Autoimmunity Reviews 16 (2017) 612–619

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

The blood brain barrier and neuropsychiatric lupus: new perspectives in light of advances in understanding the neuroimmune interface

Ariel D. Stock [a], Sivan Gelb [b], Ofer Pasternak [c,d], Ayal Ben-Zvi [b,*], Chaim Putterman [a,e,**]

[a] Department of Microbiology and Immunology, Albert Einstein College of Medicine, 1300 Morris Park Ave. F701, Bronx, NY 10461, United States
[b] Department of Developmental Biology and Cancer Research, Faculty of Medicine, The Hebrew University, Jerusalem 91120, Israel
[c] Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, 1249 Boylston St., Boston, MA 02115, United States
[d] Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, 1249 Boylston St., Boston, MA 02115, United States
[e] Division of Rheumatology, Albert Einstein College of Medicine, 1300 Morris Park Ave. F701, Bronx, NY 10461, United States

ARTICLE INFO

Article history:
Received 7 March 2017
Accepted 13 March 2017
Available online 17 April 2017

Keywords:
Blood-brain-barrier
Neuropsychiatric lupus
SLE
Blood-CSF barrier
Choroid plexus
Glymphatics

ABSTRACT

Experts have previously postulated a linkage between lupus associated vascular pathology and abnormal brain barriers in the immunopathogenesis of neuropsychiatric lupus. Nevertheless, there are some discrepancies between the experimental evidence, or its interpretation, and the working hypotheses prevalent in this field; specifically, that a primary contributor to neuropsychiatric disease in lupus is permeabilization of the blood brain barrier. In this commonly held view, any contribution of the other known brain barriers, including the blood-cerebrospinal fluid and meningeal barriers, is mostly excluded from the discussion. In this review we will shed light on some of the blood brain barrier hypotheses and try to trace their roots. In addition, we will suggest new research directions to allow for confirmation of alternative interpretations of the experimental evidence linking the pathology of intra-cerebral vasculature to the pathogenesis of neuropsychiatric lupus.

Contents

1. Introduction

Systemic lupus erythematosus (SLE) is a complex, multifactorial autoimmune disease with diverse potential targets, including the kidneys, skin, and brain. Much progress has been made to clarify many of the immunopathogenic mechanisms underlying the development of end organ disease in SLE. These often involve complex immunological

* Corresponding author.
** Correspondence to: C. Putterman, Division of Rheumatology, Albert Einstein College of Medicine, 1300 Morris Park Ave. F701, Bronx, NY 10461, United States
E-mail addresses: ayalb@ekmd.huji.ac.il (A. Ben-Zvi), chaim.putterman@einstein.yu.edu (C. Putterman).

http://dx.doi.org/10.1016/j.autrev.2017.04.008
1568-9972/

cascades, including humoral mediated immunity such as autoantibody and complement deposition, with subsequent leukocyte and cytokine driven tissue damage [1]. While this autoimmune dynamic is quite evident in certain manifestations of SLE, including nephritis, there remain many unanswered questions regarding the etiology of neuropsychiatric disease in SLE patients (NPSLE).

NPSLE is broadly defined as one of two sets of presentations: focal and diffuse disease [2]. Generally speaking, focal disease in the form of stroke or focal seizures is closely related to lupus associated coagulopathies, including the antiphospholipid syndrome. Diffuse disease, however, is quite variable between patients, and may include depression, anxiety, memory impairment, and general cognitive decline [3]. Furthermore, there likely are several distinct pathways that may yield any or all of these latter symptoms, including neurotoxic autoantibodies [4], cytokine mediated inflammation (both from the periphery as well as within the central nervous system (CNS)), and cell mediated inflammation.

Due to the relative scarcity of human brain tissue available for research purposes, an obvious necessity in the study of many neurological conditions is the use of model organisms. To that end, there are several mouse models of NPSLE with particular strengths and weaknesses. For example, passive transfer of NPSLE associated neurotoxic autoantibodies (including anti-N-methyl-D-aspartate receptor (NMDAR) and anti-ribosomal P antibodies), either directly into the CNS or through peripheral intravenous injection following experimental disruption of the blood brain barrier (BBB), has been shown to reproduce specific features of diffuse NPSLE such as memory deficits and depression [5–7]. A problem with these models, however, is an underlying assumption that circulating autoantibodies in SLE typically have a means of entry into the CNS. Furthermore, these models may not optimally represent the subtle and progressive interplay between humoral and cell mediated autoimmunity over time which is likely operative in human disease.

