The best basic science paper in multiple sclerosis in 2014: Important role for the choroid plexus in the central nervous system entry of leukocytes

Gijs Kooij and Helga E de Vries

For decades, multiple sclerosis (MS) has been considered to be an autoimmune, inflammatory disease of the central nervous system (CNS), in which CNS self-antigen-specific T cells invade the brain and cause severe tissue destruction. In particular, immune cell presence in the perivascular spaces, the cerebrospinal fluid (CSF) or in the brain parenchyma was almost always considered to be a sign of autoimmune disease or the beginning of such a disease. However, recent data challenge this dogma as these autoreactive T cells do not only induce pathology, but are also required to ensure proper maintenance and repair of the CNS after an inflammatory event, a process defined as resolution. Indeed, under physiological conditions, CNS-patrolling memory T cells are abundantly present in the CSF, where they play an important role (together with the brain-resident innate immune cells like microglia) in the detection of abnormalities (infection, tissue damage) and subsequent resolution in order to restore local tissues to their original functional state. Consequently, the presence of these CNS-specific T cells is a purposeful process that requires rigorous control, as potential dysregulation may drive CNS pathology.

Besides memory T cells, the CSF of MS patients also contains high numbers of pro-inflammatory immune cells and their presence correlates with the number of CNS lesions. MS lesion predilection sites such as periventricular areas, cortex and spinal cord are in close contact with CSF, suggesting that CSF constituents play a vital but yet unknown role in MS pathogenesis. Remarkably, little attention has been given to the choroid plexus (CP), a specialized ventricular structure continuously involved in the production of CSF. However, because of its unique anatomical location, positioned to integrate signals from the brain (via the CSF) and the periphery, this villous structure may actually play an important role in CNS immunity under healthy and pathological conditions.

Here, we have selected as the best basic science paper of 2014 the excellent work and breakthrough findings of Michal Schwartz and her group. In her review paper, she summarizes key findings in the last decade that have changed the view on the presence of leukocytes in the CNS, indicating that these cells are pivotal players in CNS immune homeostasis as well as in cognitive tasks like learning and memory. Moreover, in the highlighted manuscript, the authors describe key in vivo findings that indicate that the CP represents a primary entry site for immune cells upon CNS injuries, and that this barrier is traversed by leukocytes before crossing the blood-brain barrier (BBB). In contrast to the endothelial cells of the BBB, the epithelial cells of the CP constitutively express the molecules that are required for leukocyte trafficking like adhesion molecules and chemokines, indicating that the CSF can be entered by leukocytes at any time. Under neuroinflammatory conditions, it was shown that encephalitogenic T cells enter the CNS at the CP via CCL20/CCR6 interactions and that CCR6 mice are resistant to experimental autoimmune encephalomyelitis (EAE). Although described studies in experimental models provided first evidence that the entry route of leukocytes may occur through the CP, the exact role of the CP in a human setting, as well as under neuro-inflammatory conditions like MS, remains largely undefined.

Our recent translational findings published in Acta Neuropathologica provide first indications that the CP may play a role in the pathogenesis of MS, as we revealed CP integrity defects in patients with MS. Mechanistically, we showed that the expression of claudin-3, a tight junction selectively expressed by the epithelial cells of the CP, was significantly reduced...
in MS. Consequently, mice that lack claudin-3 display exacerbated clinical signs of EAE, which coincided with enhanced levels of infiltrated leukocytes in their CSF, before clinical signs arose. However, we must keep in mind that an important disadvantage of human post-mortem studies is the use of predominately end-stage disease tissues, which makes it difficult to define the importance of observed CP changes in disease onset. Nevertheless, mimicking CP alterations using specific knockout mice will provide further knowledge on the importance of the CP in CNS homeostasis. Therefore, research is warranted to identify the full spectrum of CP alterations in MS, and provide suitable in vitro and in vivo models to determine their consequences. In turn, understanding the functioning of the CP and potential dysfunctioning under pathological conditions may lead to new therapeutic avenues to interfere with and restore this brain barrier, thereby controlling the CNS entry of detrimental and/or resolution-inducing leukocytes and reinstate CNS homeostasis.

Although current immune-modulatory treatment regimens for MS potently reduce the inflammatory burden in the CNS, these agents only modestly affect disease progression. This may be explained by two different hypotheses: (I) the “real” MS reflects a primary degenerative disorder in which the immune system plays a less important role,7 or (II) that an active immune system is also required for proper restoration of affected tissues after an inflammatory event.1 Although we question whether inflammation is causal for disease initiation, we do believe that it plays an important role in disease pathogenesis as reflected by massive inflammatory infiltrates in the CNS of relapsing–remitting MS patients, which represent the largest population of patients. Consequently, we should adjust our therapeutic approaches by not completely preventing CNS entry of immune cells but develop more specific agents that on the one hand can hamper the excessive inflammation in the brain and on the other hand induce the tissue to return to CNS homeostasis. In order to develop such new therapies, research in the next years should provide fundamental insights into the regulation of CNS immunity under healthy and pathological conditions and, based on the highlighted manuscripts in this commentary, we propose that the CP may hold the ultimate key to hamper MS progression.

Conflict of interest
None declared.

Funding
This work was supported by a grant from the Dutch foundation of Multiple Sclerosis Research (grant MS 12-791, G. Kooij).

References