Institute of Biochemistry – Emil-Fischer-Center

Chair of Biochemistry and Molecular Medicine

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Research focus
- Molecular mechanisms of development and progression of malignant melanoma
- Molecular mechanisms of development and progression of hepatocellular carcinoma
- Chondrocytic differentiation and pathophysiological processes in cartilage
- Molecular basis of regeneration and fibrosis in liver and skin
- Molecular mechanisms of hepatic metastasis
- Structure and function of synaptic signaling complexes in the central nervous system
- Pathobiology of non-alcoholic fatty liver diseases

Structure of the Chair

Professorships: 3
Personnel: 50
- Scientists: 35 (thereof funded externally: 23)
- Graduate students: 17

Special structural feature
The Institute of Biochemistry comprises the Chair of Biochemistry and Molecular Medicine and the Chair of Biochemistry and Pathobiochemistry, as well as the professorships of Bioinformatics and of Molecular Medicine with focus on Molecular Imaging.

Research

The research groups of the Chair of Biochemistry and Molecular Medicine study basic physiological and pathophysiological principles in oncological settings and the nervous system using approaches from biochemistry, molecular genetics, embryology, cell biology and bioinformatics. Research interests focus among others on the mechanisms of receptor mediated signal transduction and transcriptional regulation in the tumor cells.

Molecular mechanisms of development and progression of malignant melanoma
PI: Prof. Dr. A.K. Bosserhoff, Prof. Dr. C. Hellerbrand, Prof. Dr. S. Kuphal, PD Dr. Dr. P. Dietrich, Prof. Dr. M. Kappelmann-Fenzl
Malignant melanoma, also called black skin cancer, shows a drastic increase in incidence and an unchanged high mortality in recent decades. Melanoma is a clinically relevant tumor, characterized by gradual progression, metastatic dissemination, rapid and pronounced resistance to therapy. For the analysis of melanoma formation, our analysis also deals with melanocytes and their embryonic precursors, the melanoblasts. As metastatic melanoma curative therapy approaches are still lacking, the 10-year survival rate is below 5%. The pathogenesis of the disease is probably due to an accumulation of specific genetic and epigenetic alterations leading to deregulation of transcriptional regulation and signaling pathways in melanocytes or their precursors. The particular malignancy of melanoma is based on a specific combination of cell cycle autonomy, differentiation defects, apoptosis resistance, deregulated interaction with stromal and immune cells as well as distinctive invasiveness and metastatic ability. We are working in this field performing fundamental studies of pathophysiological changes and covering many areas. In addition to proteins in the cell-matrix association, growth factors, metabolites, and signaling pathways, transcriptional regulators and microRNAs are investigated. Next to the analysis of the function of mature microRNA as key posttranscriptional regulatory elements, their processing in melanoma is in the center of our current research.

Molecular mechanisms of development and progression of hepatocellular carcinoma
PI: Prof. Dr. C. Hellerbrand, PD Dr. Dr. P. Dietrich, Prof. Dr. A.K. Bosserhoff
Hepatocellular carcinoma (HCC) is one of the most frequent types of cancer worldwide. Currently, there are only few therapeutic options that have only a minimal impact on the survival of patients. HCC is frequently resistant against pharmacological therapy or most patients rapidly develop resistance, respectively. We are investigating the molecular mechanisms of the development, progression, and therapy resistance of HCC. We discovered important functions of defined microRNAs and their interactions with therapeutically influenced main signaling pathways of cancer cells, such as the RAS-RAF-ERK signaling pathway.
Furthermore, we are analyzing the interaction of cancer cells with their environment (e.g. immune cells, inflammation mediators, connective tissue cells and factors) mediated by neuropeptides. Such neuroimmunological interactions could decisively influence the tumor microenvironment and thus the progression and therapy resistance of malignant diseases.

