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REVIEW ARTICLE

Role of the Blood–Brain Barrier in Multiple Sclerosis

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Multiple sclerosis (MS) is an autoimmune disease of the central nervous system associated with demyelination and axonal loss eventually leading to neurodegeneration. MS exhibits many of the hallmarks of an inflammatory autoimmune disorder including breakdown of the blood–brain barrier (BBB). The BBB is a complex organization of cerebral endothelial cells, pericytes and their basal lamina, which are surrounded and supported by astrocytes and perivascular macrophages. In pathological conditions, lymphocytes activated in the periphery infiltrate the central nervous system to trigger a local immune response that ultimately damages myelin and axons. Cytotoxic factors including pro-inflammatory cytokines, proteases, and reactive oxygen and nitrogen species accumulate and may contribute to myelin destruction. Dysregulation of the BBB and transendothelial migration of activated leukocytes are among the earliest cerebrovascular abnormalities seen in MS brains and parallel the release of inflammatory cytokines. In this review we establish the importance of the role of the BBB in MS. Improvements in our understanding of molecular mechanism of BBB functioning in physiological and pathological conditions could lead to improvement in the quality of life of MS patients.

Key Words: Blood–brain barrier, Multiple sclerosis, Central nervous system, Oxidative stress.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). Typically, the disease affects the brain, spinal cord, and optic nerves in the CNS and spares the nerve roots and peripheral nerves in the peripheral nervous system. The interplay between inflammatory and neurodegenerative processes in MS typically results in intermittent neurological disturbance followed by progressive accumulation of disability. During an MS attack, inflammation occurring in areas of the white matter of the CNS is followed by destruction of myelin in the brain and spinal cord, leading to progressive disability. Clinical symptoms of MS include motor dysfunction, fatigue, tremor, nystagmus, acute paralysis, loss of coordination or balance, numbness, disturbances in speech and vision and cognitive impairment. Usually, MS begins as a relapsing-remitting process and secondarily evolves to a progressive stage with accumulating disability. Most people experience their first symptoms of MS between the ages of 20 and 40. The clinical heterogeneity of MS, as well as the finding of different pathological patterns, suggests that MS may be a spectrum of diseases representing

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different processes (1–5). MS can be clinically categorized as acute, relapsing/remitting, primary progressive and secondary progressive forms. These forms are related to potentially different pathophysiological disease mechanisms, although this has yet to be demonstrated at the molecular level. Within a single diseased individual, the pathology pattern tends to be the same, even if the patient exhibits multiple lesions (6). There are several genes that confer susceptibility to MS. Among the most important are genes of the major histocompatibility complex like HLADRB1*1501 allele, HLA DQA1*0102 allele or HLA DQB1*0602 allele, responsible for ~50% genetic risk for MS. It has also been found that HLA DRB1 1501 allele is linked to disease severity. Other genes that have been identified code for receptors of interleukin 2 and interleukin 7 (7). MS is considered primarily an immune-mediated disease of the CNS in which auto-aggressive T-cells are thought to cross the blood–brain barrier (BBB) inflicting demyelination and axonal loss eventually leading to progressive disability. Despite intensive research, the etiology of MS is largely unknown, but recent developments in MS drug therapies have emphasized leukocyte passage across the BBB as being of paramount importance for disease pathophysiology (8). Histopathological studies have reported abnormalities of this barrier in inactive MS lesions as well as normal appearing white matter (9-11).

Blood–Brain Barrier

The BBB and the blood cerebrospinal fluid barrier (BCB) represent a complex vasculature network that forms a continuous cellular barrier between the CNS and the systemic circulation. Most of the important metabolic exchanges critical to CNS homeostasis occur through this tightly regulated network. The BBB itself is formed by two closely related entities: a) the interface between the brain and blood vessels; b) the BCB located in the choroid plexus along with the arachnoid layers of the meninges (12,13). The BBB is a membranous barrier that separates the brain tissue of the circulating blood. In the CNS, blood capillaries are structurally different from the capillaries of other tissues (14) and are covered by special endothelial cells without pores and sealed with tight junctions (15) (Figure 1A). The BCB located in the choroid plexus epithelium consists of arachnoid epithelium and choroid, which allows access to the subarachnoid ventricular samples, respectively (13). Due to its location and the direction of the flow of CSF, choroid plexus epithelium is considered the most important part of the BCB. It seems that the permeability in the choroid plexus is greater than that of the tight junctions of the endothelium of the BBB (8). Another very important part of the BCB is an epithelial layer of cells located strategically as 'intermediate cells' between CSF and brain, preventing most of the macromolecules from moving from the blood to the CSF (some authors consider other entities of the BBB) (Figure 1B). As the surface area of the BBB is much larger than the area of the BCB, the BBB can be considered as most important for the transport in the brain. Its functionality is affected by physiological and pathological processes, which can also affect transcellular and paracellular transport (8,16).

The idea of a disrupted BBB as a prerequisite for developing MS is not new. According to one major theory proposed by Poser in 1986 (10), four elements are required in order to develop MS: a) genetic susceptibility, b) environmental and probably viral immune-mediated event, c) alteration of the BBB function, d) myelinoclastic plaque forming capability in the CNS (18,19).

BBB Disruption Process in MS

BBB limits and prevents the entry of xenobiotics, toxic metabolites and immune cells into the CNS. The functionality of the BBB is achieved through intricate interactions between BBB endothelial cells, perivascular astrocytes, and pericyte vessels. As for the BCB, the anatomic basis of the barrier is on the epithelial cells making up the choroid plexus, with the soluble factors and contact-mediated mechanisms responsible for the barrier function to be established. The maintenance of a precisely regulated biochemical and immunological microenvironment is essential for proper CNS function. Changes in its delicate balance have been associated with CNS pathologies such as MS (20) (Figure 2). In MS the breakdown of the BBB is thought to be transient, although recurrence may be observed at the same or different locations within interval of weeks, months or even years. The subsequent progress and lesion development is irregular and involves additional phases of BBB leakage, immunologically mediated demyelination and various degrees of axonal transection. It is well recognized that the expression and organization of junctional proteins are known to change during neuroinflammatory and infectious processes (21,22) (Figure 2).

Access by immune cells to the CNS is restricted but not prohibited; the process of leukocyte extravasation, a critical step in the inflammatory response, involves the migration of leukocytes from the bloodstream to target tissues where they exert their effector function. The extravasation of leukocytes is orchestrated by the joint action of cell adhesion receptors and chemotactic factors and involves drastic morphological changes of both leukocytes and endothelial cells (23,24). Leukocytes in the bloodstream must make contact with the vessel wall and adhere to it, bearing shear forces to initiate the inflammatory response. Tethering and rolling of leukocytes on activated endothelium are the first steps of the sequential process of extravasation followed by firm adhesion and transendothelial migration. These initial contacts are