Department of Medicine 3 – Rheumatology and Immunology

Division of Molecular Immunology

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Research focus
- The role of miRNA in B cell maturation and pathogenesis of multiple myeloma
- Nonsense-codon mediated decay of nonfunctional mRNA
- Molecular control of early B cell differentiation
- Molecular control of peripheral B cell and plasma cell differentiation
- Selection of B cells
- Metabolic control of B cells

Structure of the Division

Professorship: 1
Personnel: 17
- Scientists: 6 (thereof funded externally: 3)
- Graduate students: 8

Research

The Division of Molecular Immunology concentrates on the development of mature B cells and their differentiation in effector cells. In addition, we develop human monoclonal antibodies against tumors of the B cell lineage.

The role of miRNA in B cell maturation and pathogenesis of multiple myeloma
PI: Prof. Dr. H.-M. Jäck, Dr. J. Wittmann
One research focus is on the role of microRNA (miRNA) during central and peripheral development of B cells, the antigen-induced differentiation of mature B cells, as well as the pathogenesis of diseases, such as multiple myeloma or Epstein-Barr virus infection. MiRNA are small, 22-nt long, non-coding RNA (ribonucleic acid) that control the expression of specific target genes at the post-transcriptional level. MiRNA bind to the 3'untranslated region of mRNA (messenger RNA) which results either in a block of translation or an acceleration of the degradation of the target mRNA. MiRNA play a significant role in the regulation of cell fate and cell differentiation processes in animals and plants. Dysregulation of miRNA expression was detected in various tumors. Therefore, we are investigating the function of miRNA during development of normal B cells as well as the pathogenesis of multiple myeloma and B cell autoimmune diseases. Currently, we are analyzing miRNA expression profiles in different B cell stages and myeloma as well as lymphoma cells by high-throughput-sequencing of miRNA libraries which will serve as a platform for further functional analysis of specific miRNA involved in the B cell maturation and the generation of multiple myeloma or B cell lymphoma.

Nonsense-codon mediated decay of non-functional mRNA
PI: Prof. Dr. H.-M. Jäck, Dr. J. Wittmann
Another research focus is the molecular control of recognition and decay of non-functional immunoglobulin (Ig)-mRNA, a pathway that is termed nonsense-codon mediated decay (NMD) of nonfunctional mRNA (mRNA surveillance). Nonsense Ig mRNA is encoded from non-productively rearranged Ig genes during B cell development because of a defective VDJ recombination. As faulty mRNA can be translated into potentially toxic proteins, the elucidation of control mechanisms and factors involved in mRNA decay is of interest for B and T cell maturation. The role of NMD in central B cell maturation is analyzed in a mouse line in which a specific NMD factor which was discovered in our laboratory can be conditionally deleted in developing B cell progenitors. In parallel, immunoprecipitation analyses followed by mass spectrometry analyses are carried out to identify novel interaction partners and their role in the degradation of faulty mRNAs and early B cell maturation.

Molecular control of early B cell differentiation
PI: Prof. Dr. H.-M. Jäck, Dr. W. Schuh
One major focus is the analysis of mechanisms that control early B cell development and signaling of the pre-B cell receptor. For example, the interaction of the pre-BCR with structures and ligands in the bone marrow microenvironment and its impact on survival and proliferation of progenitor B cells is studied using different mouse models. Using transcriptome and proteome analyses, we identified various cellular components of the pre-BCR signaling cascade, for example the transcription factor Krüppel-like factor 2 (KLF2) and several small noncoding miRNAs. In future studies, we will analyze further potential target genes of KLF2 and their role in pre-B cell differentiation.

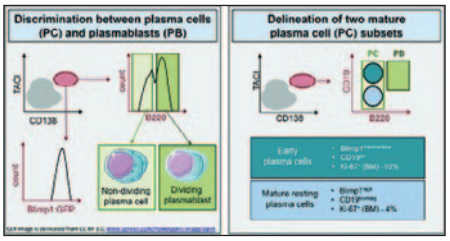
Molecular control of peripheral B cell activation and plasma cell differentiation
PI: Prof. Dr. H.-M. Jäck, Dr. W. Schuh
Immune responses are strictly dependent on proper positioning of effector cells in the body. KLF2, a target gene of the pre-BCR, plays a crucial role in differentiation, activation, and proper positioning of B cells in peripheral compartments. Furthermore, analyses of a B cell-specific KLF2 deletion showed that KLF2 is essential for the migration of plasma cells to their survival niches in the bone marrow. We are currently dissecting the underlying mechanisms by identifying new target genes of KLF2 using comparative transcriptome and single cell sequencing analyses of normal plasma cells and KLF2-deficient plasma cells. In addition, we want to analyze the role of KLF2 in B cell activation and plasma cell homeostasis in gut-associated lymphoid tissues (GALT) and in the context of IgA immune responses.