Chondrocytic differentiation and pathophysiological processes in cartilage and osteoarthritis
PI: Prof. Dr. A.K. Bosserhoff, Dr. U. Rottensteiner- Brandl
Cartilage is a tissue comprising only a single cell type, namely chondrocytes. In the development of the skeleton, cartilage precedes the bony skeleton and is replaced by the latter in the process of enchondral ossification. In the adult organism, cartilage covers the articular surfaces of our bones and is characterized, among other properties, by high pressure elasticity. Damage to the cartilage is so far not curable until today and inevitably results in osteoarthritis. By better understanding the molecular processes in chondrogenic differentiation, inflammation and cartilage degeneration, we are trying to develop new therapeutic options. As part of our research, we are focusing on different molecular pathways. We study transcriptional regulators, such as AP2Epsilon and YB1. A further focus is on the molecule MIA/CD-RAP, which plays an important role in cartilage differentiation and homeostasis.

Molecular basis of regeneration and fibrosis in liver and skin
PI: Prof. C. Hellerbrand, Prof. Dr. A. Bosserhoff, PD Dr. Dr. P. Dietrich
The liver is the central organ of the metabolism. Nutrients get to the liver from the digestive tract via the portal vein for subsequent degradation and/or metabolization. Thus, the liver supplies the body with vital components such as proteins, carbohydrates, and lipids. Another important function of the liver is detoxification. Alcohol abuse, obesity, metabolic disorders (e.g. hemochromatosis), viral infections (hepatitis B and C), or intoxication with chemicals and environmental toxins are common causes of liver damage. Hepatocellular injury can result in liver inflammation (hepatitis). Hepatitis can progress with hepatic fibrosis which can lead to liver cirrhosis. Cirrhosis is causing organ dysfunction and is the most important risk factor for the development of hepatocellular carcinoma (HCC). Thus, hepatic fibrosis is the central step in the progression of chronic liver injury. Pathological fibrosis resembles impaired wound healing in which the strictly regulated repair processes are impaired after cellular injury. Since the components that are involved in wound healing or fibrosis (connective tissue cells, extracellular matrix, growth factors) are very similar, findings from the physiological wound healing can help to better understand the processes of formation and progression of liver fibrosis/cirrhosis. In this area of our research we focus on the analysis of the newly discovered molecule MIA2 and growth factors of the FGF and BMP families. Furthermore, we could characterize BMP6 as an essential regulator of iron metabolism in recent years.

Structure and function of synaptic signaling complexes in the central nervous system
PI: Prof. Dr. R. Enz
The electric excitability of the central nervous system is regulated by a coordinated interplay of

neurotransmitter receptors and ion channels with enzymes and scaffold proteins that assemble into macromolecular signal complexes at synapses. We analyze structure, expression and function of synaptically localized signal complexes that are associated with receptors for endocannabinoids, GABA and glutamate. Malfunction of these receptors can cause neurodegenerative processes and lead to hearing impairment, tinnitus, night blindness, or epilepsy. Thus, synaptic proteins and their interactions represent interesting targets for therapeutic intervention.
We analyze expression of endoncannabinoid, GABA and glutamate receptors in retina and cochlea and identify new binding partners that regulate these receptors. Interacting protein domains are mapped, the 3D-structure of contact surfaces is analyzed and the function of new protein interactions is elucidated in terms of the activity of receptors and receptor associated signal pathways. Recently, we identified and localized endoncannabinoid and glutamate receptors at pre- and post-synaptic structures of hair cells in the cochlea. Furthermore, we identified the „Cannabinoid Receptor Interacting Protein“ CRIP1 as a new binding partner of glutamate receptors. CRIP1a binds a conserved sequence of 5 amino acids in both receptor types, which regulates their amount in the plasma membrane. Our studies describe new molecular mechanisms at synapses of the central nervous system and pave the ground for the development of new therapeutic approaches targeting neurologic disorders.

