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MATHEMATICAL MODELING REVEALING CROSSTALK MECHANISMS BETWEEN HEAT SHOCK AND NF-κB SIGNALING

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ABSTRACT

Though it is known that elevated temperature, inducing the heat shock (HS) response, modulates cell proliferation, apoptosis and the immune and inflammatory responses, specific mechanisms of such regulation are not fully understood. In [1] we used integrated computational and experimental approaches to analyze several hypothetical crosstalk mechanisms between the HS-response and the NF-κB system, which is involved in regulation of crucial intracellular processes, determining cell fate. Following initial experimental results, showing inhibition of NF-κB p65 response to TNFα treatment, we postulated several mechanisms that might be responsible for this effect at different stages of NF-κB signalling cascade. They included inhibition of the processes of activation of intermediary proteins, nuclear transport, transcription and translation.

Mathematical modeling of single cells indicated that individual crosstalk mechanisms, mentioned above, lead to the same population-level responses of the NF-κB pathway but exhibit different characteristics as far as individual cell responses are concerned. Two hypothetical mechanisms lead to almost total inhibition of NF-κB system response in majority of cells, while a small number of cells exhibited responses at normal level ("all-or-nothing" response). Other hypotheses lead to simulations in which all cells responded in a similar manner, with NF-κB system response attenuated proportionally to the HS duration.

In order to discriminate between these mechanisms, we used live-cell imaging and compared main characteristics of the NF-κB response of single cells (first peak height, time of reaching the first peak, number of cells responding) with simulation results. We concluded that the most likely crosstalk mechanism involves inhibition of activation of the IKK protein. Detailed knowledge of the kinetics of the processes involved should facilitate advances in hyperthermia-based anticancer treatment strategies.

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REFERENCES

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