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Blood-Brain Barrier Disruption and Encephalitis in Animal Models of AIDS

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1. Introduction

The pathogenesis of HIV/SIV encephalitis (HIVE/SIVE) remains incompletely understood, but is associated with alterations in the blood brain barrier. In animals infected with pathogenic strains of simian immunodeficiency virus (SIV), such as SIVmac239 and SIVmac251, the virus can be consistently found in the central nervous system (CNS) within 10 to 14 days of infection: at the time of peak viremia (Lackner et al., 1994). This also appears to be true in human immunodeficiency virus (HIV)-infected humans, but the number of cases examined during peak viremia is very small (Davis et al., 1992). In SIV-infected macaques at this early time point, endothelial cells of the blood-brain barrier (BBB) are activated and integrity of the BBB is compromised (Stephens et al., 2003). As viral loads decline toward set point at roughly two months post infection the endothelial activation subsides and BBB integrity is largely restored (Sasseville et al., 1995, Lackner et al., 1994, Annunziata, 2003, Zink et al., 1998). However, in the terminal phases of disease, viral loads rise and approximately one third of animals develop SIV encephalitis (SIVE), which is associated with breakdown of the BBB.

The exact mechanisms of BBB disruption are unclear, but it is known that numerous resident and transitory cell populations in the CNS can be infected, with CD14-positive perivascular macrophages being the primary productively-infected cell type (Little et al., 1999, Gorry et al., 2003, Bissel and Wiley, 2004, Ryzhova et al., 2002, Liu et al., 2004, Brack-Werner, 1999, Trillo-Pazos et al., 2003, Williams et al., 2001, Fischer-Smith et al., 2001). Nervous system manifestations associated with HIV infection of humans or SIV infection of rhesus macaques include an encephalitis (SIV or HIV encephalitis, SIVE/HIVE) characterized by astrocytic and microglial activation and scattered perivascular aggregates of mononuclear cells and multinucleated giant cells. These perivascular lesions contain large numbers of HIV/SIV-infected cells, the majority of which are monocyte/macrophages. The presence of cells productively-infected with SIV/HIV in the parenchyma has been shown to induce a response in astrocytes (Nath, 1999, Tyor et al., 1992, Persidsky et al., 1999, Persidsky et al., 2000) which in turn may lead to decreased tight junction protein expression and a leaky BBB (Dallasta et al., 1999, Persidsky et al., 1997, Moses and Nelson, 1994, Boven et al., 2000, Luabeya et al., 2000, Andras et al., 2003, Annunziata, 2003, Kanmogne et al., 2005, Kanmogne et al., 2007, MacLean et al., 2004b, Persidsky, 1999).

Astrocytes, along with microglia, are resident cells in the brain involved in inflammation. Their role during inflammation is not well understood; it is believed that both cell types are

involved in propagating and limiting inflammation (Kielian, 2004). Astrocytes and microglia are the primary cell types found in glia scar formation. They serve a vital role during injury to the brain: both astrocytes and microglia are capable of promoting an inflammatory response, but are also known to have cytoprotective and anti-inflammatory effects (Hauwel et al., 2005, Park et al., 2003). The complex nature of astrocytes' chemokine response has recently been shown to vary by pathogen (McKimmie and Graham, 2010).

2. Overview of viral encephalitides

There are numerous viruses that can cause encephalitis. For some of these viruses the encephalitis is such a prominent part of the subsequent disease that “encephalitis” is part of the name. Examples include Eastern, Western and Venezuelan encephalitis viruses and St. Louis encephalitis virus all caused by arthropod borne (arbo) viruses that belong to several different virus families (Togaviridae, Flaviviridae) (Adams 2008 and Ciota 2009). In most instances these “encephalitis viruses” cause disease by targeting neurons. In contrast lentiviruses of the family Retroviridae, such as HIV and SIV, which are the major focus of this review, cause disease by a much less direct means.

2.1 Lentiviral encephalitis

The precise mechanism of lentiviral entry to brain is still a subject of some debate. In 1982, Bill Narayan postulated the “Trojan Horse” hypothesis whereby visna virus (one of the first lentiviruses described in detail) entered brains of sheep and goats by hiding within circulating monocytes and then once in the brain, emerged to cause disease (Narayan et al., 1982). It has been proposed that circulating monocytes enter the brain during normal immune surveillance (Williams and Hickey, 1995). However, this remains an issue of debate (Fischer-Smith and Rappaport, 2005). Regardless, the predominate cell infected early in infection of the brain is the CD14⁺ monocyte-derived macrophage (Williams et al., 2001).

