UNIVERSITY HOSPITAL

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-mediated decay of nonfunctional mRNA
- 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: 18

- Scientists: 4 (thereof funded externally: 1)
- Graduate students: 6

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: H.-M. Jäck, 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- mediated decay of non-functional mRNA
PI: H.-M. Jäck, 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-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 peripheral B cell activation and plasma cell differentiation
PI: H.-M. Jäck, W. Schuh
Immune responses are strictly dependent on proper positioning of immune cells in the body. The transcription factor Krüppel-like factor 2 (KLF2) plays an important role in the differentiation, activation and correct positioning of B cells in the lymphatic organs. Investigations of a mouse model with a B-cell-specific deletion of KLF2 showed that KLF2 is essential for the migration of plasma cells to their survival niches in the bone marrow. The molecular mechanisms of plasma cell migration and plasma cell survival are currently being investigated through the identification and verification of new as well as known target genes of KLF2. For this purpose, comparative transcriptome and single cell sequencing analyses of "normal" plasma cells and KLF2-deficient plasma cells from different tissues are carried out. Furthermore, the function of KLF2 in B-cell activation and plasma cell homeostasis in the gut-associated lymphoid tissues (GALT) and in the context of an IgA immune response will be investigated.

Selection and differentiation of B cells in the germinal center
PI: D. Mielenz
In specialized structures, so-called germinal centers, the B cell memory and plasma cells secreting high affine antibodies are generated. Both are required to establish a long-lasting, highly specific immunity. The germinal center reaction demends a finely tuned intracellular signal transmission machinery and a flexible adaptation of the metabolism because signals from several receptors need to be integrated. Many of these elements are not yet fully characterized. The main goal of this project is to understand BCR selection the germinal center reaction. Particular attention is paid to the B cell cytoskeleton, metabolism, and intracellular transport structures.

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Metabolic control of B cells by mitochondria and autophagy
PI: D. Mielenz
B cells reprogram their metabolism after (pre) BCR activation, but also after activation via TLR4, CD40, and the interleukin-4 receptor in the course of plasma cell differentiation. In this project we investigate how the mitochondrial respiratory chain influences B cell development and plasma cell differentiation. Our results show 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. Mechanistically we show that mitochondrial respiration controls flus of the TCA cycle. This enables synthesis of phosphatidic acid, which drives the mTOR pathway required for plasma cell differentiation. We have furthermore identified a pathway that ensures homeostasis of the endoplasmic reticulum and flux of autophagy in activated B cells. This pathway, mediated by TFG (Trk-fused gene), is essential for plasma cell homeostasis.

Glucose metabolism in plasma cells
PI: H.-H. Jäck, K.Pracht
During the differentiation of mature B cells into antibody-secreting plasma cells their glucose uptake increases constantly. Glucose is an essential factor for the formation and secretion of correctly glycosylated and therefore functional antibodies.

This carbohydrate also seems to be important for the metabolic demands of long-lived plasma cells which are essential players for a longterm immune protection, as they constantly secrete protective antibodies even after the pathogen is cleared. We are using mouse lines with a B cell specific defeciency in glucose uptake to investigate whether nutrients shortage affects the establishment and maintenance of a protective humoral immune response. Furthermore, we are analyzing if differentiating B cells and antibody-secreting cells are able to adjust their metabolic processes in the absence of glucose. Our longterm goal is to understand how the B cell-mediated immune memory is established and maintained, and how altering nutrition or diet can influence these processes.

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, as well as in teaching for medical students.
Students can work on their Bachelor's and Master's theses, as well as medical doctoreal 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 and the IRTG of the transregio 130 (compare own report) by offering numerous workshops and seminars, like journal clubs or scientific writing and presentation workshops.

Selected publications

Cvetkovic, L., Perisic, S., Titze, J., Jack, H.-M., and Schuh, W. (2019). The Impact of Hyperosmolality on Activation and Differentiation of B Lymphoid Cells. Front Immunol 10, 828.

Reimer, D., Meyer-Hermann, M., Rakhymzhan, A., Steinmetz, T., Tripal, P., Thomas, J., Boettcher, M., Mougiakakos, D., Schulz, S.R., Urbanczyk, S., Niesner, R., Mielenz, D. (2020). B Cell Speed and B-FDC Contacts in Germinal Centers Determine Plasma Cell Output via Swiprosin-1/EFhd2. Cell Rep 32, 108030.

Schuh, W., Mielenz, D., and Jack, H.-M. (2020). Unraveling the mysteries of plasma cells. Adv Immunol 146, 57-107.

Steinmetz, T.D., Schlotzer-Schrehardt, U., Hearne, A., Schuh, W., Wittner, J., Schulz, S.R., Winkler, T.H., Jack, H.-M., and Mielenz, D. (2020). TFG is required for autophagy flux and to prevent endoplasmic reticulum stress in CH12 B lymphoma cells. Autophagy, 1-19.

Pracht, K., Meinzinger, J., Schulz, S.R., Daum, P., Corte-Real, J., Hauke, M., Roth, E., Kindermann, D., Mielenz, D., Schuh, W., et al. (2020). miR-148a controls metabolic programming and survival of mature CD19-negative plasma cells in mice. Eur J Immunol.

International cooperations

Prof. Dr. R.E.M. Toes, Leiden University Medical Center, Rheumatology, Leiden, The Netherlands,

Prof. Dr. Adam Cunningham, University of Birmingham, Birmingham, UK,

Prof. Dr. Marco Herold, Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia,

Dr. Rafael Arguello, CNRS, INSERM, and Aix-Marseille University, Marseille, France