PEDRO A. MONTENEGRO
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EDITORS

THE BLOOD-BRAIN BARRIER

New Research

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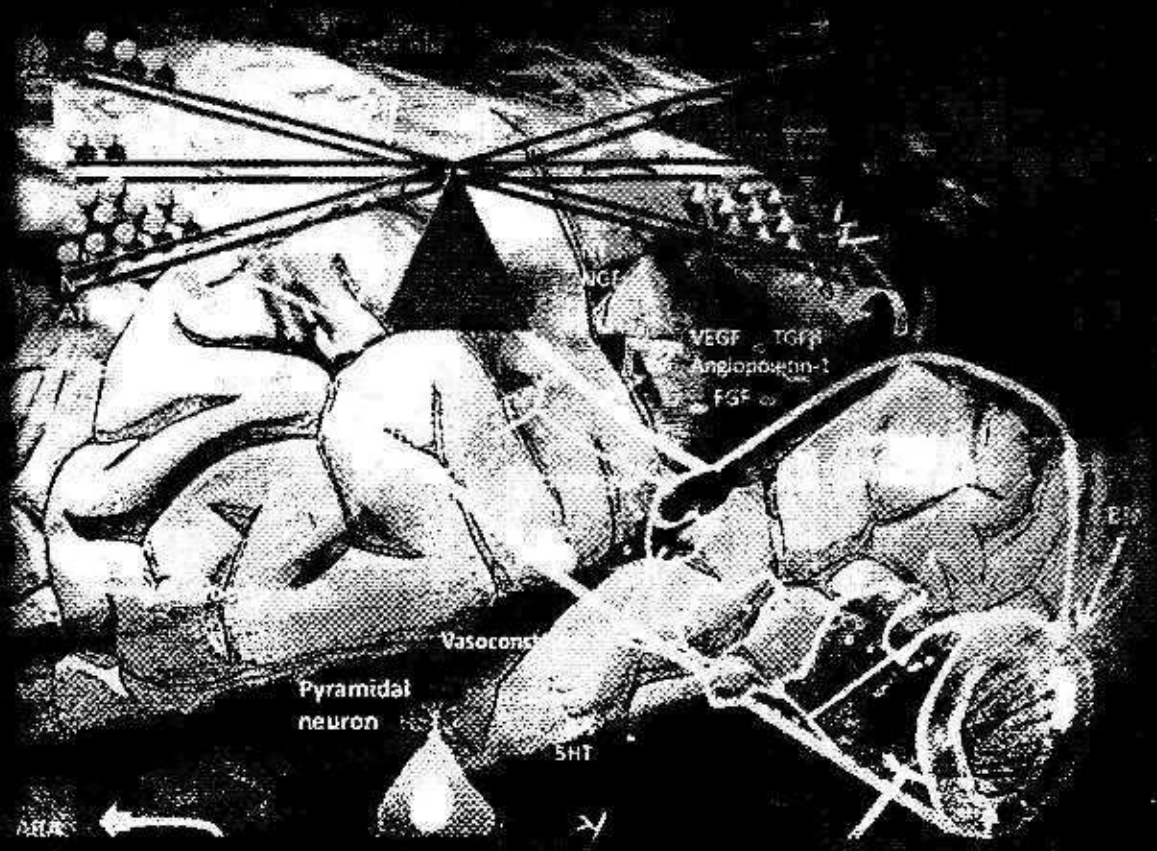

NEUROSCIENCE RESEARCH PROGRESS

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Chapter III

IT TAKES TWO TO TANGO: PROTEIN-PROTEIN INTERACTIONS IN THE TRANSLOCATION OF PATHOGENS ACROSS A BLOOD-BRAIN BARRIER

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ABSTRACT

Blood-brain barrier (BBB) is a regulatory interface between the peripheral circulation and the central nervous system (CNS), which has unique role in the protection of the brain from toxic substances and pathogens present in the blood. Many pathogens including parasites, bacteria, viruses and fungi have the potential to infect the CNS, but it is unclear why only a relatively small number of pathogens account for the most clinical cases with nervous disorders. Pathogens may enter the CNS via transcellular penetration, paracellular passage and/or via "Trojan horse" mechanism (via infected phagocytes). Interactions between protein molecules from host and pathogens are crucial to trigger translocation processes. Indeed, it takes two to tango: both host receptors and pathogen ligands. Underlying molecular basis of BBB translocation by various pathogens has been revealed in the last decade, however, an array of protein-protein interactions between many of the neuroinvasive pathogens and BBB remained fully unexplored. Identification and molecular characterization of these pathogens and host factors mediating BBB penetration can open novel ways and perspectives in the development of more specific drugs and vaccines strategies. This chapter will give new insight into the various protein-protein interactions that take place in BBB translocations process.

1. INTRODUCTION

Infections of the central nervous system (CNS) are major cause of morbidity and mortality throughout the world. A limiting factor in the prevention and therapy of CNS infections is incomplete understanding of the pathogenesis of neuroinfections at molecular level mainly because of a lack of comprehensive knowledge about protein-protein interactions, which take place during pathogens translocation across blood brain barrier (BBB).

BBB is a regulatory interface between the peripheral circulation and the central nervous system (CNS) [1]. Pathogens exploit several mechanisms that enable them to reach the CNS, like traversal of BBB or penetration through neurons by axonal flow. Almost all pathogens that can cause infection in humans have potential to infect CNS, but is still unclear why only a small number are responsible for most cases of meningitis. Neurological symptoms during the neuroinfections are associated with mode of traversal of BBB and penetration into the brain. Interestingly, some neuroinfections, for example *Chlamydiophilapneumoniae* [2] and *Borrelia burgdorferi* [3, 4] infections, are reported to be associated with multiple sclerosis (MS) and Alzheimer's disease (AD). However a tangible relationship between these organisms and neurodegenerative diseases still remains undefined with more rigorous studies.

This chapter summarizes our current understanding of pathogenesis of neuroinvasion, the BBB translocation and gives new insight into the various protein-protein interactions that take place in BBB translocation process.

2. A SPECIALIZED WALL "BLOOD-BRAIN BARRIER" AND ITS BUILDING BLOCKS: BRAIN MICROVASCULAR ENDOTHELIAL CELLS

BBB is a distinctive and protective wall composed of brain microvascular endothelial cells (BMECs), astrocytes, basement membrane, pericytes and neurons. Some of the unique properties that differentiate BBB from other barriers are: (i) presence of the intercellular "tight junction" (Tj), (ii) absence of fenestrae and reduced level of fluid-phase endocytosis, and (iii) asymmetrically localized enzymes [5-7]. Under physiological conditions, BBB regulates the entry of endogenous compounds, toxic and drug molecules as well as cellular infiltration into the CNS. The normal endothelial cell surface is a thrombo resistant and prevents platelet and leukocyte adhesion and activation of any coagulation system. Highly specialized endothelial cells (ECs) form a tight barrier, which isolates the brain and allows only few mononuclear cells (such as activated T-cells) to migrate into the CNS. Previously, it was believed that the CNS is immunoprotected site because of the low expression of major histocompatibility complex antigens, the low number of antigen-presenting cells in the healthy CNS, and the fact that the CNS is not properly drained by a fully developed lymphatic vasculature [8]. Nevertheless, recent finding shows that CNS is neither isolated nor passive in interactions with immune system and that changed the earlier viewpoint [9]. The brain necessitates maintenance of homeostasis more than anywhere else in the body. BBB prevents ion fluctuations frequently occurring in the plasma and averts brain damage. Small lipid soluble molecules like carbon dioxide or ethanol are able to penetrate through the barrier relatively easily via the lipid membranes. In contrast, water soluble molecules and

macromolecules are unable to cross BBB in absence of specialized carrier-mediated transport system [10].

Table 1. Pathogens causing central nervous system infections in human

Bacteria	*E. coli*, group *B streptococci, Listeria monocytogenes, S. pneumoniae, Neisseria meningitidis, Haemophillus influenzae* type B, *Citrobacter spp., Borrelia burgdorferi* sensu lato, *Treponema pallidum, Acinetobacter baumanni,, Serratia marcescens, Pseudomonas putida, Enterococcus faecalis, Enterococcus faecium, Klebsiella pneumoniae, Meningococcus, Salmonella meningitis, Bacillus anthracis, Bacillus cereus, Francisella tularensis, Chryseobacterium meningosepticum, Kingella kingae, Rothia mucilaginosa, Mycobacterium tuberculosis*
Fungi	*Cryptococcus, Candida albicans, Aspergillus, Zygomycetes, Blastomyces, Histoplasma capsulatum, Cladophialophora bantiana, Coccidioides immitis, Pseudallescheria boydii, Arthrographis kalrae, Exophiala dermatitidis, Ramichloridium mackenzie, Ochroconis gallopava*
Parasites	*Plasmodium falciparum, Trypanosoma* spp., *Toxoplasma gondii, Teania solium, Naegleria fowleri, Acanthomoeba, Angiostrongylus cantonensis,*
Viruses	HIV-1, herpes simplex virus, rhabdovirus (rabies), Influenza virus, parainfluenza virus, reovirus, lymphocytic choriomeningitis virus, arbovirus, cytomegalovirus, flaviviruses (West Nile virus, Japanese encephalitis virus, tick-borne virus, St. Luis encephalitis virus, Murray Valley encephalitis virus), mumps virus, parvovirus B 19, measles virus, T-cell leukemia virus, enterovirus, morbillivirus (Nipah and Hendra virus), bunya viruses and toga viruses

BMECs are connected with adherens junctions (Ajs) and tight junctions (Tjs). Tjs, the apical most constituent of intercellular junctional complexes, work as a barrier within the intercellular space and control paracellular permeability [11]. It also forms a circumferential belt that separates apical and basolateral plasma membrane domains [12], and shares biophysical properties with conventional ion channels, including size and charge selectivity, dependency of permeability on ion concentration, anomalous mole-fraction effects and sensitivity to pH [13]. These junctions contain a large number of adhesion molecules, including vascular endothelial (VE)-cadherin (CD144, cadherin-5), and a homophilic calcium-dependent transmembrane adhesion molecule. While specialized tight junction includes occludin, JAM family members, claudins, as well as proteins such as CD99 and PECAM-1 (CD31).