2.2 Simian immunodeficiency virus infection

The simian and human immunodeficiency viruses are closely related with HIV having originated from at least two cross species transmission events from monkeys to humans in West Africa in the mid 20th century (P Marx, personal communication and (Worobey et al., 2010). Infection of macaques (primarily rhesus macaques—*Macaca mulatta* and Pigtail macaques – *M. nemestrina*) with SIV follows a near identical course to HIV infection of humans with a peak viral load approximately two weeks following infection, subsiding to a viral set point which rises again with development of AIDS. The disease in brain also follows a similar course. SIV and HIV infection have, in addition to acute and terminal phases, a chronic, relatively asymptomatic, phase, during which very little is known about the physiology and pathology (or lack thereof) in brain. For this reason, we will focus on the acute and terminal stages of infection when encephalitis is an issue.

2.2.1 Acute infection

The precise mechanisms involved in the recruitment of the first viral-infected cell into the brain is the topic of much speculation and debate, although increased expression of VCAM-1 (CD106) by brain endothelial cells is a possibility (Sasseville et al., 1995, Sasseville et al., 1992). CD106 is one of several vascular adhesion molecules involved in directing leukocyte

recruitment to tissues (Luster et al., 2005). Expression of CD106 was not limited to areas immediately adjacent to viral-infected cells, but was diffuse throughout brain, remaining elevated through at least 23 weeks post infection (well beyond peak viral load and establishment of viral set point). We have shown that CD106 expression is upregulated on endothelial cells and astrocytes following incubation with either viral-infected cells or their supernatants (MacLean et al., 2004a, MacLean et al., 2004b), and by others on astrocytes using Theiler's Murine Encephalomyelitis Virus (Rubio et al., 2010). That cell-free virus was able to stimulate endothelial cells to express CD106 may explain the diffuse staining earlier observed by Sasseville *et al.*

Both HIV and SIV use two cellular receptors in combination for infection: the CD4 molecule and a chemokine receptor, the two most common being CCR5 and CXCR4 (Moore et al., 2004). Monocyte/macrophages express these receptors and thus SIV and HIV are macrophage tropic (Salazar-Gonzalez et al., 2009). During early SIV infection, the predominate cell type productively-infected in brain is the monocyte-derived macrophage (Williams et al., 2001). Due to the many similarities between HIV infection of humans and SIV infection of macaques, SIV infection of macaques, particularly of Indian-origin rhesus macaques, has become the most widely used model for HIV pathogenesis studies.

2.2.2 Terminal disease

In humans with symptoms of AIDS dementia complex (the clinical spectrum of illness that includes individuals with HIV encephalitis), there are altered subpopulations of circulating monocytes; CD14 expression is lower, and CD16 and CD69 are both increased (Pulliam et al., 1997, Zhou et al., 2007, Munsaka et al., 2009). Similar changes in monocyte / macrophage populations are also observed throughout disease progression in macaques infected with SIV (Bissel et al., 2006b, Bissel et al., 2006a, Kuroda, 2010, Kim et al., 2005, Williams and Hickey, 2002).

While circulating monocytes are not thought to be productively-infected, the increased numbers of primed monocytes would likely lead to an increased potential for trafficking of cells capable of being infected to brain. The presence of infected monocytes is known to activate endothelial cells of the BBB to express CD106 (MacLean et al., 2004a, MacLean et al., 2004b) and leads to disruption of tight junction proteins including ZO-1 and claudin 5 (Andras et al., 2003, Ivey et al., 2009b, Kanmogne et al., 2007, Luabeya et al., 2000, Persidsky et al., 2006, Huang et al., 2009).

In contradistinction to CD106 expression, the loss of tight junction proteins is largely limited to areas close to viral infected cells (Luabeya et al., 2000, Andras et al., 2003, Kanmogne et al., 2005, Kanmogne et al., 2007, Persidsky et al., 2006), and Renner et al, in press. In those areas where encephalitis is observed, the loss of tight junction protein expression can extend over 150µm (MacLean et al., 2005). As with primary infection, productively-infected cells in brain are largely monocyte-derived macrophages, including microglia in close proximity to blood vessels (Roberts et al., 2004b, Gonzalez-Scarano and Martin-Garcia, 2005). The conceptual framework for interactions of the various cell types involved is summarized in Figure 1.

