

Blood-brain barrier center: from blood-brain barrier damage to the pathogenesis of neurovascular and cardiovascular disease

Our Mission:

The mission of Förster research group (BBB Center) is to seek fundamental knowledge about the role of neurovascular changes in brain and cardiovascular disorders and to use that knowledge to reduce the burden of cardiovascular disease.

I. BACKGROUND:

Neurological disorders represent one of the greatest threats to public health, with increasing global public health importance of common neurological disorders such as dementia, autoimmune disease (Multiple Sklerosis), Parkinson s disease, stroke and traumatic brain injuries, neurological disorders associated with malnutrition, but also epilepsy, headache disorders, neuroinfections, pain associated with neurological disorders. So that a clear message emerges that unless immediate action is taken globally, the neurological burden is likely to become an increasingly serious and unmanageable problem in all countries.

The blood-brain barrier (BBB)

The blood–brain barrier (BBB) acts as a strict control point for the regulation and differentiation of the central nervous system (CNS) to control its energy supply and permeability. It is formed by the cerebral microvascular endothelium, which, through its tight junctions (TJ) works to control the paracellular transport of hydrophilic and charged substances .

The research focus of the BBB Center is laid on the cell biology and molecular medicine of the BBB and concentrates on cellular and molecular mechanisms of neurodegeneration following inflammation, brain injury (traumatic brain injury, stroke), but also on the role of the BBB in development of brain cancer and metabolic disorders. Through the combined approaches of “BBB integrity-” and “inflammation-”research we characterize the early phase of disease initiation in order to identify the intervention points that occur during the development of clinical symptoms.

II. RESEARCH AREAS:

The major lines of research the BBB Center persue the role of cerebrovascular (BBB) changes in the etiology and pathology of

1. Neuroinflammation
2. Ischemic brain damage
3. Brain cancer
4. Aging-associated neurological and cardiovascular disease, dementias of aging
5. cardiovascular diseases that involve the heart
6. In silico analyses and mathematical modelling of blood-brain barrier pathology and cardiovascular system

We build accurate *in silico* replicates of the investigated biological system and pathologies with the the ultimate goal to have a detailed understanding of the function of molecular networks as they appear in, for example, ischemia, brain cancer or metabolism, gene regulation, or signal transduction. This is best achieved by using a level of mathematical abstraction that

needs a minimum of biological information to capture all physiologically relevant features of a cellular network.

III. ONGOING RESEARCH PROJECTS:

1. Neuroinflammation – key driver in the early phase of disease initiation

Inflammatory reaction in CNS is recognized to be a feature of all neurological disorders. In neurological degenerative diseases, such as Parkinson's disease (PD) and Alzheimer's disease (AD), there is prominent infiltration of various leukocyte subsets into the CNS or there is intense activation of microglia with resultant elevation of many inflammatory mediators within the CNS. In acute critical CNS diseases, such as ischemic stroke, spontaneous intracerebral hemorrhage (ICH), and traumatic brain injury (TBI), recent evidences show that inflammation may be a potential target for therapy. To the role of inflammation in brain cancer, it has been described that within the tumor microenvironment, infiltrating immune cells increase oxidative DNA damage, likely promoting both genetic and epigenetic changes that occur during glioma evolution. One major field of interest includes gene regulation by noncoding RNA (microRNA) in pathogenesis of neuroinflammation.

1.1 Molecular mechanism of glucocorticoid action at the BBB

1.2 Neurodegenerative disease during development - role of glucocorticoids

1.3 Development - Vasoprotective effects of selected human milk component on the Blood Brain Barrier (BBB)

1.4 Malnutrition as a mechanisms towards neuroinflammation - role of altered BBB glucose transport

1.5 microRNA control of gene expression noise at the BBB

Responsible: Prof. Dr. Carola Förster, PD Dr. Malgorzata Burek

2. Ischemic brain injury (stroke, brain trauma)

Injury to the brain (stroke, brain trauma) is succeeded by a multitude of delayed secondary processes on cellular and molecular level, which contribute to neuronal cell loss and ultimately lead to a secondary expansion of the primary lesion into surrounding healthy tissue (secondary brain damage). Brain edema formation is considered to be one of the most deleterious sequelae of ischemic brain injury leading to increased intracranial pressure (ICP) and brain herniation. Alterations in BBB integrity can profoundly affect edema formation, as recently described by our groups in the tMCAO-model of stroke and traumatic brain injury. In this division, we design studies to elucidate how brain ischemic brain injury alters the integrity of the BBB, to determine the role of the BBB in the process of edema formation and neurologic outcome, and to test therapeutic effect antiedematous drugs.