3. Special Features of BBB and its Bulding Blocks: The BMECs

Infections are quite common, but why do we only see infections of the CNS in rare occasions? One major preventing factor is the special barrier BBB and its building blocks: the BMECs. BMECs share many common features with peripheral endothelial cells (ECs); however, they possess unique characteristics. BMECs and normal ECs differ from each other in functional and structural terms. Some of these differences are with respect to cytokine and growth-related molecules, stress-related proteins, metabolic enzymes and signal transduction

proteins [14]. Several Tj transmembrane protcins, including occludin, claudin-1, claudin-3, claudin-5, claudin-12, junctional adhesion molecules JAM-A, JAM-B, JAM-C, endothelial cell-selective adhesion molecule, zonula occludens proteins (ZO-1, ZO-2), cingulin, 7H6 antigen and PAR-3, are expresed differentially in BMECs and peripheral vascular ECs [15]. BMECs express more vascular endothelial VE-cadherin and less endothelial nitric oxide synthase than pulmonary ECs [16]. P-selectin, another cell adhesion molecule, is expressed relatively higher in the lung than in brain. It is the first cell adhesion molecule whose surface expression on ECs increases during the inflammation and plays a role in the recruitment of inflammatory cells into the CNS. Occludin, an integral plasma-membrane protein of the ECs is expressed much higher in BMECs compared to non-neuronal tissues, suggesting that occludin may be the major regulatory protcin that reduces paracellular permeability across Tjs in BBB [17]. Similarly, researchers observed high expressions of Lutheran membrane glycoprotein, CD46 complement regulator and autoantigen Ro52 at BBB [18, 19].

It is interesting to note that BMECs express unique cell surface glycoproteins that are not found on other ECs, such as the cerebral cell adhesion molecule, LK48, BBB-specific anion transporter 1, angiogenic factors (vascular endothelial growth factor, follistatin, fibroblast growth factor 1 and 5) and CXC chemokines with Glu-Leu-Arg (ELR) motifs (epithelial cell-derived neutrophil-activating peptide 78 and growth regulated oncogene-α) [20].

4. Crossing of the Wall, Transcellular vs. Paracellular Translocation

The barrier function of the BBB can change dramatically during various diseases of the CNS, i.e., during hypertension and cerebral inflammation such as multiple sclerosis or cerebral infections. Enhanced BBB permeability is considered to be the result of either opening of tight junctions [21] or of enhanced pinocytotic activity and the formation of transendothelial channels [22]. The BBB itself may play an active role in the mediation of the neuroimmune response either by production of inflammatory mediators or by the expression of adhesion molecules.

One of the central events in the development of neuroinfections is hematogenous dissemination of pathogens followed by their translocation across BMECs. However, the translocation event must be well orchestrated by pathogen to evade BBB defense. Such orchestrated cell-signaling events take place during the translocation of leukocytes across endothelial barrier. In general, leukocyte adhesion and translocation at sites of inflammation is a two-step process. Weak binding by oligosaccharides and members of the selectin family results in short-term interaction (rolling) of passing leukocytes. This is followed by firm adhesion and transmigration mediated by activated integrins and adhesion molecules, particularly VCAM-1 and ICAM-1. It is postulated that many pathogens like *Borrelia* might mimic the orchestral events in leukocyte transmigration.

Several pathogens are able to cross the BBB and infect central nervous system (Table 1). Pathogens may cross BBB transcellulary (free pathogen), paracellulary (briefly opening of the junctional complexes allowing transport of free pathogen) and/or by means of infected phagocytes (so-called Trojan horse mechanism) (Figure 1) [23]. In any case, in response to infection, BMECs undergo dramatic changes in their cytoskeletal structure, expression and

activation of cell adhesion molecules, expression of cytokines, thrombotic and coagulant properties, and permeability to plasma proteins. In the Trojan horse mechanism, pathogen first infects leukocytes, primarily lymphocytes and/or mononuclear cells, and translocates the BBB by hitching a ride across the BBB [24]. This mechanism has been suggested for *L. monocytogenes*, *M. tuberculosis* [25, 26] and HIV [27]. Either the transcellular and/or the paracellular route may serve as possible modes of amoebae entry into the CNS [28]. Both routes have also been suggested for *Cryptococcus neoformans* [29, 30] and Lyme disease pathogen *Borrelia burgdorferi* [31, 32].

In the further parts, we have focused mainly on the transcellular and paracellular traversal of the microbes, as the majority of host-pathogen interactions at the protein level occur during these translocation processes.

Transcellular passage involves penetration of the pathogens through BMECs, without evidence of pathogenic organisms between the cells and intercellular junction disruption. It is engineered by adherence of the pathogen to the blood vessels and subsequent pathogenic entry into the ECs via pinocytotic or receptor-mediated mechanisms (Figure 1) [33]. It is possible that some pathogens are able to bind to the host cell receptor by producing a molecule that resembles a natural host ligand [34]. The role of selective BMEC recognition sites such as receptor-ligand interactions in traversal process remains unclear yet. However, it is clear that there is increase in number of microvilli on the BMEC surface similar to other types of endothelial cells under pathological conditions [35] and increase of ICAM-1 expression on the surface of BMEC caveolae and vacuoles [24]. Passage of pathogen mediated through mimicking the host's proteins is designated as "bacteria-directed trancytosis," and has been showed mainly for the bacterial invasion processes of both epithelial and ECs. In recent years, role of cytoskeleton, microtubular, microfilamentous and probably adhesion proteins was confirmed in modulating molecular and cellular migratory events across the ECs. Cytoskeletal proteins have been suggested to be involved with transvascular transport of macromolecules, as well as modulating cell-to-cell adhesion and may play a specific role in vesicle shuttling [36]. Transcellular traversal of the BBB has been demonstrated for several bacterial pathogens, such as *Escherichia coli* [37], group B streptococci [38, 39], *Streptococcus pneumoniae* [40], *Listeria monocytogenes* [41], *Mycobacterium tuberculosis* [42], *Treponema pallidum* [43], fungal pathogens such as *Candida albicans* [44], *Cryptococcus neoformans* [29], and is also suggested for West Nile virus [45].

The paracellular route is defined as microbial infiltration between barrier cells. This traversal involves loosening the Tjs or disturbing the supporting components of Tjs, i.e., basement membrane and glial cells [46]. The paracellular transmigration of the BBB has been suggested for the *Trypanosoma* [47] and *Treponema pallidum* [48]. Either the transcellular and/or the paracellular route may serve as possible modes of amoebae entry into the CNS [28]. Both routes have also been suggested for *Cryptococcus neoformans* [29, 30], Lyme disease pathogen *Borrelia burgdorferi* [31, 32] and *Treponema*.

During the translocation, pathogens breach the barrier either by targeting junctions or cells. On the other hand, host-cell actin cytoskeleton undergoes through the extensive remodeling and repairing during pathogen invasion [49-52]. Although the way of BBB translocation depends upon the pathogen species, interestingly, some host factors may also influence the mode of the pathogen entry. For example, IL-1β and CXCL8 appear to affect

the paracellular permeability as an inducers of BBB hyperpermeability, while TNF-α contributes to increase in transcellular permeability [53].

In general, trans- and paracellular routes differ in respect of physical properties: a) the migration across the transcellular pathway can be either passive or active as long as transmigration through paracellular pathway is solely passive and it is powered by electrochemical, hydrostatic and osmotic gradients, b) as compared with the transcellular route, the paracellular route is described by higher electrical conductance and lower selectivity, c) paracellular transport is not adjusted with the comparable conductance and selectivity in either apical to basal or basal to apical ways; d) paracellular travels have good specified values of electrical conductance as well as charge and size selectivity [54]. Otherwise, differences include the location of passage.

5. Traversal Mechanisms and Host: Pathogen Interactions

5.1. Bacteria

Bacteria have exploited various strategies to penetrate host cells in which ligand-receptor interactions are inevitable for penetration through BBB (Table 2). Studies in humans and experimental animals point towards a relationship between the level of bacteraemia and the development of meningitis in infection like *E. coli* [37], group B streptococci [55] and *S. pneumoniae*. However, for successful translocation merely high bacteraemia level is not sufficient, unless proper adhesion of bacteria to BBB occurs [23].

Esherichia Coli

Recent findings indicate that *E. coli* invades human BMECs through ligand-receptor interactions. Pivotal steps in the pathogenesis of meningitis are microbial binding to BMEC surface and their invasion. AslA protein, member of the arylsulfatase enzymes family, cleaves sulfate esters and plays a role in the penetration of the BBB. AslA is expressed under sulfur starvation conditions [37, 56, 57]. Other membrane proteins IbeA, IbeB and YijP are also important candidates in the invasion of *E. coli* into BMECs. YijP is minor protein that has many features of outer membrane protein, including a signal peptide-like sequence and five or six transmembrane segments at its N terminus [58]. IbeB and outer membrane protein A (OmpA) interact with different receptors on BMEC, and the effects of these interactions are at least additive (Table 2). OmpA is a major outer membrane protein, which is highly conserved among gram-negative bacteria. OmpA interacts with glycoprotein gp96 of BMEC via N-glucosamine epitopes that facilitates *E.coli* invasion (Table 2). It was shown that blocking of OmpA by antibodies inhibits the invasion of *E. coli* into the brain [59].