3. Blood-brain barrier disruption in HIVE/SIVE

As outlined above, lentiviruses are thought to enter the brain within circulating infected monocytes during immune surveillance. Numerous studies have been undertaken to

determine the reasons underlying increased monocyte migration into brain following lentiviral infection. HIV-infected leukocytes are primed for adhesion (Hallett, 1995), having already shed L-selectin, and increased expression of CD11b/CD18 compared with monocytes from healthy controls (Elbim et al., 1999). Therefore, it is possible that even barely increased levels of chemokines expressed within the parenchyma would lead to increased migration of monocytes. Recent studies have shown that glial cells are stimulated to produce chemokines in response to inflammatory cytokines (Renner et al., 2011, Thompson and Van Eldik, 2009) known to be secreted by SIV-infected macrophages (Orandle et al., 2002). Therefore, the role played by glial cells and tight junctions requires further discussion.

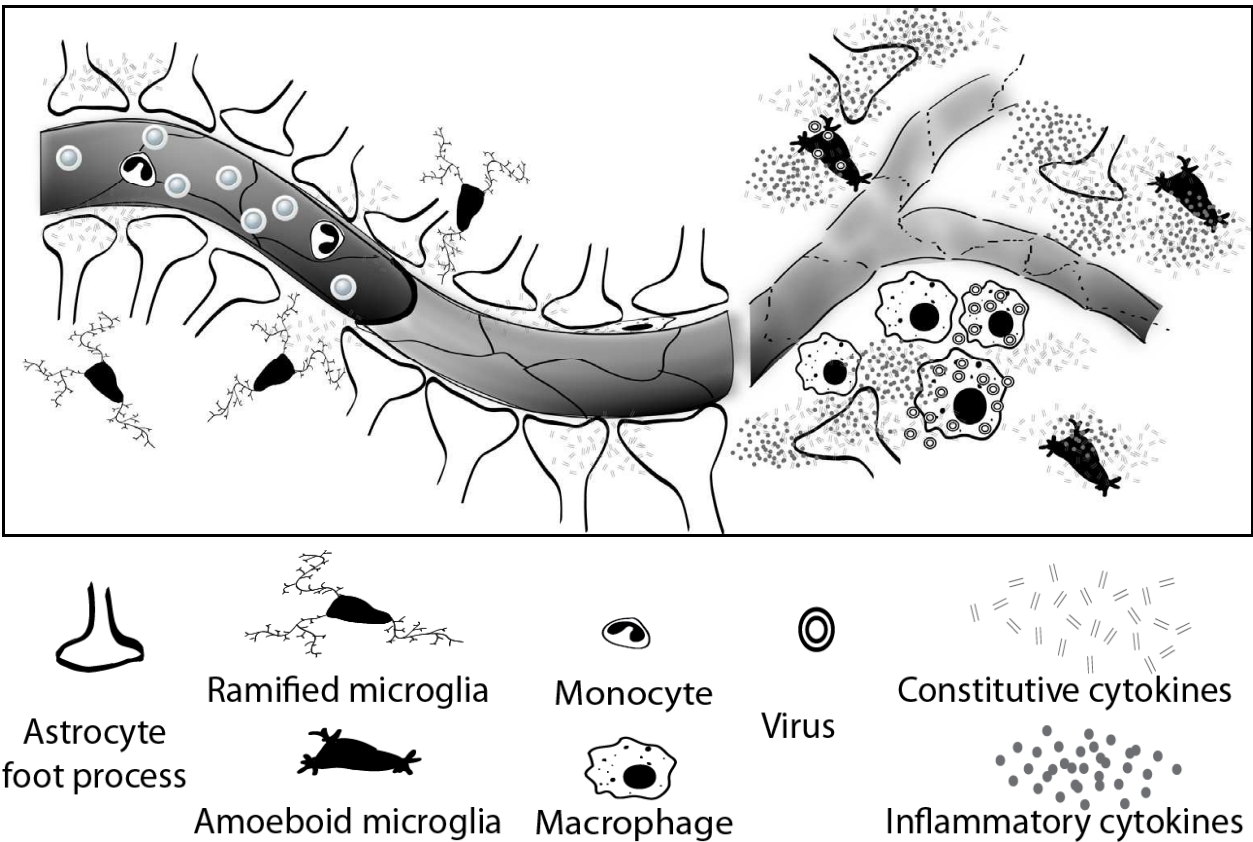


Fig. 1. Schematic of key players in the development of SIV encephalitis. At left, a cutaway section of a cerebral microvessel showing circulating blood cells. At center, normal blood vessel with tight junctions (solid lines) evident between endothelial cells. Astrocyte foot processes are highly evident with occasional microglia. Low levels of cytokines and chemokines are expressed. At right a microvessel in an encephalitic lesion, showing disrupted junctions (dashed lines), leakage of serum proteins into parenchyma, displaced astrocyte foot processes and increased cytokines/ chemokines concomitant with increased numbers of perivascular macrophages.

3.1 Tight junction proteins

The primary defining feature of the blood brain barrier (BBB) is the presence of tight junction proteins between brain microvascular endothelial cells (BMEC). Immediately

subadjacent to the endothelial cells, and anchoring them to the underlying tissues, is the basement membrane which is composed largely of Type IV collagen and laminin. Perivascular macrophages and the foot processes of astrocytes and microglia surround the endothelial cells (Hickey and Kimura, 1988, Graeber et al., 1992, Streit and Graeber, 1993, Lassmann et al., 1991).

Tight junctions are a fibrillary network of transmembrane proteins that can be phosphorylated to regulate physiologic processes such as replacement of perivascular macrophages by circulating monocytes. This phosphorylation can function differently depending if the stimulus is from the luminal or parenchymal side of the BBB. The presence of adhesion molecules on the luminal surface of BMEC is very important