Several spontaneous models of SLE with CNS manifestations exist, including NZB/W-F1, BXSB, and MRL/*fas*$^{lpr/lpr}$ (MRL/lpr) mice [8,9]. Of these, the MRL/lpr mouse has proven to be the most useful spontaneous model of NPSLE, for several reasons. Both the NZB/W-F1 and BXSB strains are confounded by neuroanatomical anomalies [10], while in BXSB only males are affected, which is inconsistent with the human SLE 9:1 female to male ratio. The MRL/lpr mouse, however, besides a strong female bias, has a very similar overall disease pattern to human SLE including renal and cutaneous manifestations [11,12], as well as a neuropsychiatric profile consistent with the diffuse manifestations of NPSLE including depression-like behavior and memory deficits [13,14]. There is a significant and growing body of research into manifestations of NPSLE in MRL/lpr mice, including extensive behavioral characterization and brain tissue evaluation. Furthermore, several means of immunomodulation, including gene knockout and pharmacological interventions, have been applied to MRL/lpr mice, clarifying the relative importance of several cytokine and autoantibody contributors [15–22].

An overarching topic in the discussion of neuroimmune interactions is the unique nature of the brain vasculature. In particular, the CNS has long been believed to be immunoprivileged with limited routine exposure to systemic immune mediators, owing in large part to the highly restrictive and selective nature of CNS endothelium, known as the BBB. There has been much progress in our understanding of neuroimmune interfaces in recent years, including identification of novel routes of leukocyte migration in and out of the CNS which bypass the BBB, and a unique mechanism of interstitial fluid clearance [23–25]. In this review, we will carefully explore the long-standing belief in BBB disruption in SLE, and address the potential role other brain barriers may play in the pathogenesis of NPSLE.

2. Vascular pathology and NPSLE

Studies geared toward understanding vascular involvement in SLE, primarily focusing on peripheral tissues outside the brain, suggest that circulating autoreactive antibodies may interact with the endothelial lumen and only subsequently with parenchymal determinants. In most lupus target organs, there is believed to be a vascular component, including (albeit uncommonly) overt vasculitis [26]. From this perspective, it is therefore not surprising that NPSLE manifestations in some patients may have a vascular component. Indeed, when evaluating the focal manifestations of NPSLE, the direct contributions of vascular abnormalities are clear. Multifocal microinfarcts consistent with thrombotic disease, including macro and microthrombosis, have been found in lupus patients *post mortem*, mainly associated with anti-phospholipid antibodies [27].

A role for a vascular component in the diffuse manifestation of NPSLE (*e.g.* depression, anxiety, headaches) is less obvious, but microinfarcts, microhemorrhages, and vasculopathy have been reported in autopsies of patients with diffuse NPSLE [27]. Additionally, MRI evaluation of NPSLE patients supports the notion that vascular disease is a hallmark of NPSLE, despite variations in the actual brain regions affected. One such study examining a newly diagnosed NSPLE cohort (108 patients within 6 months of NPSLE diagnosis, with data collected over 9 years [28]), found imaging evidence for large vessel disease (brain infarcts in large arterial supply territories) as well as small vessel disease (small subcortical infarcts, lacunar infarcts, and microbleeds).

Capillaries are the vascular element that allows for all metabolic exchanges between blood and brain. Consequently, an insult to CNS capillaries can yield dramatic effects in brain function. Moreover, from a vascular biology perspective, it is well appreciated that the CNS capillaries are not only the functional unit in the vascular tree responsible for blood-tissue molecular influx and efflux, they are also physically the major interface between the vasculature and the parenchyma (far bigger in total surface area than large and medium diameter vessels). While both post-mortem and MRI data in lupus emphasize the vascular pathology at the level of large and small vessels (arteries and penetrating arterioles), information regarding an important, if not most central component of the vascular tree, the CNS capillary bed, is distinctly missing. In Section 3, we will explore some of the unique characteristics of CNS capillaries in their role as the BBB.

3. The BBB is one of three brain barriers

The BBB is the defining feature of brain vasculature. It insulates the brain from unwanted blood borne materials, provides for the special metabolic needs of the brain, and defines the stable environment crucial for brain homeostasis. The function of blood vessels in the brain is very different from that of peripheral blood vessels: brain capillaries primarily isolate the brain from the blood, and only then allow for influx/efflux of materials through the capillary wall in a tightly regulated manner. CNS capillaries are lined by a single layer of endothelial cells and therefore the physical barrier starts with the luminal plasma membrane and extends through the scant cytoplasm of the endothelial cell, the basolateral plasma membrane, and a specialized basal lamina (extracellular matrix produced by both endothelial cells and surrounding astrocytes). As such, it is the functional characteristics of CNS endothelial cells that serve as the foundation of the unique physiological phenomenon that is the BBB (Fig. 1) [29]. Conceptually extending beyond BBB endothelial cells, the neurovascular unit (NVU) also consists of pericytes, astrocytic end-feet, and neuronal termini that contribute to the modifiable functions of the BBB. NVU cells provide continuous signaling to the endothelium that facilitates the maintenance of its barrier properties but also actively participate in barrier function, including regulation of water homeostasis, solute transport, and contribution to basement membrane composition [30].

In their widely referenced review, Abbott, Mendonca, and Dolman extensively describe how BBB pathology may be involved in the development of NPSLE [27]. Though these authors also emphasized the importance of the two other major brain barriers, the blood cerebrospinal fluid barrier (BCSFB) and the meningeal barrier, there is a surprising dearth of experimental data or even discussion about