FimH, a major adhesion protein, has lectin-like activity with high affinity to mannose residues. FimH is localized at the tip of the fimbrial shaft. Mannose-recognition domain induces $[Ca^{2+}]$ surge in human BMEC, which leads to actin cytoskeleton rearrangement. FimH also activates Ras homolog gene family member A (RhoA), and this may contribute to bacterial entry [60]. Cytotoxic necrotizing factor-1 (CNF-1) of *E.coli* plays an important role in invasion of BMEC and traversal of the BBB. CNF-1 is dermonecrotic, high-molecular weight protein that activates Rho GTPases by deamidation of glutamine, converting it into

glutamic acid, inhibiting GTP-hydrolyzing activity and constitutive activation of Rho, resulting in polymerization of F-actin and increased formation of stress fibres [61]. CNF1 has also been suggested to be internalized via receptor-mediated endocytosis upon binding to a cell surface of receptor 37-kDa laminin receptor precursor (37LRP)/67-kDa laminin receptor (67LR) [62].

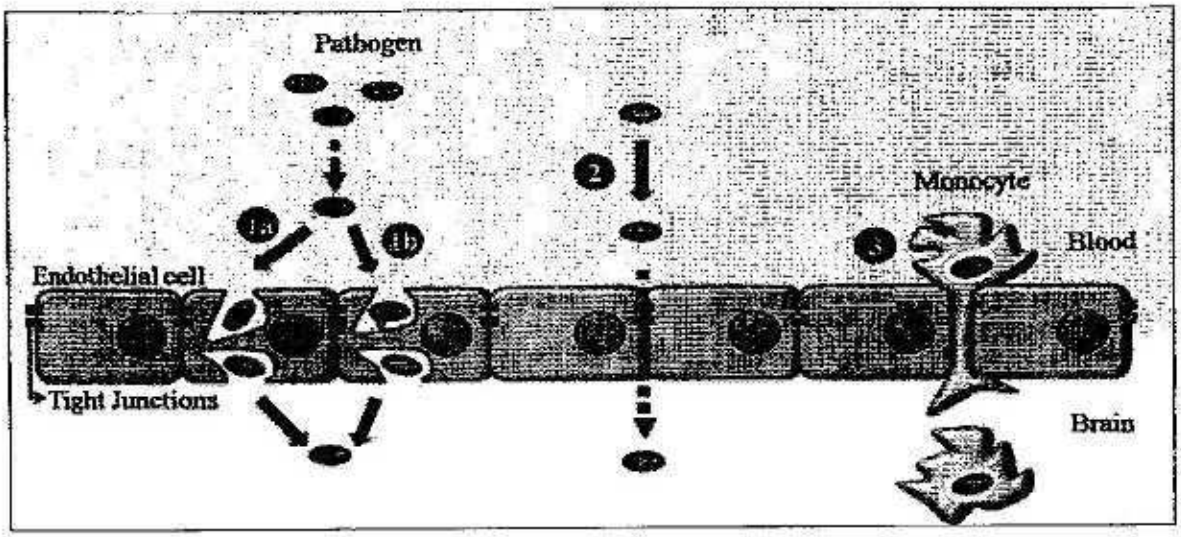

Figure 1. Various ways of pathogen translocation cross BBB.
Pathogens may disrupt the blood-brain barrier and enter into the CNS through transcellular penetration (1a – pinocytosis, 1b – receptor mediated mechanism), paracellular entry (2) or transmigration through infected leukocytes - Trojan horse mechanism (3).

Group B Streptococci (GBS)

Some GBS molecules, like fibrinogen-binding protein A [63], PilA, PilB [64], laminin binding protein [65], beta-hemolysin/cytolysin [66], serine-rich repeat-1 [67], and lipoteichoic acid (LTA) [68], mediate interaction of the pathogen with BMECs and penetration of the BBB. Many of these GBS ligands are known to bind extracellular matix molecules such as fibronectin, fibrinogen and laminin. GBS ligands also bind host-cell-surface integrins. β-hemolysin/cytolysin secreted by GBS encourages invasion, conceivably by breaking down host barriers to disclose receptors on the basement membrane, such as laminin, which promotes internalization of CNF-1 [69, 70]. GBS can bind lysine residues of host plasminogen on its surface [71], whereas, *iagA* gene plays prime role in advancing GBS invasion through BBB. This gene encodes an enzyme (homolog of glycosyltransferase) that plays defined roles in biosynthesis of diglucosyldiacylglycerol, a membrane glycolipid that works as an anchor for LTA [68].

Previous studies revealed that internalized bacteria are found within membrane-bonded vacuoles of BMECs and transmigrate without multiplication and are protected from fusion with lysosomes [23, 72]. Electron microscopy studies have shown that *E. coli, M. tuberculosis* and group B streptococci invasion is associated with microvilli like protrusions at the entry site on the surface of human BMEC [38], suggesting a rearrangement of host cell actin cytoskeleton. Actin cytoskeleton rearrangements are necessary for BMEC invasion by meningitis-causing bacteria, but the signaling mechanisms involved in actin differ between meningitis-causing bacterial species.

Table 2. Host - pathogen proteins interacting during translocation across endothelial cells

Protein ligand (Synonym) [Pathogen]	Molecular weight (kDa) /pI	Coding gene (Genebank access)	Length (amino acids)	Chemical nature	General biological functions of the protein, **possible way of pathogen translocation**	Domain	Start (amino acid)	End	Host receptor
Mannose-binding protein (MBP) [*Acanthamoeba castellanii*]	87.416/4.41	*mbp1* (Q6J288-1)	833	glycoprotein	mediates the adhesion of parasites to the host cells, **in transcellular/ paracellular translocation** [28, 135]	CXCX repeat CXCX repeat	317 602	330 615	ND
70-kDa BPBP (plasminogen binding protein) [*Borrelia burgdorferi*]	59.857/5.64	*bpbp70* (O31313-1)	523	lipoprotein	transport, transporter activity, **in paracellular translocation** [31, 203]	SBP bac 5	70	441	Plasminogen
Erp A [*Borrelia burgdorferi*]	19.57/5.84	*erpA, erpA5* (Q44781-1)	173	lipoprotein	**paracellular translocation** [31, 87]	OspE	41	147	Plasminogen
ErpC [*Borrelia burgdorferi*]	20.2/5.28	*erpC* (Q44790-1)	179	lipoprotein	**paracellular translocation** [31, 87]	OspE	41	155	Plasminogen
ErpP (Complement regulator-acquiring surface protein 3) [*Borrelia burgdorferi*]	20.6/8.36	*erpP, crasp3* (Q9S036-1)	186	lipoprotein	**paracellular translocation** [31, 87]	OspE	54	160	Plasminogen
OspA (Outer surface protein A) [*Borrelia burgdorferi*]	31/8.77	*ospA* (P0C926-1)	273	lipoprotein	transmigration of ECs, **in paracellular translocation** [31, 206]	Lipoprotein 1	1	273	Plasminogen

Vsp1 (Surface protein VspA) [*Borrelia burgdorferi*]	21.9/8.57	*vspA* (O34000-1)	214	lipoprotein	defense response, **in paracellular translocation** [31, 88]	Lipoprotein 6	1	207	Glycos- amino-glycans
Als1 (Agglutinin-like protein 1) [*Candida albicans*]	132.6/4.28	*als1* (P46590-1)	1260	glycoprotein [44, 111]	adhesion, pathogenesis, **in transcellular translocation**	Repeat domains (1-12)	433	1152	ND
Eno1 (Enolase-1, 2-phospho-glycerate dehydratase, 2-phospho-D-glycerate hydro-lyase) [*Candida albicans*]	47.2/5.54	*eno1* (P30575-1)	440	glycolytic enzyme	glycolysis, entry into host, induction by symbiont of host defence response, **in trans-cellular translocation** [44, 114]	Enolase N Enolase C	4 145	135 438	Plasminogen
Isc1 (Inositol phospo-sphingolipid-phospho-lipase C1) [*Cryptococcus neoformans*]	58.6/6.77	*isc1* (Q1HG89-1)	529	sphingolipid	ion tolerance, heat stress response, **in transcellular translocation** [109]	P40015	39	341	ND
Urease (UREA_CRYNE, URE1) [*Cryptococcus neoformans*]	90.6/5.65	*ure1* (Q5KCQ6)	833	amidohydro-lase	urea metabolic process, increase micr oenviromental pH, **in transcellular translocation** [110]	Urease gamma1 Urease beta Urease alpha Amidohydro1	100 134 265 391	 233 385 702	ND
Yps3p [*Cryptococcus neoformans*]	20.4/7.94	*yps3* (Q00950-1)	184	ND	fungal transition, pathogenicity [205]	Calcium-binding EGF	49	87	TLR2
AslA (Arylsulfatase, Aryl-sulfate sulphohydrolase, AS)	60.7/5.93 *G616)*	*aslA (b3801, ECK3793, atsA, JW3773, gppB,*	551	sulfatase enyzme	calcium ion binding, sulfor metabolic process, metal ion binding, hydrolase	Sulfatase	86	516	ND