for leukocyte extravasation into the CNS (see our recent review for further details (Ivey et al., 2009a)). Tight junctions consist of at least 40 transmembrane proteins, anchorage proteins and tight junction-associated proteins in the membrane and cytosol of endothelial cells. Tight junctions are characterized as having high transendothelial electrical resistance values between 1000 and 1500 Ω/cm^2 (Butt et al., 1990).

A recent study by Strayer et al. has shown that either cell-free or cell-associated gp120 (the outer envelope glycoprotein of HIV) leads to increased matrix metalloproteinase 9 (MMP9) expression which causes decreased expression of laminin and the tight junction protein claudin 5 (Louboutin et al., 2010). A possible mechanism for this could be mediated through focal adhesion kinase, which has been shown to be upregulated in areas of increased neurovascular permeability (Lee et al., 2010).

3.2 Signalling pathways in BBB disruption in HIVE/SIVE

We have recently shown that viral infected macrophages are important in disruption of the BBB *in vitro* (MacLean et al., 2004a, MacLean et al., 2004b), *ex vivo* (Ivey et al., 2009b, Renner et al., 2011) and *in vivo* (Renner et al., in press). The precise mechanisms of BBB disruption are a subject of active research by numerous groups (Luabeya et al., 2000, Andras et al., 2003, Kanmogne et al., 2005, Kanmogne et al., 2007, Persidsky et al., 2006). All of these distinct signal transduction mechanisms have a common factor, however: the tight junctions are linked to the actin cytoskeleton, and the dynamics of the cytoskeleton are therefore important regulators. The importance of cytoskeleton activation will be revisited later when discussing glial cell activation.

4. Astrocytes

4.1 Summary of astrocytes in encephalitis

As illustrated in Figure 2, astrocyte foot processes are closely apposed to BMEC and ensheath more than 60% of the vessel exterior (Mathiisen et al., 2010). Through these contacts astrocytes are able to affect changes in BBB integrity during health and disease, and recruit or repel inflammatory cells through cytokines (Figure 2).

4.2 Role of astrocytes in BBB physiology

The BBB is formed during early infancy in primates (Bayer et al., 1993). The exact mechanisms underlying BBB formation are not clear, but it is known that astrocytes are critical in both maturation and maintenance of the barrier integrity (Willis et al., 2004, Al Ahmad et al., 2010). Astrocytes also act to repel circulating immune cells through secretion

of eotaxin (Cardona et al., 2003), reinforcing the brain's immune-privileged status in conjunction with the selective physical properties of the BBB.



