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Molecular hematopoiesis and dendritic cell development

Research interests

My research focuses on understanding the genetic determinants of human hematopoietic stem cell and dendritic cell differentiation and to alter the properties of these cells for medical applications.

Basic models and techniques: We have established cytokine-dependent serum-free differentiation cultures to generate various subsets of granulo-monocytic (GM) and dendritic cells (DC) from CD34⁺ cord blood progenitor/stem cells *in vitro*. Additionally, we have developed inducible retroviral vector-based expression systems for performing genetic perturbation studies in progenitor cells as well as in post-mitotic leukocyte subsets generated *in vitro*. For all projects studies we use advanced multiparameter flow cytometry as well as molecular techniques such as DNA cloning and quantitative real time RT PCR.

Thesis projects

Visit Dr. Strobl's web site for details on current projects and publication list.
<http://www.meduniwien.ac.at/immunologie/strobl/>

We currently study the role of genetic networks in hematopoiesis and DC development. Two future projects will address the roles of transcription factor and miRNA networks in hematopoietic stem cell differentiation and dendritic cells. A brief description of two projects is given below.

Role of miRNAs in the regulation of DC subsets. We recently identified and validated several miRNAs differentially expressed by Langerhans-type DCs and interstitial/monocyte-derived DCs (Jurkin, J, J Immunol, 2010). These DC subsets substantially differ in function. We will ask whether miRNAs are involved in DC subset development or function. Promising

candidates among approximately 30 differentially expressed miRNAs will first be selected based on predicted molecular targets. Subsequently we will modulate their expression in monocyte/interstitial DC and LC lineage differentiation models of CD34⁺ progenitor cells or peripheral blood monocytes using methods well established in our lab. Alterations in DC phenotype and function will be assessed. Subsequently, we will perform molecular studies to identify the underlying mechanism.

Lineage fate decisions of common DC progenitor cells. Using gain and loss of function studies we previously found that the transcriptional regulator RelB promotes monocyte/macrophage and monocyte-derived interstitial DC differentiation from hematopoietic stem cells, whereas LC differentiation or granulopoiesis remained unaffected. Preliminary unpublished data show that RelB inhibition in cooperation with Notch ligand Delta-1 promotes a third DC subset pathway, i.e. plasmacytoid DC (pDC) differentiation from CD34⁺ hematopoietic progenitors. Given the common origination of all three DC sublineages from myeloid/monocytic committed progenitors, we will ask whether RelB is a regulator of DC sublineage fate decisions of such progenitors. First we will isolate and analyze progenitor cells still capable of simultaneous monocyte, LC and pDC differentiation (phenotyping and analysis of transcription factors). A tet-on inducible retroviral system established in our lab will allow to address how RelB alone or in cooperation with additional factors may control the differentiation of these cells. Furthermore, we will build upon our recent finding that RelB controls DC activation (Jörgl, 2007) and will test whether RelB can be targeted for obtaining DCs with enhanced immunostimulatory properties.

Selected publications

Taschner S, Koesters C, Platzer B, Jörgl A, Ellmeier W, Benesch, T, Strobl H. Downregulation of RXRa expression is essential for neutrophil development from granulocyte/monocyte progenitors. *Blood*, 2007 October 3; (Epub ahead of print)

Jörgl, A., B. Platzer, S. Taschner, L. X. Heinz, B. Höcher, P. M. Reisner, F. Göbel, and Strobl H. Human Langerhans cell activation triggered in vitro by conditionally expressed MKK6 is counter regulated by the downstream effector RelB. *Blood* 2007; 1;109(1):185-93, Epub 2006 Sep 7.

Göbel, F, Taschner S, Jurkin J, Vaculik C, Richter S, Kneidinger D, Mühlbacher C, Bieglmayer C, Elbe-Bürger A, Strobl H. Reciprocal role of GATA-1 and vitamin D receptor in human myeloid dendritic cell differentiation. *Blood*. 2009 prepublished online Aug 31. DOI 10.1182/blood-2009-03-210484

Jurkin J, Schichl YM, Köffel R, Bauer T, Richter S, Konradi S, Gesslbauer B, and Strobl H. miR-146a is differentially expressed by myeloid dendritic cell subsets and desensitizes cells to TLR2-dependent activation. *J Immunol.* (2010) April 7, online