Table 2. (Continued)

[*Escherichia coli*]	(P25549-1)				activity, **in trans cellular translocation** [57]			
CNF [*Escherichia coli*] **transcellular**	113/5.26	*cnf1* (Q46962-1)	1014	AB-type toxin protein SA	activate small GTPase of Rho family, **in translocation** [61]	CNF1	20 1014	40S ribosomal
FimH [*Escherichia coli*]	30/8	*fimH* (P08191-1)	300	immuno-globulin-like	cell adhesion, **in transcellular translocation** [60]	FimH mannose bindin Fimbrial C	4 151 92 300	CD48
IbeA (Ibe10) [*Escherichia coli*]	61.6/4.96	*ibeA (ibe10)* (Q1R2H6-1)	456	lipoprotein	oxidoreductase activity, invasion, FAD binding, **in transcellular translocation** [206]	GIDA	18 387	Polypyrimidine tract binding protein-associated splicing factor, Vimentin
IbeB (Cation efflux system protein CusC, ylcB) [*Escherichia coli*]	50.7/5.93	*ibeB* (P77211-1)	460	lipoprotein	pathogenesis, invade BMEC, **in trancellular translocation** [207]	OEP OEP	63 247 270 455	ND
OmpA (Outer membrane protein A , Outer membrane protein II B0957, Tut, Con, TolG) [*Escherichia coli*	37.2/6.4	*ompA* (*con, tolG,tut*) (P0A910-1)	346	porin	conjugation, ion transport, phage recognition, **in trans-cellular translocation** [59]	OmpA-like TD OmpA family	6 195 222 319	C4BP
TraJ [*Escherichia coli*]	26.4/8.23 (P05837-1)	*traJ*	228	ND	regulate expression of transfer genes, transcription activator,	PAS fold	21 125	ND

					in transcellular translocation [208]					
YijP [*Escherichia coli*]	68.3/6.91	*yijP (b3955 ECK3945*, (Q8FB99-1)	592	peptido-glycan	invade BMEC, **in transcellular** [58]	Dufl 705 Sulfatase	64 252	226 580		ND
Tat [virus HIV]	71.1/9.58	*tat* (P04608-1)	86	peptide	apoptosis, interaction host: virus, transcription, **in Trojan horse mechanism** [27]	Tat	1	65		CD 309
Internalin B (INLB) [*Listeria monocytogenes*] [41]	22.7/6.47	*inlB* (P25147-1)	630	leucine-rich repeat protein	mediate entry of bacteria, **in transcellular translocation**	Internalin N LRR 1 LRR adjacent FLG new 3		3 165 264 50	59 185 321 395	gC1q-R
PLB1 (Phospholipase B) [*Listeria monocytogenes*] **translocation** [209]	21.7/4.16	*plb* (E0ACX6)	187	glycoprotein	phospholipid catabolic process, **in transcellular**					ND
Vip (Lmo0320, Proline rich protein) [*Listeria monocytogenes*]	43.1/4.47	*lmo0320* (Q9EXF9-1)	399	ND	mediate entry of bacteria, **in Trojan horse mechanism** [98]	Pfam-B Gram positive anchor		1 370	369 399	TRA1
GrcC2 (Polyprenyl-diphoshate synthase) [*Mycobacterium tuberculosis*]	34.7/5.2	*grcC2* (O05572-1)	325	polyprenyl synthase	isoprene biosynthesis, transferase activity, **in transcellular translocation** [96]	poyprenyl synthetase	38	276		ND
PPE29 [*Mycobacterium tuberculosis*]	41.4/4.8 (Q7D7X9-1)	*ppe29 (rv1801Mt1850)*	423	ND	cell invasion, intra-cellularsurvival,**in transcellular translocation** [42]	PPE PE PPE C	5 317	162 407		ND
Opc (Outer membrane protein) [*Neisseria meningitidis*]	29.9/9.7	*opc, opcA* (Q51227-1)	272	ND	adhesion, **in transcellular translocation** [73]	OpcA	21	264		Fibronectin

Recent studies also indicated that other meningeal pathogens invade human BMECs via ligand-receptor interactions. For example, *S. pneumoniae* invades BMECs in part via interaction between cell wall phosphorylcholine and the BMEC platelet activating factor receptor [40]. *Listeria monocytogenes* invasion of BMEC has been shown to be mediated by internalin B [41]. *N. meningitidis* invasion of human BMEC is mediated by bacterial outer membrane protein, OspC, binding to fibronectin, thereby anchoring the bacteria to the integrin a5b1- receptor on human BMEC surface [73]. Further studies are needed to understand contribution of these interactions to BMEC invasion and BBB traversal.

Treponema pallidum

Treponema pallidum can invade through the intercellular junction of aortic endothelial cells [74], which suggests that usage of paracellular mechanism of penetration of the vascular endothelium, but it is unclear whether a similar mechanism is involved in *T. pallidum* penetration of the blood-brain barrier. The pathogenic *T. pallidum* adheres to the vascular endothelium and readily penetrates surrounding tissues [75]. Lee and coworkers [75] have also proposed a role of fibronectin in the mediation of the attachment of *T. pallidum* to host cells, including ECs. It is also predicted that *T. pallidum* interacts with laminin with its molecule Tp0751 and may promote tissue invasion [76]. Other studies have supported the specific adhesion of *T. pallidum* to vascular endothelium and separation of basement membranes [75, 77]. Tp0751 binds to laminin-1, -2, -4, -8, and -10. It was also shown that ten amino acids between the positions 98 to 101, 127 to 128 and 182 to 185 in Tp0751 are critical for the laminin attachment [76].

T. pallidum induces the expression of ICAM-1 and procoagulant activity on the surface of HUVEC. ICAM-1 expression in HUVEC is promoted by a 47-kDa integral membrane lipoprotein of *T. pallidum* [78]. 47 kDa lipoprotein also induces other adhesion molecules like VCAM-1 and E-selectin, and promotes adherence of T-lymphocytes to ECs [79]. This indicates an important role of spirochete membrane lipoproteins in ECs activation and translocation.

Borrelia burgdorferi

Neuroborreliosis and earlier described neurosyphilis (*Treponema pallidum)* are prototypes for spirochete infection of the CNS. *Borrelia* strains traverse human BMEC without obvious change in the integrity of the host cells [20]. This translocation is facilitated by host proteases, which are involved in plasminogen activation system and fibrinolysis [80-84]. The fibrinolytic system linked by an activation cascade may lead to focal and transient degradation of tight junction proteins, allowing *B. burgdorferi* to invade the CNS. The role of plasmin in infection is crucial, however, other host proteases like matrix metalloproteases could also take part in the enhancement of translocation [85]. OspE/F-related protein (Erp)-P, ErpA, and ErpC are significant for the binding of plasminogen [86, 87]. High lysine residue contained in these three Erps (nearly 13% lysine residues) indicates that plasminogen binding is lysine dependent.

Variable small protein 1 (Vsp1) of *B. turicatae* has been shown to bind to the BMECs [88] and is predicted to be involved in passage of *Borrelia* through BBB. In addition, *B. burgdorferi* is able to adhere to proteoglycans in the extracellular matrix of the peripheral nerves and ECs [89-91]. *Borrelia* is also capable of stimulating adhesive proteins like E-selectin, ICAM-1, VCAM-1, etc., and modulates adhesion receptors [92-94], that renders host

cells more susceptible to pathogen invasion. Processes in the adhesion receptor modulation and exploitation of cytoskeleton-linked pathways (integrin-associated signaling) by microbes are extensively reviewed elsewhere [95] (Table 2).

Mycobacterium tuberculosis

At least 33 proteins of *M. tuberculosis* play a role in BMEC invasion. Among these, proline glutamic acid-polymorphic GC-rich repetitive sequences (PE-PGRS) family protein, adhesion component transport transmembrane protein ABC transporter, polyprenyl pyrophosphate synthetase and proline glutamic acid (PPE) family protein PPE29 are possibly needed for ECs invasion and/or intracellular survival. Furthermore, transmission electron microscopy revealed that mycobacterial–BMEC interactions induce actin cytoskeleton reorganization and formation of microvilli-like protrusions to promote bacterial internalization into human BMEC [42]. Last but not least, *M. tuberculosis* also owns plasminogen binding and activating molecules (30kDa, 60kDa, and 66kDa cell wall proteins) through which this bacteria may increase local concentration of plasmin/plasminogen to disrupt intercellular junctional molecules [96].

***Citrobacter* spp.**

Citrobacter spp. are gram-negative bacteria and are associated with neonatal meningitis [97]. The unique feature of meningitis caused by *Citrobacter* spp. is their frequent association with brain abscess formation. The pathogenesis of *Citrobacter* spp. meningitis and brain abscess is not well characterized. *C. freundii* is able to invade and cross human BMECs *in vitro*. Invasion of BMECs by *C. freundii* was found to be dependent on microfilaments, microtubules, endosome acidification, and *de novo* protein synthesis. In contrast to other meningitis-causing bacteria, *C. freundii* is able to multiply within human BMECs. This may be a mechanism whereby *C. freundii* traverses the BBB via transcellular route [34].

