SAT-417 - Characterisation of cell-type-specific responses in the liver towards IL-1β by a mathematical model for the p38MAPK/MK2 pathway [Abstract]

A. Kulawik, R. Engesser, C. Ehlting, Andreas Raue, U. Albrecht, S. Wolf, M. Gaestel, U. Klingmüller, D. Häussinger, J. Timmer, J. G. Bode

Angaben zur Veröffentlichung / Publication details:

Kulawik, A., R. Engesser, C. Ehlting, Andreas Raue, U. Albrecht, S. Wolf, M. Gaestel, et al. 2017. "SAT-417 - Characterisation of cell-type-specific responses in the liver towards IL-1β by a mathematical model for the p38MAPK/MK2 pathway [Abstract]." *Journal of Hepatology* 66 (Issue 1, Supplement): S642. https://doi.org/10.1016/s0168-8278(17)31739-7.

Background and Aims: The intercellular communication between hepatocytes and macrophages mediates innate immune responses in the liver upon challenge. In this context the activation of the $p38^{MAPK}$/MK2 signaling pathway by IL-1β is important for the regulation of the acute phase response as well as for regenerative processes. Little is known about key characteristics of this pathway in terms of concentration-dependent signal propagation and cell-type specific responses. In this study a mathematical model has been developed to analyse $p38^{MAPK}$/MK2 mediated signal propagation induced by IL-1β in hepatocytes and in macrophages. Using this system biological approach we investigated the different responsiveness of individual cell types within the liver towards cytokine treatment as for example in case of IL-1β.
Methods: Data from immunoblot analyses of IL-1β treated murine primary hepatocytes and bone marrow derived macrophages were subjected to a system biological analysis.
Results: This study provides evidence that signal transduction from IL-1β via $p38^{MAPK}$ to MK2 is characterized by a strong signal amplification. Quantification of the intracellular phosphorylation level of $p38^{MAPK}$ and MK2 reveals that in hepatocytes at maximum 11.3% of $p38^{MAPK}$ and 36.5% of MK2 molecules are activated by IL-1β. In contrast to this in macrophages at maximum only 4.5% of $p38^{MAPK}$ and 17.2% of MK2 molecules are activated upon treatment with IL-1β. In addition, quantification of $p38^{MAPK}$ and MK2 total protein reveals that the intracellular concentration in macrophages is approximately three times higher than in hepatocytes. We conclude that even with a lower percentage of activated $p38^{MAPK}$ and MK2 macrophages display comparable or even higher phosphorylation levels than hepatocytes. Furthermore, the prediction following an in silico analyses reveals that regarding a half maximal effective concentration (EC50) macrophages need three-times more IL-1β than hepatocytes to achieve nearly similar phosphorylation levels, which was thereafter validated by in vitro experiments.
Conclusions: Using the mathematical model presented in this study we uncover a strong signal amplification of the $p38^{MAPK}$/MK2 pathway to guarantee signal propagation and cellular response. Moreover, the model-based predictions reveal cell-type-specific differences between hepatocytes and macrophages concerning the responsiveness towards the treatment with IL-1β.

SAT-417

Characterisation of cell-type-specific responses in the liver towards IL-1β by a mathematical model for the p38MAPK/MK2 pathway

A. Kulawik[1], R. Engesser[2], C. Ehlting[1], A. Raue[2], U. Albrecht[1], S. Wolf[1], M. Gaestel[3], U. Klingmüller[4], D. Häussinger[1], J. Timmer[5], J.G. Bode[1].
[1]Clinic for Gastroenterology, Hepatology and Infectious Diseases, Heinrich-Heine-University, Düsseldorf; [2]Institute of Physics, Albert-Ludwigs-University, Freiburg; [3]Institute of Physiological Chemistry, Hannover Medical School, Hannover; [4]Division Systems Biology of Signal Transduction, German Cancer Research Center, Heidelberg; [5]Institute of Physics, Albert-Ludwigs-University, Düsseldorf, Germany
E-mail: Christian.Ehlting@uni-duesseldorf.de