Selection of B cells
PI: Prof. Dr. Dr. D. Mielenz
The hallmark of every B cell is the B cell receptor (BCR), which specifically recognizes a foreign antigen and thus mediates on the one hand the effective and specific immune response, but at the same time prevents potentially dangerous interactions of B cells with endogenous substances. Newly formed B cells must therefore be selected positively for the presence of BCR. At the same time, a negative selection is required in which self-reactive B cells are sorted out. In addition, the BCR must be able to recognize foreign substances (= antigens) of any structure without the humoral immune system reacting with hypersensitivity reactions, such as IgE-mediated type I allergy. In specialized structures, so-called germinal centers, the B cell memory is generated, which is needed to establish a long-lasting, highly specific immunity. The various demands imposed on the BCR in the course of development and selection therefore require a finely tuned intracellular signal transmission machinery and a flexible adaptation of the metabolism. Many of these elements are not fully characterized yet. The main goal of this project is to understand BCR selection during B cell development and germinal center reaction. Particular attention is paid to the B cell cytoskeleton, metabolism, and intracellular transport structures.

Metabolic control of B cells

PI: Prof. Dr. Dr. D. Mielenz

B cells reprogram their metabolism after BCR activation, but also after activation via TLR4, CD40, and the interleukin-4 receptor in the course of plasma cell differentiation. The reprogramming of the metabolism also plays an important role in particular in the case of the pre-BCR checkpoint. In this project we investigate how the mitochondrial respiratory chain and the mitochondrial Ca2+ concentration influence the pre-BCR control point and plasma cell differentiation. We also work on a mitochondrial, Ca2+ binding protein, Swiprosin-2/EFhd1, which influences the mitochondrial Ca2+ concentration after ROS Induction and Cxcr4 activation in pro-B cells and thereby possibly regulates the mitochondrial respiratory chain. Our results to date suggest that the mitochondrial respiratory chain is essential for the development of B cells in the bone marrow at the pre-BCR checkpoint as well as for the development of plasma cells. The focus is now on the mitochondrial control of transcription factors such as Bach-2 and Blimp-1. Based on this work, in-depth analyses could lead to targeted manipulation of B cell metabolism during plasma cell differentiation and selective depletion of unwanted plasma cells.



Establishment of a four-color fluorescence-based flow cytometry protocol that distinguishes viable dividing plasmablasts from nondividing plasma cells and, based on CD19 surface abundance, identifies two mature plasma cell populations in the spleen and the bone marrow of mice
(according to Pracht K et al., Eur. J. Immunol. 2017)

Teaching

The Division of Molecular Immunology participates in undergraduate and graduate education within the bachelor and master degree programs in biology, life science engineering, and Molecular Medicine.

Students can work on their Bachelor's and Master's theses embedded in the research focus of the Division of Molecular Immunology. Furthermore, the Division of Molecular Immunology engages in educating and training doctoral students from GK 1660 (compare own report) by offering numerous workshops and seminars, like journal clubs or scientific writing and presentation workshops.

Selected publications

Stein M, Dütting S, Mougiakakos D, Bösl M, Fritsch K, Reimer D, Urbanczyk S, Steinmetz T, Schuh W, Bozec A, Winkler TH, Jäck HM, Mielenz D. A defined metabolic state in pre B cells governs B-cell development and is counterbalanced by Swiprosin-2/EFhd1, Cell Death Differ. 2017, 24(7): 1239-1252

Pracht K, Meinzinger J, Daum P, Schulz SR, Reimer D, Hauke M, Roth E, Mielenz D, Berek C, Côrte-Real J, Jäck HM, Schuh W. A new staining protocol for detection of murine antibody-secreting plasma cell subsets by flow cytometry, Eur J Immunol. 2017, 47(8): 1389-1392

Lang SC, Harre U, Purohit P, Dietel K, Kienhöfer D, Hahn J, Baum W, Herrmann M, Schett G, Mielenz D. Neurodegeneration Enhances the Development of Arthritis. J. Immunol. 2017, 198, 2394–2402

Urbanczyk S, Stein M, Schuh W, Jäck HM, Mougiakakos D, Mielenz D. Regulation of energy metabolism during early B lymphocyte development. Int J Mol Sci. 2018 Jul 27;19(8). pii: E2192

Haberland K, Ackermann JA, Ipseiz N, Culemann S, Pracht K, Englbrecht M, Jäck HM, Schett G, Schuh W, Krönke G. Eosinophils are not essential for maintenance of murine plasma cells in the bone marrow, Eur J Immunol. 2018, 48(5): 822-828

Meinzinger J, Jäck HM, Pracht K. miRNA meets plasma cells „How tiny RNAs control antibody responses", Clin Immunol. 2018 Jan;186:3-8

International cooperations

Prof. A. Cunningham, University of Birmingham: UK

Dr. O. Baris, CNRS Angers: France

Dr. E. Greotti, University of Padova: Italy