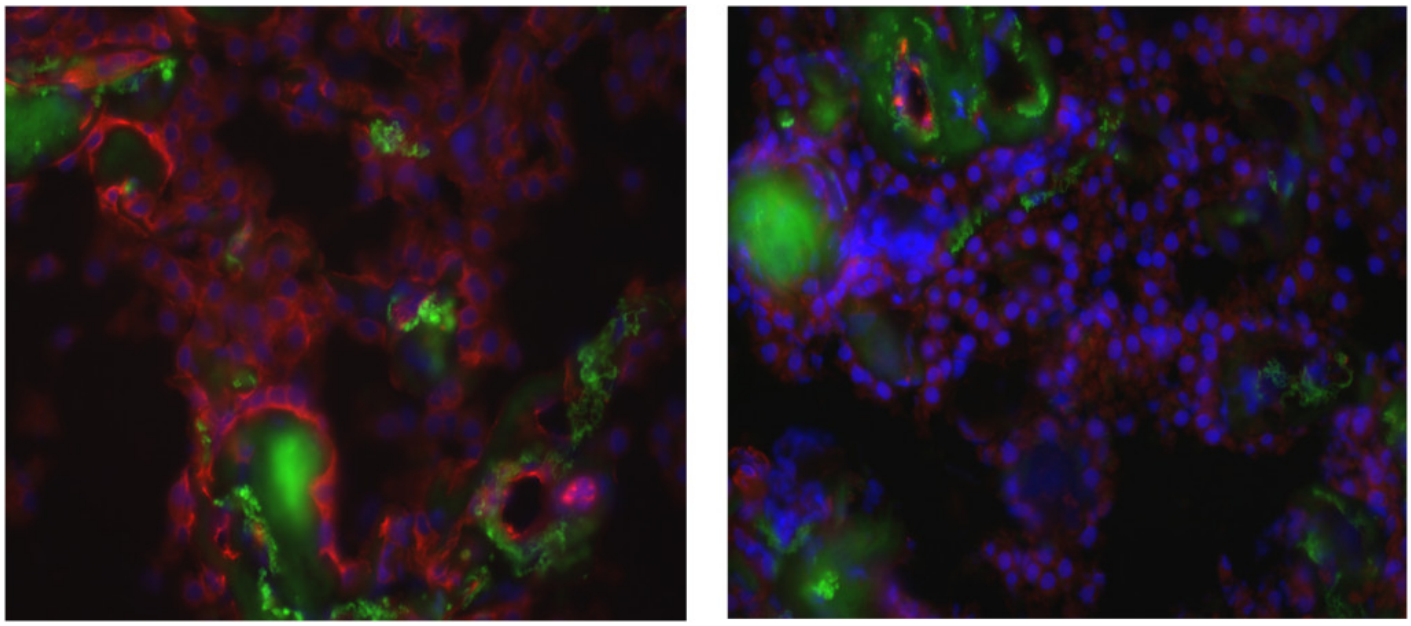
Human blood brain barriers malfunction in Alzheimer's disease

While the ancient Greeks and Romans already associated old age with dementia, it was not until 1901 that the German psychiatrist Alois Alzheimer diagnosed the first case of Alzheimer's disease in a fifty year old woman. Today, Alzheimer's disease accounts for 60-80 % of cases of dementias world-wide. Hallmark abnormalities of patients with Alzheimer's disease are progressive loss of (short term) memory, apathy, depression, impaired communication, poor judgment, behavioral changes, disorientation, confusion, increasingly poor mental and physical abilities. So far, the etiology of the disease is largely unknown, and treatment is not available.

Within the healthy brain, nerve cells continuously secrete a protein called amyloid beta (aß) into the the brain's cerebrospinal fluid (CSF). Normally, excess aß is cleared from the brain and CSF to the blood through the blood-brain barriers. In the Alzheimer's disease brains, aß is present in high levels and forms aggregates. These so called amyloid plaques are one of the hallmarks of Alzheimer's disease.



Two stainings of the human choroid plexus. On the left a healthy choroid plexus (from Braak 0,1 stage donor brain); To the right: an Alzheimer's disease affected choroid plexus (Braak 5). In both pictures, blue dots are nuclei of cells. Note that strings of cells are present in cauliflower-like form, indicating the structure of the choroid plexus.In both pictures there is also similar green staining, which indicates autofluoresence of aging tissue. In the left picture (healthy choroid plexus) considerable red staining of the protein Claudin 5 can be seen, while this red staining is almost absent in the right picture. These data indicate that in the affected choroid plexus barrier, Claudine 5 protein is absent, and, consequently, that this barrier is probably leaky in persons with

Alzheimer's disease.

Several types of blood-brain barriers exist. The most well studied barrier (in Alzheimer research) is called the blood-brain barrier (BBB) which lines the major blood vessels in the brain. The less well-known barrier is the blood-cerebrospinal fluid barrier (BCSFB) , which lines a small cauliflower-like structure (called choroid plexus)that protrudes into the brain ventricles. Recent evidence, primarily from animal model research, suggest that malfunction of the choroid plexus plays an important, if not essential, role in neurodegenerative disease and may have serious consequences for normal brain function.

In our study, we aimed to discover whether choroid plexus malfunction in humans plays a role in Alzheimer disease. Also, we wanted to find out about the series of molecular events what potentially causes malfunction of the human choroid plexus in this disease. Indeed, the latter question is particularly important, if one wants to rationally design future molecular or cellular therapies.

We isolated choroid plexus from human donors brains with (Braak stages 5 or 6) and without

(Braak stages 0 or 1) Alzheimer disease. We compared these choroid plexus samples by microscopy, protein staining and on a molecular level. We asked ourselves the question: which genes from the entire human DNA, of course carried by each cell of the choroid plexi, are expressed (used) specifically in the healthy and in the diseased choroid plexus? Technically, we used a few thousand cells from each choroid plexus and visualized the gene expression on micro-arrays containing 44.000 human genes.

We found many molecular differences between healthy and Alzheimer disease affected choroid plexi. Using advanced bioinformatics, we were able to categorized these differentially expressed genes in molecular pathways, relevant for Alzheimer disease. For example, we found that the Claudine 5 gene is less expressed in Alzheimer disease affected choroid plexi compared to healthy choroid plexi. Since we know that Claudin 5 gene is the gatekeeper of paracellular transport, we concluded that the BCSFB barrier becomes more permeable, if not leaky, in Alzheimers disease.

In summary, we found that human choroid plexus failure in persons with Alzheimer disease exists.

We also found that a range of normal functions of the BSCFB barrier, including CSF production, aß clearance, transport and barrier function is impaired in Alzheimer disease, and provided (part of) the molecular background for these.

These results opens new aveneus for future rational therapeutic designs for this devastating disease.

Publication

Gene expression and functional annotation of human choroid plexus epithelium failure in Alzheimer's disease.

Bergen AA, Kaing S, Ten Brink JB; Netherlands Brain Bank, Gorgels TG, Janssen SF

BMC Genomics. 2015 Nov 16