Using time-resolved transcriptional profiling to untangle gene regulatory dynamics in response to MAP kinase signaling

Florian Uhlitz[1,2], Bertram Klinger[1,2], Johannes Meisig[1,2] and Nils Blüthgen[1,2]

Aberrant MAP kinase signaling drives various forms of cancers. With help of microarray time course data obtained from a highly controllable cell culture system we quantified gene regulatory dynamics in response to MAP kinase signaling. Model-based inference strategies allowed identification of differently regulated mRNA clusters taking into account their transcriptional kinetics and temporal organization. Based on our model, we were furthermore able to quantitatively predict the transcriptional response profiles to different MAP kinase activity patterns. Thereby, we help to better understand how a single signaling pathway can elicit a large variety of different response kinetics.

***Keywords* — MAP kinase signaling, Transcriptional profiling, Quantitative modeling.**

THE classical MAP kinase signaling pathway controls fundamental cellular processes such as growth and differentiation and is deregulated in at least one-third of all cancers [1]. Whereas the quantitative details and dynamics of signal transduction have been studied extensively the gene regulatory response to MAP kinase signaling and its network organization lacks detailed understanding.

On the basis of microarray time course data obtained from a human cell culture system which short-cuts signaling and limits cross-talk we used mathematical modeling and computational data analysis to investigate how MAP kinase signaling regulates transcription and transcript stability.

Taking temporal organization of primary and secondary response genes into account, we inferred gene regulatory dynamics from the given expression data to develop characteristic transcriptome-wide response profiles to both normal and aberrant MAP kinase signaling. Here, we describe different transcriptional waves and how they relate to each other, complementing and advancing earlier studies on the transcriptional response to normal MAP kinase signaling [2,3,4]. Moreover, we reveal different transcript clusters sensitive or insensitive to subsequent targeted inhibition of MAP kinase signaling in our highly controllable model system.

Our computational model furthermore allows us to quantitatively predict the transcriptional response profiles to different MAP kinase activity patterns. In accordance with the literature [5,6,7], we can account different cellular outcomes to differential pathway activation kinetics. Here, only sustained activation of the system results in transcriptional upregulation of genes associated with cellular differentiation, whereas transient activation leads to cellular proliferation.

To conclude, by illuminating the gene regulatory dynamics in response to both normal and aberrant MAP kinase signaling we help to better understand crucial regulatory layers controlled by this highly relevant signaling network.

Acknowledgements: This work was funded by the German Federal Ministry of Education and Research (BMBF) and the Berlin School of Integrative Oncology (BSIO).

[1]Group of Computational Modelling in Medicine, Institute for Theoretical Biology, Humboldt-University of Berlin, Berlin, Germany.

[2]Laboratory of Molecular Tumour Pathology, Institute of Pathology, Charité - Universitätsmedizin Berlin, Berlin, Germany. E-mail: florian.uhlitz@charite.de

REFERENCES

[1] Dhillon, A. S. et al. (2007). MAP kinase signalling pathways in cancer. *Oncogene*, *26*(22), 3279–3290.

[2] Amit, I. et al. (2007). A module of negative feedback regulators defines growth factor signaling. *Nature Genetics*, *39*(4), 503–512.

[3] Saeki, Y. et al. (2009). Ligand-specific sequential regulation of transcription factors for differentiation of MCF-7 cells. *BMC Genomics*, *10*(1), 545.

[4] Nagashima, T. et al. (2009). Mutation of epidermal growth factor receptor is associated with MIG6 expression. *FEBS Journal*, *276*(18), 5239–5251.

[5] Marshall, C. J. (1995). Specificity of receptor tyrosine kinase signaling: Transient versus sustained extracellular signal-regulated kinase activation. *Cell*, *80*(2), 179–185.

[6] Murphy, L. O., Smith, S., Chen, R.-H., Fingar, D. C., & Blenis, J. (2002). Molecular interpretation of ERK signal duration by immediate early gene products. *Nature Cell Biology*, *4*(8), 556–564.

[7] Sasagawa, S., Ozaki, Y.-I., Fujita, K., & Kuroda, S. (2005). Prediction and validation of the distinct dynamics of transient and sustained ERK activation. *Nature Cell Biology*, *7*(4), 365–373.