Molecular mechanisms of hepatic metastasis
PI: Prof. Dr. C. Hellerbrand, Prof. Dr. A.K. Bosserhoff, PD Dr. Dr. P. Dietrich
Metastasis determines morbidity and mortality in most cancer patients. Most frequently, the majority of tumor entities metastasize into the liver. Only in part this can be explained by the blood flow or the anatomical localization of the liver, respectively. So far it is still unknown, which underlying mechanisms of the liver attract the tumor cells. We are analyzing the reasons of this phenomenon in experimental models and human tissue samples from primary tumors and hepatic metastases. We were able to show that defined non-parenchymal liver cells (hepatic stellate cells) interact with tumor cells and thus induce different steps of metastasis. Our current aim is to identify the mediators of this interaction and to analyze whether such factors can be therapeutic targets.

Pathobiology of non-alcoholic fatty liver diseases
PI: Prof. Dr. C. Hellerbrand, PD Dr. Dr. P. Dietrich
Almost all individuals with obesity develop significant lipid accumulation (steatosis) in the liver. Steatosis can progress with inflammation (steatohepatitis) and fibrosis. The pathological picture is very similar to alcoholic liver injury and is called non-alcoholic fatty liver disease (NAFLD). Today, NAFLD is the most common type of liver disease worldwide. We are analyzing in experimental *in vitro* and *in vivo* models the mechanisms driving the progression of NAFLD, trying to inhibit already early steps of the pathobiological cascade. We could identify defined hop constituents as promising therapeutic targets, which can inhibit the uptake of fatty acids into hepatocytes as well as the development of steatohepatitis.
Application of some chemotherapeutic drugs can cause steatohepatitis, too, which can significantly affect morbidity and mortality of cancer patients. We were able to identify the molecular mechanisms by which irinotecan und fluorouracil (5-FU) cause hepatic steatosis and inflammation. Currently, we are investigating strategies to interfere with these pathomechanisms to improve the tolerability of chemotherapeutic drugs.

Teaching

Both chairs of the Institute jointly carry out the curricular education (lectures, seminars, practical courses) in biochemistry and molecular biology for students of Medicine, Dentistry, and Molecular Medicine as well as the biochemical practical courses of students of pharmacy.
Both chairs supervise Bachelor's and Master's theses as well as PhD students.

Selected publications

Dietrich P, Wormser L, Fritz V, Seitz T, De Maria M, Schambony A, Kremer AE, Günther C, Itzel T, Thasler WE, Teufel A, Trebicka J, Hartmann A, Neurath MF, von Hörsten S, Bosserhoff A, Hellerbrand C. Molecular cross-talk between Y5-receptor and neuropeptide Y drives liver cancer. J Clin Invest. 2020; 130(5):2509-2526.

Seitz T, Freese K, Dietrich P, Thasler WE, Bosserhoff A, Hellerbrand C. Fibroblast Growth Factor 9 is expressed by activated hepatic stellate cells and promotes progression of hepatocellular carcinoma. Sci Rep. 2020; 10(1):4546.

Klotz L, Wendler O, Frischknecht R, Shigemoto R, Schulze H, Enz R. Localization of group II and III metabotropic glutamate receptors at pre- and postsynaptic sites of inner hair cell ribbon synapses. FASEB J. 2019; 33(12):13734-13746.

Liebig JK, Kuphal S, Bosserhoff AK. HuRdling Senescence: HuR Breaks BRAF-Induced Senescence in Melanocytes and Supports Melanoma Growth. Cancers (Basel). 2020; 12(5):1299.

Kappelmann-Fenzl M, Kuphal S, Krupar R, Schadendorf D, Umansky V, Vardimon L, Hellerbrand C, Bosserhoff AK. Complex Formation with Monomeric α-Tubulin and Importin 13 Fosters c-Jun Protein Stability and Is Required for c-Jun's Nuclear Translocation and Activity. Cancers (Basel). 2019; 11(11):1806

Kappelmann-Fenzl M, Gebhard C, Matthies AO, Kuphal S, Rehli M, Bosserhoff AK. C-Jun drives melanoma progression in PTEN wild type melanoma cells. Cell Death Dis. 2019; 10(8):584.

International cooperations
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