Listeria monocytogenes

L. monocytogenes, a gram-positive bacterium, causes rhombencephalitis in humans and animals. This pathogen has ability to cross intestine, placenta and the BBB. Internalin B (InlB) is an important protein for the invasion of numerous cell lines, such as HeLa (human epithelial cervical cancer), hepatocytes and human BMECs. Efficient invasion of *L. monocytogenes* depends on the InlB, which binds to VE-cadherin [41]. Surface Vip (Lmo0320), bacterial cell wall anchored protein, is required for mammalian cells entry, including BMEC. This protein is also important in late stages of the infectious process [98].

Chlamydiophila pneumoniae

Chlamydiophila pneumoniae is characteristically a respiratory pathogen but has neuroinvasive character and has been associated with multiple sclerosis (MS) and Alzheimer's disease (AD) pathogenesis. However, scientific evidence for relationship between this organism and neurodegenerative diseases still remains controversial. Potential way of infection is through the junctional complexes between BMEC. *C. pneumoniae* infection may lead to endothelial damage, junctional alterations, BBB breakdown that result in increased expression of the zonula adherens proteins (beta-catenin, N-cadherin and VE-cadherin), and decreased expression of the tight junctional protein occludin. These events may be the basis

for the regulation of paracellular permeability while maintaining barrier integrity during *C. pneumoniae* infection associated with neuropathologies such as MS and AD [2].

Several *Chlamydiophila* ligands have been suggested to mediated attachment including heparan sulfate, chlamydial heat shock protein Hsp70, OmcB and major outer membrane protein (MOMP) [99]. *C. pneumoniae* may reside and replicate in different cell types and induce a chronic immune activation but little is known about the mechanisms of *C. pneumoniae*–induced target cell alteration [100].

Other Neuroinvasive Bacteria

Filamentous hemagglutinin (FHA), surface-exposed and secreted protein, plays main role in the host specificity of *B. pertussis*. Studies with anti-FHA monoclonal antibodies have shown that FHA mimics the native ligand for CR3 integrin on ECs and induces endothelial permeability [101].

Plasmin-binding protein (PAM) of Streptococcus pyogenes is homologous (mimics) with glycolytic enzyme GAPDH. Plasminogen with PAM is activated by streptokinase and this plasminogen remained bound to streptococcal surface. Plasmin bound to bacterial surface inactivates chemo-attractants and modulates tissue tropism. In addition, PAM also plays a role in the breaking of host barriers, e.g., BBB, and promotes dissemination of the bacteria [102].

The zonula occludens toxin produced by *V. cholerae* causes Tj disruption by triggering signaling processes, which include phospholipase C-, PKCα-activation, and actin polymerization. Zonula occludens toxin along with its human homolog zonulin is able to bind surface receptor in the brain [103]. Direct influence of bacterial toxin on the BBB alone or in combination with host's inflammatory mediators such as nitric oxide, TNF-α and IL-1 enhances BBB permeability [104].

5.2. Fungi

Several fungi have been shown to cause CNS infections in humans, either acute or chronic meningitis or space-occupying lesions. Most of the neurotropic fungi are saprobes with a worldwide distribution. A considerable number of cases of CNS fungal infections in immunocompetent hosts have been reported. *Cryptococcus neoformans*, *Candida albicans*, *Coccidioides immitis*. *Histoplasma capsulatum* are the most common causes of fungal meningitis. While fungi like *C. neoformans*, *Cladophialophora bantiana*, *Exophiala dermatitidis*, *Ramichloridium mackenzie*, *Ochroconis gallopava* are considered as true neurotropic fungi [105]. Occurrence of *Aspergillus* spp., *Candida* spp. and *Zygomycetes* in CNS is sporadic, and they may cause lesions in brain.

Cryptococcus neoformans

Cryptococcus neoformans is a common cause of culture-proven meningitis in areas where HIV-1 is endemic [106]. It can be acquired by inhalation to cause a pulmonary infection and meningitis. Brain invasion does not require recruitment of host inflammatory cells [29, 107], which eliminates possibility of Trojan horse mechanism. Recent studies indicate that *C. neoformans* uses a transcellular mechanism of BMEC traversal [29] and

requires protein kinase C-alpha activation [108]. The CPS1 gene is required for *C. neoformans* adherence to the surface protein CD44 of human BMECs [108].

Isc1 gene encodes an enzyme that hydrolyzes inositol sphingolipids is critical for controlling the dissemination of pathogen into the brain. In addition, Isc1 regulates intercellular survival through the protection against acidic, oxidative and nitrosative stresses and phagolysosome [109]. An important virulence factor of *C. neoformans* is urease. Urease is not required for optimal growth in CNS, but recent studies suggest that it is important in pulmonary-to-CNS dissemination process and invasion [110].

Candida albicans

C. albicans is able to adhere, invade and transcytose across BMECs without affecting the integrity of the monolayers by a poorly understood process. *Candida* crosses the BMEC by transcellular way [44]. It remains unclear what structures of *C. albicans* play a key role in invasion and transcytosis in human BMECs. It was shown that expression of the Als1 protein (agglutinin like Als1 protein) is responsible for adherence to HUVEC and epithelial cells [111]. N-terminal domain of Als1 proteins includes three IgV motifs, probable sites responsible for binding activity and the C-terminal conserved hydrophobic sequence has features of the position for glycosylphosphatidylinositol [112, 113]. It is also predicted that interaction between enolase of *Candida* and plasminogen system enhances *C. albicans* traversal through HBMEC [114]. Fibronectin, laminin and vitronectin have been shown to participate in adherence of *C. albicans* to extracellular matrix [115-117]. *C. albicans* invades human BMEC from the apical side, crosses the BMEC, and exits from the basolateral side. The trafficking mechanism is unclear, but the exit of *Candida* cells from the basolateral side could occur by exocytosis or by growth of germ tubes across the human BMEC monolayer [44].

Histoplasma capsulatum

Histoplasma capsulatum is a common cause of fungal infection especially in immunocompromised individuals [118]. *H. capsulatum* may cause meningitis in 5-25% of its victims, especially in AIDS patients. Interaction of *H. capsulatum* Yps3p with microglial cells leads to NF-κB activation via the TLR2 pathway [118]. A deeper understanding host-*Histoplasma* interaction is still needed.

3. Parasites

Plasmodium falciparum

Malaria seems to be a major public health problem in many parts of the tropical world. One of the *P. falciparum* important virulence mechanisms is the ability of *P. falciparum* trophozoites and schizonts to sequester in the vasculature of diverse host organs, including the brain [119, 120]. *P. falciparum*-infected red blood cells express 32-kDa human protein gClqR/HABP1/p32 as a receptor to bind to human brain microvascular endothelial cells [121]. *P. falciparum* erythrocyte membrane protein (PfEMP-1) mediates endothelial binding and affects barrier integrity. PfEMP-1, encoded by the variable *var* gene family, binds to ICAM-1, CD36, chrondroitin sulphate and other trypsin-sensitive binding determinants [122].

Pathogen matures in parasitized red blood cells, which get attached to BMECs. This process is mediated by specific molecular adhesive events. This binding is not solely static but can be a rolling interaction, similar to the early rolling that allows subsequent leukocyte tethering to ECs during physiological responses to inflammatory stimuli [123]. Other0 mechanisms by which *P. falciparum* is able to cross BBB are the exposure of phosphatidyl serine, which promotes adhesion to ECs thrombospondin, and bridging between EC receptors and parasite ligands by molecules such as fibrinogen [124, 125].

Recently, fifty-nine putative *Plasmodium* apoptogenic genes are known to have the potential to cause cell death in parasite-induced cell [126]. It can be hypothesized that increased expression and secretion of soluble factors from infected RBCs contributes to human BMEC activation and apoptosis, which perturbs the BBB and subsequently directly or indirectly induces neuroglial apoptosis.

Trypanosoma brucei

Neurological manifestations of sleeping sickness in man caused by *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* are attributed to the penetration to CNS, but how trypanosomes cross the human BBB remains unclear [127]. The forms of trypanosomes found in the bloodstream efficiently cross human BMECs by a paracellular route [47]. In rodent model, the parasite can pass through the BBB across or between endothelial cells. Interferon-γ has been shown to have an important role in regulating trypanosomal trafficking into the brain [128]. A trypanosome apoptotic factor (TAF) expressed by *T. brucei* that mediates apoptosis in mouse and human-BMECs was identified and characterized earlier [129]. Process of trypanosomal traversal across the human BBB also requires the participation of a PAR-2-mediated calcium signaling pathway. Work of Grab and his colleagues (2004) showed that *Trypanosoma* translocate BBB by generating Ca^{2+} activation signals by parasite cystein proteases. Trypanosomal cathepsin (brucipain) can initiate BBB translocation and increases vascular permeability by interaction with host G protein coupled receptor (also known as 7 transmembrane receptors).

