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Wolfgang Baumgärtner

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| 1979 – 1981 | Doctoral fellow at The Ohio State University, Columbus, USA |
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Current Research

The main focus of our research is aimed to further elucidate the pathogenesis of neurotropic viral infections in the CNS using canine distemper (CD) virus, Theiler’s murine encephalomyelitis (TME) virus and Borna disease (BD) virus. Special emphasis is given to virus persistence, induction and progression of demyelination and virus-induced autoimmunity in the central nervous system

(CNS). All three viruses represent valuable animal models to further investigate the cellular and molecular pathogenesis of human debilitating CNS diseases including multiple sclerosis (MS) and psychiatric disorders. Currently, *in vivo* and *in vitro* investigations upon the complex interactions between matrix-metalloproteinases (MMPs), their tissue inhibitors (TIMPs), cytokines, and transcription factors using mRNA and protein gene expression studies represent the center of our research activities.

1. Pathogenesis of demyelination in canine distemper virus encephalitis

Canine distemper virus, a member of the Morbilliviruses, closely related to the measles virus, causes a systemic disease in carnivores. CNS involvement is a common finding and neurological signs in CD can be observed during the acute phase or as a late sequel of infection. Distemper leukoencephalitis (DL) is the main finding in the CNS and white matter lesions resemble morphologically human demyelinating diseases including MS. Though the mechanism of demyelination in nervous distemper is still undetermined, recent investigations revealed a biphasic disease process. Initiation of demyelination is ascribed to a direct action of the virus associated with prominent intralésional expression of viral proteins and mRNA accompanied by few infiltrating CD8+ lymphocytes, less CD4+ cells and moderate lesional up-regulation of MHC II. In this phase, TNF- α , CD44, a hyaluronate receptor, and MMPs as well as their inhibitors TIMPs are up-regulated. Similarly, there is increased gene expression of pro-inflammatory cytokines such as IL-6, IL-8, IL-12, and TNF- α . In contrast IL-1 β , IL-2, and interferon- γ are not detectable. The anti-inflammatory cytokines IL-10 and transforming growth factor- β remain unchanged indicating a possible derailment of the immune response as a possible triggering mechanism for early myelin loss. Plaque progression seems to be an immunopathological process associated with reduction or absence of viral protein and mRNA expression. In the chronic phase, dominated by a strong MHC II up-regulation, CD8+ lymphocytes are prominent within lesions, whereas CD4+ lymphocytes and B cells are found perivascularly. CD44, TIMPs, and some MMPs are strongly diminished. Summarized, to further understand and elucidate the complex plaque genesis in distemper demyelinating leukoencephalitis and associated axonal changes the interactions and expressions of cytokines, MMPs and TIMPs and immediate early genes are currently investigated in detail.

2. Pathogenesis of Theiler’s murine encephalomyelitis

Theiler’s murine encephalomyelitis caused by a cardiovirus of the Picornaviridae family represents an other important experimental model for human demyelinating diseases like MS. Following intracerebral infection of susceptible mice, a polioencephalitis with replication of the virus in neurons or a biphasic demyelinating encephalomyelitis develops depending on the virus, mouse strain, age and sex of the animal. TMEV strains are classified into two major groups. GDVII and FA strains cause a fatal polioencephalitis, whereas DA, WW, BeAn, To, and Yale strains are small plaque forming variants, whose cell

tropism is extended to glial cells and macrophages. Hence, they induce a demyelinating encephalitis and myelitis, and are able to persist in the CNS. As our aim is to study the role of the extracellular matrix in the development of demyelinating lesions after TMEV infection we currently investigate in the CNS tissue of susceptible mouse strains the role of extracellular degrading MMPs, their inhibitors TIMPs and the expression of immediate early genes.

3. Pathogenesis of Borna disease virus encephalitis

Borna disease (BD) is a characteristic neurobehavioral disorder first reported in horses and sheep over 200 years ago. The infectious agent, Borna disease virus (BDV) is the prototype of the new family Bornaviridae within the order Mononegavirales. Whether BDV can infect humans and cause psychiatric disease has been discussed controversially and the debate is still ongoing. Experimental BDV-infection causes a persistent infection of the CNS characterized by a nonpurulent meningoencephalitis. The neurological signs are caused not by the virus itself. They are based upon a T-cell-mediated immunopathological reaction. Mice and Lewis rats serve as reliable animal models for the study of the virus-induced immunopathogenesis. The onset of clinical signs correlates with the occurrence of mononuclear inflammatory lesions in the brain. In rats, the major infiltrating cell type consists of T-cells and macrophages and at later stages of the disease, an increase of B cells is also noted. Beside CD4+ and CD8+ T-cells, cytokines such as TNF α , IL-1, IL-6, IL-2 and IFN- γ , chemokines and other inflammatory mediators play an important role in the virus-induced delayed-type hypersensitivity reaction. TNF α is a main component in this immune response. Its role/impact on the immunopathogenesis of experimental BD is currently investigated by the experimental infection of TNF-transgenic mice with the neurotropic BDV. Furthermore, the effect of neuronal over-expression of TNF on virally induced immunopathological reactions in the CNS will be studied in detail. In addition to the typical neurobehavioral disorder, infection with certain strains of BDV leads to the development of an obesity syndrome without significant neurological signs. The analysis of the pathogenesis of this virally-induced neuroimmune-endocrine disorder is another topic in the BDV research program.

Projects and Goals

The role of MMPs and TIMPs and their interactions with cytokines as well as their regulation by transcription factors such as immediate early genes will be further investigated *in vivo* and *in vitro*. Using knock-out and transgenic mice or specific inhibitors of the expression of the selected candidate mediators during early and chronic immune-mediated phases will be investigated *in vivo* and *in vitro*. The aims are twofold (i) to provide a better understanding of the underlying pathogenetic mechanisms in myelin loss, axonal damage and development of autoimmunity in the CNS, and (ii) to outline new therapeutic approaches and strategies to combat nervous disorders in humans.

Selected Publications

- [1] Herden C., Herzog S., Nessler A., Christ M., Failing K., Richt J.A. und K. Frese (2000). Distribution of Borna disease virus antigen in the brain of rats infected with an obesity-inducing virus strain. **Brain Pathol.** 10: 39 – 48
- [2] Gröne A., Alldinger S. und W. Baumgärtner (2000). Interleukin-1 β , -6, -12 and tumor necrosis factor- α expression in brains of dogs with canine distemper virus infection. **J Neuroimmunol.** 110: 20 – 30
- [3] Markus S., Failing, K. und W. Baumgärtner (2002). Increased expression of pro-inflammatory cytokines and lack of up-regulation of anti-inflammatory cytokines in early distemper CNS lesions. **J Neuroimmunol.** 125: 30 – 41
- [4] Oglesbee, M.J., Alldinger, S., Vasconcelos, D., Diehl, K., Shinko, P., Baumgärtner, W., Tallman, R. und M. Podell (2002). Intrinsic thermal resistance of the canine brain. **Neuroscience** 113: 55 – 64
- [5] Qin, M., Baumgärtner, W., Failing, K. und S. Alldinger (2003). Phase-dependent expression of matrix metalloproteinases and their inhibitors in demyelinating canine distemper encephalomyelitis. **Acta Neuropathol.** 106: 486 – 494

Group Structure

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