2.1 Investigation of the causal contribution of selective blood-brain barrier glucose transport processes to brain edema formation

2.2 Role of cerebral L-arginine BBB uptake and cellular distribution for vascular tone regulation, microthrombosis and BBB integrity after ischemic and traumatic brain injury

Responsible: Prof. Dr. Carola Förster, PD Dr. Malgorzata Burek

3. Guarding the brain – innovative strategies to prevent brain metastases

Brain metastases (BM) are the most common type of intracranial neoplasms occurring in 25% of patients with advanced cancer. 100,000-170,000 new cases of BM are diagnosed yearly in

the USA, increasing morbidity and mortality of cancer patients, of which up to 40% have BM at autopsy. Multiple BM are found in more than 50% of cases and are associated with poor outcome. Surgical resection followed by radiotherapy offers the best survival benefit, but is only applicable in a minority of patients with a single and accessible lesion. Therefore, innovative treatment modalities should aim at an effective prevention of metastatic spread into the brain. The majority of BM originate from malignant melanoma (10%), breast- (15-25%) and lung-cancer (40%) . To reach the brain parenchyma, metastatic cells have to transmigrate through the endothelial cell layer of brain capillaries forming the BBB.

3.1 Development of estrogen receptor beta-selective therapies for the prevention and treatment of brain metastasis of breast cancer

Responsible: Prof. Dr. Carola Förster, N.N.

4. Aging-associated neurological and cardiovascular disease, dementias of aging

Aging can be defined as a progressive loss of cellular functions and increasing mortality of cells over time. In the course of life, the loss of cellular rescue functions and cellular stress response in cellular senescence is linked to the emergence of aging-associated diseases such as degeneration and cancer. AG Förster's goal is to elucidate the fundamental biochemical, genetic and physiological mechanisms underlying the aging process and age-related changes in the cerebrovascular system in humans and in animal models of human aging:

4.1 Development of in vitro-models of the aging BBB, investigation of senescence markers

4.2 Effects of cellular senescence of brain endothelial cells on neurovascular integrity using established mouse-models of accelerated and delayed aging

4.3 Role of anomalies in the transport of A β at the BBB in the development of Alzheimer's disease

Responsible: Prof. Dr. Carola Förster

5. Cerebrovascular diseases that involve the heart

The recognition that certain inflammatory stimuli, such as infection – or maybe emotional stress? - transiently increase the risk of stroke above and beyond the underlying level of risk due to conventional chronic risk factors may have important implications for the prophylaxis of stroke. Increasing evidence implicates inflammation as a causative factor in the development and/or progression of this disease.

Responsible: Prof. Dr. Carola Förster, PD Dr. Malgorzata Burek, Dr. Sergey Shityakov

5.1 stress-induced cardiomyopathy (broken-heart-syndrome, Takotsubo syndrome) with stroke as comorbidity – role of systemic catecholamines and inflammatory mediators

5.2 Mathematical modelling - finite-element method to investigate the impaired electrical activity in cardiac tissue in patients with Takotsubo syndrome

6. *In silico* analyses and mathematical modelling - Computational simulation and modeling of blood-brain barrier pathology

In silico methods and models in the pathology of the blood-brain barrier (BBB) or also called BBB "computational pathology" used in our lab ("Virtual Screen lab"), are based on using ma-

thematical approaches together with complex, high-dimensional experimental data to evaluate and predict disease-related impacts on the CNS. These computational methods and tools have been designed to deal with BBB-linked neuropathology at the molecular, cellular, tissue, and organ levels. The molecular and cellular levels mainly include molecular docking and molecular dynamics simulations (atomistic and coarse-grain) of mutated or misfolded tight junction proteins, receptors, and various BBB transporters. The tissue and organ levels encompass the mechanistic and pharmacokinetic models as well as finite-element method and pathway analyses enriched with multiple sources of raw data (e.g., in vitro and in vivo, histopathological records, “-omics”, and imaging data). Overall, this review discusses comprehensive computational techniques and strategies at different levels of complexity, providing new insights and future directions for diagnosis, treatment improvement, and a deeper understanding of BBB-related neuropathological events.

Responsible: Prof. Dr. Carola Förster, Dr. Sergey Shiyakov

Other research areas concern the development and characterization of cell culture models and in vitro disease models of other biological barriers:

- lung alveolar epithelium
- kidney proximal tubulus
- secretory epithelium of the