Acanthomoeba

Pathogenic *Acanthomoeba* is common cause of keratitis but sporadically causes fatal granulomatous amoebic encephalitis. The mechanism that the pathogen uses to cross BBB is still unclear. Some studies revealed the ability of several genotypes of *Acanthomoeba* to bind human BMEC and cause cytotoxicity in BMEC [130]. Traversal process may involve both pathogen (adhesins, proteases and phospholipases) as well as host factors (IL-β, IL-α, TNF-α, IFN-γ and host cell apoptosis). The overall consequence of these factors is increased permeability and/or apoptosis of the brain ECs, which encourages BBB disruptions leading to CNS invasion [131]. Adhesion to BMEC appears to be an important step in invasion of *Acanthamoeba*, since non-pathogenic environmental isolates show minimal binding to BMEC [130]. Phospholipases influence the release of arachidonic acid from the cell surface [132, 133]. Arachidonic acid is a prostaglandin precursor that increases BBB vascular permeability and nitric oxide production in BMECs [134]. Similarly, serine proteases and/or mannose-binding protein cause redistribution/alteration of Tj proteins, such as ZO-1 and occludin, contributing to increased barrier permeability [135]. Serine proteases also degrade extracellular matrix, fibrinogen, albumin and plasminogen [136, 137]. In addition, it is

ported that during the process of adhesion to BMEC, *Acanthamoeba* upregulates the oduction of proteases [138].

oxoplasma gondii

Encephalitis is a serious complication of the infection with the obligate intracellular arasite *Toxoplasma gondii*. There are two possible routes by which parasites may cross the BB. *T. gondii* may enter into the CNS through infected cells, such as monocytes and acrophages. Besides, the parasites may infect and destroy ECs [139]. Surface antigen 1 AG1), major tachyzoite surface molecule, has been proposed as a ligand that mediates MEC invasion [140]. Further studies are needed to elucidate the mechanisms that are volved in toxoplasmosis of the central nervous system.

4. Viruses

Viruses probably account for the most cases of meningitis. For the commonest viruses using meningitis—enteroviruses and flaviviruses--this is usually the case; however, viral eningitis in immune-compromised individuals or infants leads to substantial neurological mplications and a significant mortality. Remaining viral meningitis and CNS infections are used by herpes simplex virus (HSV) and flaviviruses, although mumps infection has ently reemerged [141]. Viruses enter the CNS through several mechanisms: i) by ematogenous spread and direct traversal through BBB (enteroviruses), ii) virus particles are ried across in infected leukocytes (mumps, measles or herpesviruses), iii) axonal flow ough peripheral and cranial nerves (polio, rabies and HSV) [141, 142].

The penetration of HIV into the CNS through neurons by axonal flow, as occurs with rpes virus and rabies virus, is less probable because the CD4 receptor, the main receptor t enables HIV to infect the cell, is absent on neurons [143]. The Trojan horse mechanism transport across BBB is considered to play a crucial role in pathogenesis of viral meningitis the late phase of AIDS. This model has gained rapid favor, however, recent studies allenge this model by showing that the vast majority of virions transmitted in trans ginate from the plasma membrane rather than from intracellular vesicles [144].

The mechanisms of BBB disruption during retroviral-associated pathologies are not fully derstood yet. Most of the studies are focused on the effect of soluble molecules secreted by cted lymphocytes on BBB functions and intercellular TJ organization. In case of HIV ction, the viral protein Tat has been shown to induce an inflammatory process in brain othelial cells, or endothelial cell apoptosis [145, 146], and to be able to disrupt the rcellular TJs.

West Nile virus (WNV)-associated encephalitis is characterized by disruption of the od-brain barrier (BBB), enhanced infiltration of immune cells into the CNS, microglia vation, inflammation and eventual loss of neurons [147, 148]. WNV gains entry into the S via the transcellular pathway, without compromising the BBB integrity instead of cellular pathway, in which case it would be expected an increase in WNV RNA at earlier e points, due to passive diffusion [45]. WNV does not induce cytopathic effect and ces an expression of claudin-1 and upregulation of VCAM-1 and E-selectin [149].

Tick-borne encephalitis (TBE) virus causes severe encephalitis with serious sequelae in ans and can be fatal. The mechanisms underlying how TBEV gains access to the CNS are

neither completely understood. There are several hypothetical routes for TBEV traversal across BBB. These include (i) cytokine-mediated BBB breakdown, (ii) "Trojan horse" theory, and (iii) virus entry into the vascular endothelial cells of brain capillaries, transcytosis, and the release of virus into the brain parenchyma [150].

6. Pathogen Translocation and Activation of Signaling Pathway in ECs

Ultimate stage of dissemination for neuroinvasive pathogens is traversal of BBB. This requires active engagement of BMECs wherein formation of docking structure, reorganization of the cytoskeleton, disengagement of TJ complexes and formation of the migration pores are the crucial steps for successful pathogen translocation. These dynamic processes are under the coordinated control of a wide range of signaling pathways, many of which require a crosstalk between pathogen and BMEC through cell surface receptors. Initial transient engagement of the pathogen to BMEC and formation of docking structure between pathogen and BMEC lead to further crosstalk via induction of downstream signaling pathways.

Further, we are discussing about three major pathways that may occur during pathogen translocations.

ICAM-1 Signaling

ICAM-1 has been identified as a key cell adhesion molecule (CAM) in the leukocyte traversal to the CNS [151]. Cross-linking of ICAM-1 results in ICAM-1-mediated *outside-in* signal transduction leading to activation of the tyrosine kinase p60src, phosphorylation of cortactin (substrate involved in cortical actin dynamics) [152], mobilization of intracellular calcium and activation of Rho GTPase (key regulator of actin cytoskeleton). Activation of RhoA mediates phosphorylation of the cytoskeletal associated proteins focal adhesion kinase, paxilin and p130 [153] and thus increases BBB permeability, that may be exploited by pathogen to invade TJs. Clustering of ICAM-1 results in the formation of docking structures (transmigratory cup) (Figure 2), which anchors and partially embraces circulating cells and pathogens. This event plays an inevitable role in the firm adhesion of pathogens to the surface of endothelial cells.

Other downstream functional events have also been proposed for ICAM-1 signaling-mediated BBB evasion. ICAM-1 modulates gene expression through activation of transcription factors such as serum response factor and NFκB [154]. This indicates that ICAM-1 and other CAMs can regulate gene expression and hence cell phenotype; this raises the possibility that CAMs mediated pathways might be evoked during inflammations [155], and probably also during neuroinfections. ICAM-1 signaling also affects status of junctional proteins. ICAM-1 engagement enhances tyrosine phosphorylation of the cell–cell junction that correlates with tyrosine phosphorylation of the adherens junction protein VE-cadherin [79]. VE-cadherin is a key regulator of the EC junction; this suggests that one aspect of ICAM-1 signaling is junctional disengagement. TJs disengagement results in a tightly

controlled and reversible opening that causes little increased permeability. Whether this tightly controlled permeability is sufficient for successful translocation of pathogens across BBB still remain questionable. Data derived from non-CNS endothelium support that ICAM-1-mediated signaling results in VE-cadherin phosphorylation which is necessary for successful transmigration across endothelium [156].

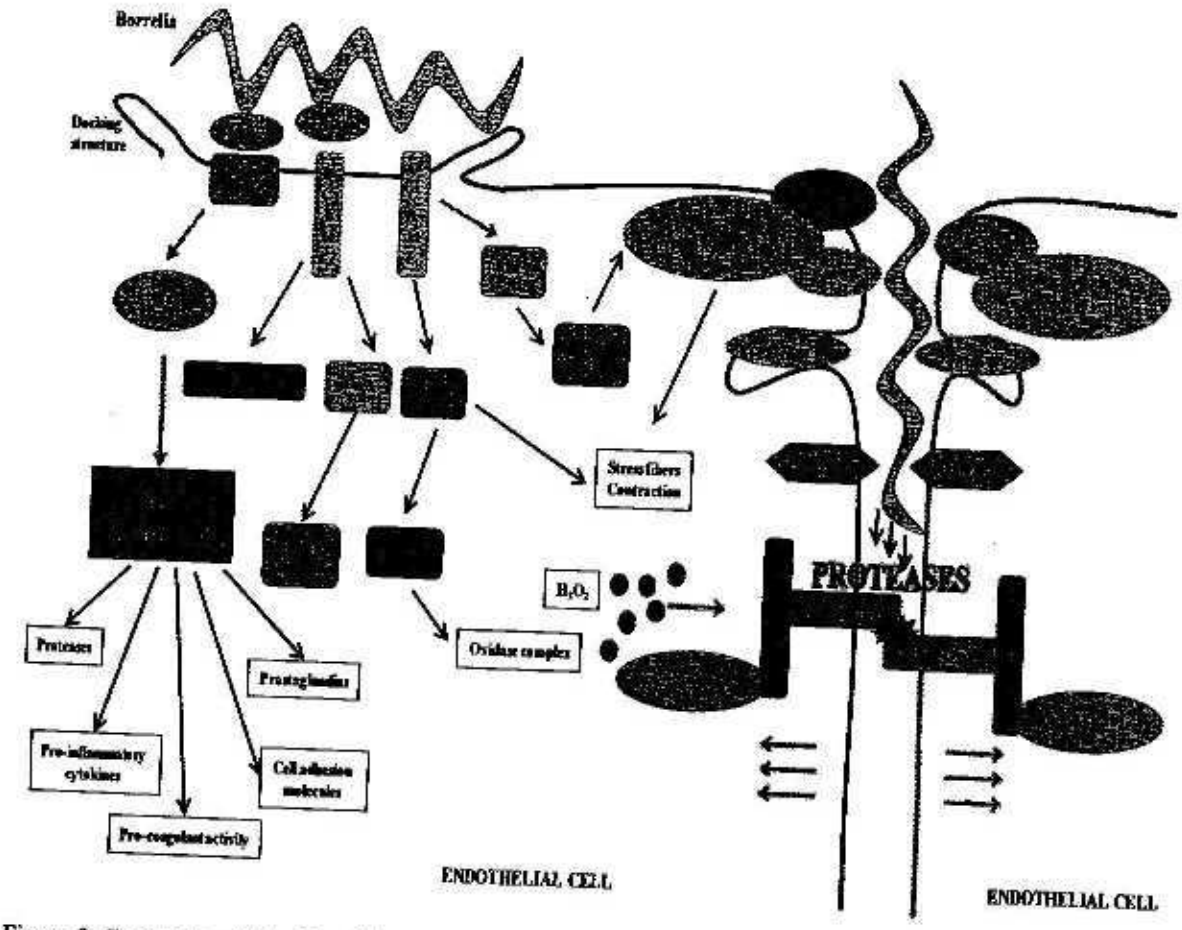

Figure 2. Summary of the signalling events associated with paracellular migration of pathogen through the blood-brain barrier.

