Ependyma: a new target for autoantibodies in neuromyelitis optica?

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Neuromyelitis optica (NMO) is an autoimmune demyelinating disease of the central nervous system characterized by the presence of autoantibodies (called NMO-IgG) targeting aquaporin-4. Aquaporin-4 is expressed at the perivascular foot processes of astrocytes, in the glia limitans, but also at the ependyma. Most studies have focused on studying the pathogenicity of NMO-IgG on astrocytes, and NMO is now considered an astrocytopathy. However, periependymal lesions are observed in NMO suggesting that ependymal cells could also be targeted by NMO-IgG. Ependymal cells regulate CSF-parenchyma molecular exchanges and CSF flow, and are a niche for sub-ventricular neural stem cells. Our aim was to examine the effect of antibodies from NMO patients on ependymal cells. We exposed two models, i.e. primary cultures of rat ependymal cells and explant cultures of rat lateral ventricular wall whole mounts, to purified IgG of NMO patients (NMO-IgG) for 24 hours. We then evaluated the treatment effect using immunolabelling, functional assays, ependymal flow analysis and bulk RNA sequencing. For each experiment, the effects were compared with those of purified IgG from a healthy donors and non-treated cells. We found that: (i) NMO-IgG induced aquaporin-4 agglomeration at the surface of ependymal cells and induced cell enlargement in comparison to controls. In parallel, it induced an increase in gap junction connexin-43 plaque size; (ii) NMO-IgG altered the orientation of ciliary basal bodies and functionally impaired cilia motility; (iii) NMO-IgG activated the proliferation of sub-ventricular neural stem cells; (iv) treatment with NMO-IgG up-regulated the expression of pro-inflammatory cytokines and chemokines in the transcriptomic analysis. Our study showed that NMO-IgG can trigger an early and specific reactive phenotype in ependymal cells, with functional alterations of intercellular communication and cilia, activation of sub-ventricular stem cell proliferation and the secretion of pro-inflammatory cytokines. These findings suggest a key role for ependymal cells in the early phase of NMO lesion formation.

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Received March 01, 2022. Revised August 26, 2022. Accepted November 28, 2022. Advance access publication November 30, 2022
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Conclusion

Using original in vitro and ex vivo models, merging proteomic, transcriptomic and functional evaluation, we showed that ependymal cells in contact with autoantibodies from NMO patients become reactive and display rapid morphological and functional changes that could enhance and facilitate tissue injury. This study provides a new perspective on NMO that should be considered not only as an astrocytopathy but also as an ependymocytopathy and opens the path for targeted modulation therapy on ependyma.