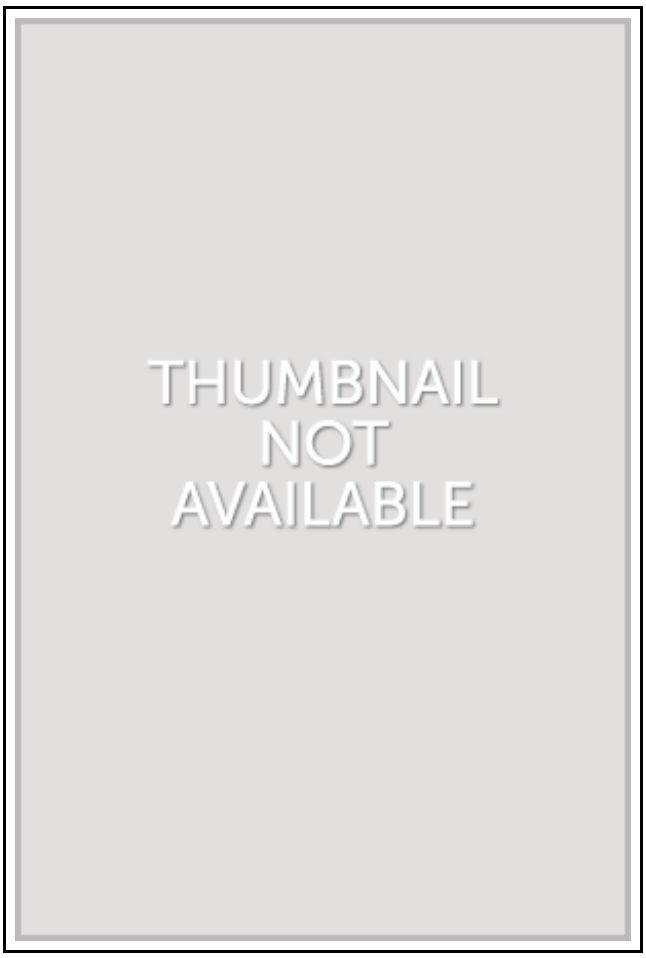
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HETEROGENEITY IN TUMOUR NECROSIS FACTOR INDUCED PRO- AND ANTI-APOPTOTIC SIGNALLING FROM A SYSTEMS BIOLOGY PERSPECTIVE

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Shaker Verlag Mrz 2013, 2013. Buch. Book Condition: Neu. Neuware - 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,...

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