Binding to CAMs (ICAM-1 and VCAM-1) triggers diverse signaling pathways within ECs. Phosphorylation of target proteins, particularly the VE-cadherin complex and cortactin, production of ROS, activation of Rho family GTPases and calcium signaling are centrally involved. These pathways all contribute to the junctional disruption and/or actin remodeling that is permissive for leukocyte transendothelial migration to occur.

Adhesion of pathogen ligand to VCAM-1 signals via Rac1-mediated ROS generation. ROS inhibition of phosphatases and activation of redox-sensitive kinases serve to increase phosphorylation of junctional proteins, which leads to junctional disruption and stress fibres contraction.

CD40-mediated signal transduction induces the transcription of a large number of genes implicated in host defense against pathogens. This is accomplished by the activation of multiple pathways including NF-KappaB (Nuclear Factor-KappaB), MAPK (Mitogen-Activated Protein Kinase) and STAT3 (Signal Transducers and Activators of Transcription-3). Activation of CD40 dependent pathway causes augmentation in the production of proteases like MMP-1, MMP-3 and MMP-9 that leads to disruption of junctional molecules, thus facilitates pathogen translocation via paracellular way.

CD40 Signaling

Despite the plethora of studies on CD40 molecule, our understanding about CD40 signaling in BMECs remains incomplete and controversial. CD40-mediated transduction can vary among cell types, furthermore it can vary within the same cell type depending on stage of differentiation [157]. CD40 is a transmembrane-signaling protein expressed on the surface of B cells, monocytes, dendritic, epithelial and endothelial cells. However, under resting conditions, the level of CD40 on microglia is relatively low but is markedly increased upon challenge with pro-inflammatory stimuli such as INF-γ, TNF-α and lipopolysaccharide. Thus, it seems that CD40 on microglia serves as an amplifier of inflammatory responses in the CNS. Cellular responses induced by ligation of CD40 are important in both inflammation and immunity. Signaling via CD40 is mediated through interaction with a family of proteins known as tumor necrosis factor receptor-associated factors (TRAFs). Ligation of CD40 on endothelial cells activates tyrosine kinases and tyrosine phosphatases and affects downstream gene expression. This leads to production of pro-inflammatory cytokines (IL-1, IL-2, IL-4, IL-8, IL-10, IL-12, TNFα and TGFβ) [158], chemokines (MIP-1α, MIP-1β, MCP-1, ABCD-1 and CCR7), matrix metalloproteases (MMP-1, MMP-2, MMP-3, MMP-9, MMP-11 and MMP-13), tissue factor, Cox-2 and nitric oxid (NO). It enhances expression of CD54 (ICAM-1), CD62E (E-selectin) and CD106 (VCAM-1) with a consequent increase in pathogen-cell binding to the endothelium. Recent study in our laboratory shows that only neuroinvasive *Borrelia,* but not non-neuroinvasive strains, make a transient attachment with BMEC surface via CD40 molecule and induce production of ICAM-1, PECAM-1, MMP-1, MMP-3, MMP-9, IL-1 and TNFα. While treatment of BMEC with anti-CD40 antibody and subsequent infection with *Borrelia* causes downregulation of integrins expression, binding to adhesion molecules seems to be the main prerequisite for successful translocation of BBB by pathogens. For example, PECAM-1 appears to play role in guiding pathogen to intercellular junctions (Figure 2). Activation of ICAM-1 results in actin remodeling, which is important in migration across brain EC.

VCAM-1, PECAM-1 and ALCAM Signaling

Other cell adhesion molecules (CAMs), such as VCAM-1, PECAM-1 and activated leukocyte cell adhesion molecule (ALCAM/CD166), also contribute to the signaling that facilitates leukocyte recruitment across the BBB. The relative contribution of these CAMs likely determines the extent of recruitment for different leukocyte sub-populations [159]. VCAM-1 associates with the ezrin/radixin/moesin proteins, which is closely associated with actin cytoskeleton and promotes its remodeling. VCAM-1 downstream pathway is predominantly targeted on intercellular junctions and contributes in gap formation mediated through Rho and Rac-1 activation [160]. It was found that infection of endothelial cells with *E. coli, Chlamydiophilapneumoniae* results in stimulation of wide variety of cytokines, chemokines (MCP-1, IL-6,7,8,9 and 14) and adhesion molecules (VCAM-1, ICAM-1, ELAM-1) through NFκβ activation [161]. *Francisellatularensis* also exploits VCAM-1 as an adhesive molecule and selectively activates its downstream cascade that causes augmentation of CXCL8. CXCL8 appears to affect paracellular permeability, as an inducer of BBB hyperpermeability, to host cells as well as pathogens. Recent studies reveal that CAMs not

ly act as receptors for ligands of pathogens but also act as signal transducers. While many f the relevant molecules in the transmigration cascade have been identified, at present it is ot clear to what extent these molecules mediate passage through the transcellular versus the racellular pathways. Many of VCAM-1-signaling events are similar to those associated ith ICAM-1 clustering. ICAM-1 clustering can lead to VCAM-1 recruitment to the gnaling molecule; therefore, it makes difficult to distinguish between pathways induced by ese two CAMs.

The role of PECAM-1 in regulation of BBB traversal is less understood. It has been own that PECAM-1is employed in leukocyte translocation of endothelium at the site of tercellular junctions. PECAM-1 is adhesion receptor that can transduce stimulatory and hibitory signals [162, 163]. The PECAM-1 also acts as an antagonist of ICAM-1 induced rosine phosphorylation of cortactin and thus inhibits actin cytoskeleton remodeling [164].

Activated leukocyte CAM (ALCAM) is expressed by immune cells and various non-ematopoetic cells including BMEC. The role of endothelial ALCAM at the level of the BB remains to be established, but under pathological neuroinflammatory conditions, it cilitates extravasation of immune cells in CNS that can be mediated via heterotypic teractions with CD6 or homotypic through ALCAM-ALCAM interactions [165]. The sessment of ALCAM and junctional complex protein expression in primary cultures of MEC associated with multiple sclerosis lesions indicates that ALCAM upregulation is sociated with a disturbed junctional and cytoskeletal architecture [166]. There are limited ta about intercellular signaling events, although docking structure was found to be rich in LCAM molecules. It can be suggested that signaling mechanisms described for ICAM-1 d VCAM-1 are most likely mirrored by ALCAM.

7. Exploitation of Host's Proteases by Pathogens to Degrade ECM of BBB

In the earlier parts of this chapter, we saw how pathogens employ various ligands to tivate cell-signaling cascades and take advantage of adhesive molecules and host proteases cross endothelial barriers. Amongst all, two mechanisms mediated by host proteases are most important for pathogen entry into the CNS—the first, plasmin/plasminogen mediated d the second, metalloproteases mediated crossing of BBB. That is why we are trying to borate these two mechanisms in detail.

lasmin and Plasminogen Mediated BBB Translocation

Gram positive and negative bacteria are able to express surface receptors for proteases at digest ECM and components of basal membrane. This is an important strategy of thogens to cross various barriers. Serine protease plasmin degrades many blood plasma oteins, mostly fibrin clots. In serum, free plasmin is quickly inactivated by α_1- and α_2-tiplasmins [167], however, cell surface-associated plasmin cannot be regulated by the um inhibitors and degrades high molecular weight glycoproteins such as fibronectin, minin and collagen IV, which are essential for proper BBB function.

Most of the bacterial plasminogen receptors are extracellular metabolic enzymes [168] that fall into two major categories: (a) filamentous protein structures that are morphologically similar to fibrin–fimbriae proteins; (b) non-filamentous surface proteins, usually abundant proteins, with enzymatic activity and multiple-binding properties [167]. The non-filamentous plasminogen receptors have relatively low affinity for plasminogen, which recognizes the lysine-binding sites of a receptor molecules [169]. Fimbriae and flagella form a major group of plasminogen receptors in gram negative bacteria, whereas, surface-bound enzyme molecules and M protein-related structures possess affinity to plasminogen in gram positive bacteria [86].

The first-time binding of human plasmin to bacteria was reported for group A streptococci in 1987 [170]. Over the next years, exploitation of host's plasmin and plasminogen for proteolysis of ECM, mediated by their surface proteins (Table 2), was showed in many other bacteria like *S. aureus, N. meningitidis, N. gonorrhoeae, Y. pestis* and *B. burgdorferi*. Binding of plasminogen to receptors of *B. burgdorferi, B. hermsii, M. tuberculosis* and group A streptococci takes place via lysine residues [80, 171]. ErpP, ErpA and ErpC proteins are the major plasminogen-binding proteins of *B. burgdorferi* [87]. It has been shown that plasminogen bound to the surface of *B. burgdorferi* can be activated and turned into plasmin by urokinase-type plasminogen activator (uPA) to protect the enzyme from autodigestion [172]. GlnA1, one of the few plasminogen receptors of *M. tuberculosis*, binds host's fibronectin to degrade ECM [173]. *C. albicans* binds both plasminogen and plasmin. Plasminogen receptor binding is mediated by *Candida* enolase, activated by tissue-type plasminogen activator, while inhibited by ε-aminocaproic acid. Binding of fungal enolase to plasmin is also lysine-dependent and can be inhibited with arginine, aspartate and glutamate [114]. Direct binding of plasmin and plasminogen in *Streptococcus* group A is mediated by three receptors: 1) plasminogen-binding group A streptococcal M-like protein, 2) α-enolase, and 3) glyceraldehyde-3-phosphate-dehydrogenase [86, 174]. Surprisingly, *S. pyogenes* protein Prp does not interact with plasminogen and plasmin via lysine, however only via arginine and histidine residues [175]. *S. agalactiae*, a member of the group B streptococci, binds plasminogen only by the glyceraldehyde-3-phosphate-dehydrogenase [71].

