Langmann Laboratory and Center of Excellence for Fluorescent Bioanalytics

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The People: From left to right: Marcus Karlstetter (Graduate Student), Claudia Harpaintner (Medical Student), Tobias Schoeberl (Medical Student), Katharina Stoecker (Graduate Student), Karin Weigelt (Ph.D. Student), Yana Walczak (Lab Technician), Thomas Langmann (Principal Investigator), Stefanie Ebert (Ph.D. Student), Christoph Moehle (Research Scientist, CEFB), and Thomas Stempfl (Research Scientist, CEFB). Not pictured: Bernhard H.F. Weber (Director, Institute of Human Genetics).

The Research

Our major research interests are signaling mechanisms that regulate innate immune cell activation in neurodegeneration. We especially focus on gene expression patterns as molecular signatures and transcription factor profiles controlling macrophage and microglia activation in retinal dystrophies. For molecular phenotyping of cellular activation, we use transgenic mouse models, primary cell culture, and macrophage/microglia model systems. Currently, our lab has characterized neurotoxic and neuroprotective microglia subtypes in retinal degeneration. In order to define gene regulatory networks, DNA microarrays, TaqMan low-density arrays, and promoter assays are being applied. We thereby identified the transcription factor PU.1 as a major regulator of gene expression in activated microglia. Our current goals are to identify novel target genes and define the complete PU.1 regulatory network. For genome-wide identification of PU.1 target genes in macrophages, chromatin-immunoprecipitation (ChIP) coupled with DNA microarrays (ChIP-chip) was performed. Our lab is in the process of developing straightforward computational approaches for connecting ChIP-chip data with in silico promoter predictions and pathway/network modeling. Our work is funded through the German Research Foundation and the Pro Retina Foundation.

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The Technique

Despite its power in the discovery of transcription factor target genes, ChIP-chip data analysis, with its steps involving genomic annotation of promoters and correlation with binding sites, is still a laborious process. Seven expert-level bioinformatic steps and individual software solutions are required even for raw data analysis of commercial microarrays. Therefore, while collaborating with Genomatix GmbH, our group sought to develop a single workflow integrating all of the steps of primary ChIP-chip data analysis, identification of enriched genomic regions, correlation with transcription factor binding sites, and gene network analysis. Useful features of the software include significance analysis of microarrays (SAM) with calculation of false-discovery rates, a genomic position–based or annotation-based view of enriched probes, prediction of promoters, and motif analysis with orthologous sequences. We applied the ChipInspector workflow on a replicated dataset from Affymetrix GeneChip Mouse Promoter 1.0R Arrays for genome-wide identification of target promoters for the hematopoietic transcription factor PU.1 in macrophages. More than 1200 in vivo PU.1-bound promoters were identified with a high overlap of in silico predicted sequences. The ChipInspector platform accepts several microarray formats including files from Affymetrix, Illumina, Agilent, and Nimblegen. For that reason, our tool should be very valuable for a wide range of labs performing ChIP-chip experiments.

See "An integrated workflow for analysis of ChIP-chip data" on page 131.