6. Abstract

Glaucoma, an irreversible degeneration of retinal ganglion cells and optic nerve fibers, is a worldwide problem. The current treatments are not really effective to stop the degeneration in the moment. Therefore, further analyses have to be performed to get new information about the causes of this disease.

In the present work, cellular alterations were investigated in two established animal models of retinal degeneration. The experimental autoimmune glaucoma model (EAG) is based on the systemic immunization with optic nerve homogenate (ONA) or the protein S100. In contrast, the N-Methyl-D-Aspartat-model (NMDA) uses the excitatory effect of intraocular injected NMDA. In both models, the degeneration process and the function of the glia cells, which could be protective or destructive, revealed unknown.

For glaucoma patients it was postulated that the known axon damage is based on a so-called Wallerian degeneration. At first, the axons are affected, later on also the myelin fibers and the cell bodies. In this present work, we showed that the degeneration mechanisms developed differently. The Wallerian degeneration took place only in the S100 group. The ONA or NMDA injection induced a retinal degeneration followed by a damage of the optic nerve structures. The direct injection of NMDA induced a very fast response, while ONA led to damage through immunological mechanisms. The NMDA-model exhibited signs of a late Wallerian degeneration of the optic nerves in the present work, which is also described in the literature. A similar mechanism was assumed for the ONA-group, due to the loss of the retinal cell bodies, which could induce axonal damage at a later point in time. Although, the structural degeneration differs between the models, similar apoptosis mechanisms were detected. For example, the cytokine FasL was involved in the optic nerve degeneration process in the S100- and NMDA-group. FasL is also linked to the glia response, because microglia produced FasL. Possibly, the microglia were active before the degeneration took place. The question arises, if the glial response is only an epiphenomenon? In both models, early microglia activation could be detected, which is a typical sign for the initial state of
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neurodegenerative models. For the first time, we observed that microglia immigrate into the retina before the cell degeneration takes place in the EAG-model. Furthermore, the microglia activity was limited to early periods of this model. These are hints for a possible participation of microglia to the cell death mechanisms. Otherwise, the long lasting activation of microglia in the NMDA-model could only be an epiphenomenon with an additionally reinforced degenerative effect on the neurons. Yet, the microglia are not the only cell type, which response is based on the noted structural changes, the macroglia also play a role in this mechanism. It was verified that the macroglia activation was rather a consequence of existing apoptosis mechanisms, which correspond with the epiphenomenon theory. The cause of this reaction, protective or destructive, is still unknown. Due to the early response in the optic nerve, the macroglia reaction could be protective, since the response stagnated during the degeneration progression. Yet, the macrogliosis in the NMDA-model and in the ONA-retinae took place in apoptotic and degenerated structures at later points in time. Therefore, the macrogliosis was considered as a secondary mechanism, which pushed the damage.

For the first time, lymphocytes were investigated in the EAG-model, because these immune cells play an important role in several neurodegenerative diseases. The T-cell response seemed to be only, if at all, a secondary effect on the already existing damage and not an initiating mechanism. The similar result applies to the B-cells. Possibly, the B-cells were not directly involved in the retina, but induced their effect through antibodies, which were detected in the EAG-model later on.

In conclusion, the glial response, especially of the microglia, is the connecting element between both animal models and the possible cause of degeneration in the EAG model. The inhibition of an early microglia activity could be a potential therapy approach for glaucoma.