Metalloproteases Mediated BBB Crossing

Matrix metalloproteinases/metalloproteases (MMPs) are zinc- or cobalt-dependent enzymes that play a crucial role in normal function and development of CNS. This large group includes collagenases, gelatinases, stromoelysins, matrilysin, membrane-type metalloproteinases and metalloelastases. MMPs differ in cellular sources and substrate specificity, but structural domains remain the same [176]. MMPs may alter inflammatory cytokine activity, cleave cell surface receptors, activate caspase-3, and regulate other MMPs family members [177-181]. Together with serine and cysteine proteases, they are able to degenerate and remodulate connective tissues. This damage leads to extravasation of blood-borne proteins, formation of brain edema and neuronal damage. Pathogens exploit this extravasation to cross various barriers including BBB.

Basal level of MMPs expression in the brain is low, however, under pathological conditions (Alzheimer's disease, multiple sclerosis, aneurism formation and cerebral ischemia) and infections, the level elevates markedly. MMPs are expressed by most of the

resident CNS cells such as ECs, astrocytes, microglia and neurons, together with the infiltrating immune cells [182-184].

Infection of BMECs with neurotropic viruses has been connected with decrease and/or redistribution of Tj proteins *in vitro* and *in vivo* [185, 186]. Lentiviruses, like HIV-1 and FIV, are able to infect the brain and cause chronic neurological disease. MMP activity is highly increased in HIV-infected cells migrating into CNS. Human neuronal and glial cells infected with this virus have been shown to produce large amounts of MMP-2 [187]. During the West Nile virus infection, it has been observed that inflammatory cytokines, such as TNF-α, macrophage migration inhibitory factor and MMP-9, play an essential role in BBB disruption [188-190]. It is likely that activation of MMP-9 in West Nile virus-infected astrocytes is via MMP-3 [191].

MMPs also play role in bacterial meningitis. In fact, MMP-8 and MMP-9, but not MMP-2 and MMP-3, are upregulated in cerebrospinal fluid (CSF) during the meningitis caused by *H. influenzae, N. meningitidis* and *S. pneumoniae* [192]. *T. denticola* [193] and cell wall of *S. suis* strongly stimulates production of MMP-9, whereas zinc metalloproteinase ZmpC of *S. pneumoniae* cleaves human MMP-9 into its active form [194], which leads to the tissue destruction and BBB disruption [195]. MMP-8 is also associated with tissue destruction during *S. sanguinis, N. meningitidis* and *Fusobacterium nuclearum* infections [196, 197]. Tissue destruction by *N. meningitidis* is a consequence of proteolysis of Tj protein occludin by MMP-8. Furthermore, MMP-8 activity also participates in BMECs detachment from the underlying matrix that arose during extended time of infection with *N. meningitidis* [197]. Meningitis caused by *S. pneumoniae* in the neonatal rats is associated with the higher expression of MMP-3, MMP-8 and MMP-9 whereas, in rabbits only MMP-2 and MMP-9 are found to be responsible for the impairment of BBB and blood–CSF barriers [198]. *M. tuberculosis* uses MMPs more effectively for the tissue and neural damage. Infected monocytes induce MMP-9 secretion from astrocytes, afforded by IL-1ß and TNF-α [199]. The importance of MMP-9 in BBB disruption was proved elsewhere by diminishing the process of BBB disruption in MMP-9 knockout mice [200]. *B. burgdorferi* causes the release of MMP-1 and MMP-9 from human cells, while plasmin-coated *B. burgdorferi* stimulates pro-MMP-9. This triggers a cascade that leads to degradation of basement membranes [85]. *B. burgdorferi-Anaplasma phagocytophilum* co-infection of human brain microvascular endothelial cells leads to increased reductions in transendothelial electrical resistance and elevated production of MMPs (MMP-1, -3, -7, -8, and -9) [201]. Together with other factors, such as cytokines and chemokines, this expression leads to increase in vascular permeability and inflammatory responses. In fact, co-infection results in the higher production of MMPs than *B. burgdorferi* alone [201]. *Acanthamoeba* serine proteases have been demonstrated to disrupt human BMEC monolayers [138]. Moreover, to the serine proteases, *Acanthamoeba* is able to use metalloproteinase activity [137]. In general, expression of MMP-9 during the bacterial meningitis is 10- to 1000-fold higher than in the cases of viral meningitis [202].

CONCLUSION

Almost all bacteria that are pathogenic to humans have the potential to infect the CNS but it is unclear why only a relatively small number of pathogens account for most clinical cases. Recent studies with the *in vitro* BBB model provided much insight to the mechanisms of microbial translocation of the BBB. Similarly, multiple microbial determinants have been shown to contribute to the bacterial penetration of the BBB. Complete insight on pathogen-host BMEC interactions that involve in translocation is crucial for understanding the molecular basis of pathogenesis of neuroinvasion. Nonetheless, identification and molecular characterization of these bacterial and host factors mediating the bacterial penetration may lead to new avenues in the development of more specific vaccines strategies.

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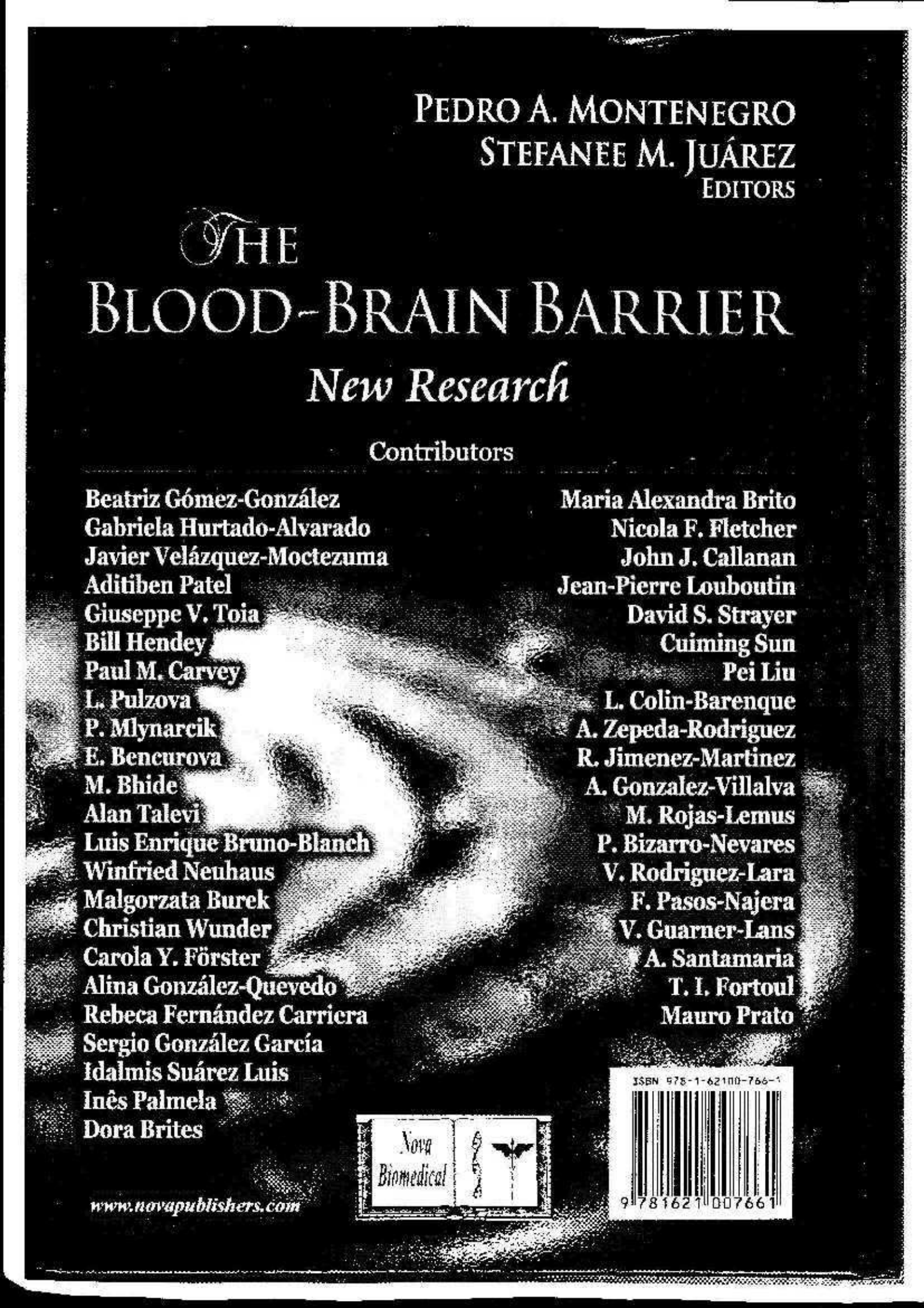

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