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
- Physiological and pathological functions of alpha synuclein
- 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: 52
- Scientists: 34 (thereof funded externally: 26)
- 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, PD Dr. S. Kuphal, Dr. Dr. P. Dietrich, 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, 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

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. By better understanding the molecular processes in the chondrogenic differentiation, 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, 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.

Physiological and pathological functions of alpha synuclein

PI: PD Dr. W. Xiang

Parkinson disease (PD) is one of the most common neurodegenerative diseases. Abnormal aggregation of the protein alpha synuclein (αSyn) plays a crucial role in the pathogenesis of PD. We are interested in mechanisms underlying the unusual aggregation of αSyn and the detrimental effects of aggregated αSyn on neurons. Our data show that oxidative stress promotes αSyn aggregation though posttranslational modifications. Oxidative stress-induced αSyn alterations in turn lead to neuronal loss. In addition to its intracellular effects, extracellular aggregated αSyn can be preferentially incorporated by neighboring cells. Internalized exogenous αSyn triggers the aggregation of endogenous αSyn and evokes further damage, e.g. disturbances in protein degradation pathways, to recipient cells. Deleterious effects of aggregated αSyn can be induced by the loss of its physiological structure and function. To understand physiological structure and function of αSyn, we are currently characterizing changes in structure and subcellular localization of αSyn during the differentiation of neurons.

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. Malfunction may cause diseases, including epilepsy and autism. Thus, synaptic proteins represent interesting targets for therapeutic intervention. To investigate molecular mechanisms of synaptic signal transduction, we analyze structure, expression, and function of synaptically localized macromolecular signal complexes that are associated with receptors for endocannabinoids, GABA and glutamate. We compare the expression of interacting proteins in retina and cochlea, map binding regions, and analyze their 3D-structure. With Simiate we discovered a new synaptic protein regulated by FRMP (fragile X mental retardation protein) that functions as a molecular link between nuclear gene expression and dendritogenesis.

Molecular mechanisms of hepatic metastasis

PI: Prof. Dr. C. Hellerbrand, Prof. Dr. A.K. Bosserhoff, 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, Dr. A. Mahli, 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

Bosserhoff AK, Schneider N, Ellmann L, Heinzerling L, Kuphal S. The neurotrophin Neuritin1 (cpg15) is involved in melanoma migration, attachment independent growth, and vascular mimicry. Oncotarget. 2017;8(1):1117-1131

Mascia F, Klotz L, Lerch J, Ahmed MA, Zahng Y, Enz R. CRIP1a inhibits endocytosis of G-protein coupled receptors activated by endocannabinoids and glutamate by a common molecular mechanism. J Neurochem. 2017; 141:577-591

Dietrich P, Koch A, Fritz V, Hartmann A, Bosserhoff AK, Hellerbrand C. Wild type Kirsten rat sarcoma is a novel microRNA-622-regulated therapeutic target for hepatocellular carcinoma and contributes to sorafenib resistance. Gut. 2018;67(7):1328-1341

Mahli A, Koch A, Fresse K, Schiergens T, Thasler WE, Schönberger C, Bergheim I, Bosserhoff A, Hellerbrand C. Isoalpha acids from hops (Humulus lupulus) inhibit hepatic steatosis, inflammation, and fibrosis. Lab Invest. 2018;98(12):1614-1626

Mahli A, Saugspier M, Koch A, Sommer J, Dietrich P, Lee S, Thasler R, Schulze-Luehrmann J, Luehrmann A, Thasler WE, Müller M, Bosserhoff A, Hellerbrand C. ERK activation and autophagy impairment are central mediators of irinotecan-induced steatohepatitis. Gut. 2018; 67(4):746-756

Linck L, Liebig J, Völler D, Eichner N, Lehmann G, Meister G, Bosserhoff A. MicroRNA-sequencing data analyzing melanoma development and progression. Exp Mol Pathol. 2018 Dec;105(3):371-379

International cooperations

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