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MATHEMATICAL MODELING OF INTERACTIONS BETWEEN HSF AND NFkB PATHWAYS

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ABSTRACT

Multimodal oncological strategies which usually combine chemotherapy or radiotherapy with hyperthermia, have been recently the subject of increasing interest, because of their potential of improving the efficacy of the nonsurgical methods of cancer treatment. However a good understanding of the cell regulatory mechanisms is necessary to develop proper therapy protocols.

In this paper we propose a combined model of two pathways, HSF and NF-κB, which are both known to be involved in the cellular response to heat shock and chemo- or radiotherapy. Using heat shock as a therapeutic procedure leads to HSF pathway activation and HSPs production. On the other hand, chemotherapy or radiotherapy induce various cellular responses, including NF-κB activation which can determine cell fate. It is also known that after a heat shock treatment the response of the NF-κB pathway is damped. In this work we present computational analysis of possible interactions between HSF and NF-κB pathways (inhibition of IKK activity through association HSP with the IKK complex).

The results of simulations show that the response of NF-κB pathway can be suppressed for a certain time after a heat shock and the developed model can be used to predicting time range in which NF-κB pathway suppression is observed. We believe that our model may help improve the combined anticancer therapy protocols by giving hints about the time course for the second part of treatment.

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REFERENCES

[1] A. Cataldi, M. Rapino, L. Centurione, N. Sabatini, G. Grifone, F. Garaci, and R. Rana: *activation plays an antiapoptotic role in human leukemic K562 cells exposed to ionizing radiation*, Journal of Cellular Biochemistry **89** (2003), 956–963.

[2] P. Janus, M. Pakula-Cis, M. Kalinowska-Herok, N. Kashchak, K. Szołtysek, W. Pigłowski, W. Widlak, M. Kimmel, and P. Widlak: *NF-kB signaling pathway is inhibied by heat shock independently of active transcription factor HSF1 and increased levels of inducible heat shock proteins*, Genes to Cells **16** (2011), 1168–1175.

[3] Z. Zheng, J.Y. Kim, H. Ma, J.E. Lee, and M.A. Yenari: *Anti-inflammatory effects of the 70 kDa heat shock protein in experimental stroke*, J Cereb Blood Flow Metab **28** (2007), 53–63.

[4] R. Ran, A. Lu, L. Zhang, Y. Tang, H. Zhu, H. Xu, Y. Feng, C. Han, G. Zhou, A.C. Rigby, and F.R. Sharp: *Hsp70 promotes TNF-mediated apoptosis by binding IKKγ and impairing NFkB survival signaling*, Genes Dev **18** (2004), 1466–1481.

[5] S. Dai, L. Jiang, G. Wang, X. Zhou, X. Wei, H. Cheng, Z. Wu, and D. Wei: *HSP70 interacts with TRAF2 and differentially regulates TNFα signaling in human colon cancer cells*, J Cell Mol Med **10** (2010), 710–725.

[6] P.W. Sheppard, X. Sun, M. Khammash, and R.G. Giffard: *Overexpression od Heat Shock Protein 72 Attenuates NF- κB Activation Using a Combination of Regulatory Mechanisms in Microglia*, PLOS Computational Biology **10** (2014), 1–14.

[7] T. Lipniacki, P. Paszek, A.R. Brasier, B. Luxon, and M. Kimmel: *Mathematical model of NFkB regulatory module*, J Theor Biol **228** (2004), 195–215.

[8] Z. Szymańska and M. Zylicz: *modeling of heat shock protein synthesis in response to temperature change*, J Theor Biol **259** (2009), 562–569.

[9] M. Rybinski, Z. Szymanska, S. Lasota, and A. Gambin: *Modelling the efficacy of hyperthermia treatment*, J. R. Soc. Interface **10** (2013), 20130527.

[10] I. Petre, A. Mizera, C.L. Hyder, A. Meinander, A. Mikhailov, R.I. Morimoto, L. Sistonen, J.E. Eriksson, and R. Back: *A simple mass-action model for the eukaryotic heat shock response and its mathematical validation*, Nat. Comp **10** (2011), 595–612.

[11] A. Peper, C.A. Grimbergen, J.A.E. Spaan, J.E.M. Souren, and R. van Wijk: *A mathematical model of the hsp70 regulation In the cell*, Int J Hyperth **14** (1997), 97–124.