Fig. 2. Schematic of role of astrocytes in pathogenesis. Normal astrocytes (at left) have foot processes ensheathing over 60% of the endothelium and express low levels of GFAP and cytokines / chemokines. In encephalitis, there can a loss of connection to the endothelial cells, increased cytokine / chemokine secretion and altered expression of intermediate filaments, including GFAP and peripherin (right).

4.3 Astrocytes and signaling in encephalitis

Astrocytes are the primary cell type found in glia scar formation (Voskuhl et al., 2009, Kielian, 2004), and secrete cytokines and chemokines to elicit increased trafficking of leukocytes into the brain (Renner et al., 2011, Cota et al., 2000, Eugenin et al., 2006). Astrocytes also may provide a role for the resolution of inflammation by reducing the secretion of pro-inflammatory cytokines and increasing anti-inflammatory processes (Kielian, 2004, Hauwel et al., 2005, Park et al., 2003).

Decreased BBB integrity early in SIV/HIV infection allows latently-infected monocytes to enter the brain (Fischer-Smith and Rappaport, 2005). Circulating virus could induce BMEC to express CD106 diffusely (Sasseville et al., 1995, Sasseville et al., 1992) leading to increased monocyte migration into brain, where they become productively infected. Astrocytes respond to these macrophages resulting in a wide-range of cellular changes referred to as astrogliosis.

4.3.1 Astrogliosis

On activation, astrocytes undergo a morphological change: most notably an increase in ramification concomitant with upregulation of GFAP, and thickened processes. We have also observed some astrocytes in the proximity of SIV lesions to express peripherin, an alternative type III intermediate filament not normally expressed in brain (Mathew et al., 2001). Immunologically, astrocytes respond to HIV/ SIV infection through increased production of inflammatory cytokines. As outlined above, the predominate inflammatory cell type in HIVE/SIVE is the monocyte-derived macrophage. The chemokines upregulated by astrocytes in HIVE/SIVE are largely specific to monocyte/macrophages (Renner et al., 2011, Sasseville et al., 1996). This suggests the possibility of a positive feedback system being initiated: a productively-infected macrophage induces nearby astrocytes to upregulate secretion of macrophage-specific chemokines, leading to lesion formation.

The cytokine response of astrocytes includes a cornucopia of molecules including a variety of cytokines and chemokines. It is intriguing that astrocytes will secrete a different “barcode” of cytokines and chemokines in response to different classes of stimuli

(McKimmie and Graham, 2010). Below we discuss key cytokines and chemokines that are thought to play a role in SIVE/HIVE.

4.3.2 Expression and secretion of selected cytokines

Productively-infected macrophages in the encephalitic brain express Tumor Necrosis Factor alpha (TNF- α) (Orandle et al., 2002). TNF- α receptors are present in the non-encephalitic brain (Shaw and Greig, 1999), such that normal brains are primed to respond quickly to low levels of TNF- α . TNF- α induces increased chemokine production and secretion by astrocytes, and these chemokines induce monocyte migration preferentially over lymphocytes (Renner et al., 2011).

Vascular Endothelial Growth Factor (VEGF) promotes proliferation of BMEC, resulting in reorganization of the cytoskeleton and TJ proteins. This induces a decrease in BBB integrity, creating a permissive environment for monocyte migration, and also bidirectional leakage of proteins across the BBB. A possible mechanism for the VEGF pathway could be as follows: tat binds to the VEGF receptor (Nyagol et al., 2008). The VEGF receptor binds to focal adhesion kinase (Garces et al., 2006), increases of which have been implicated in BBB disruption (Ivey et al., 2009b).

Other pro-inflammatory cytokines, including interferon- γ and IL-6 are upregulated in the encephalitic brain, with far-reaching effects in neuroinflammatory events (Roberts et al., 2004a). The complement pathway is also known to be induced through interferon- γ and IL-6 signaling, propagating inflammation in the area surrounding a lesion/lesions.

4.3.3 Expression and secretion of selected chemokines

An early study of chemokine expression in brains of macaques infected with SIV showed increased CCLs 3-5 & 7, and CXCL10 (Sasseville et al., 1996), although no increase in CCLs 2 or 8 nor CXCL8 was observed in this definitive study, other later studies have “muddied the waters” somewhat: Penton-Rol used dexamethasone to stimulate cells to have increased CCL2 receptors before infecting with HIV 89.6 (Penton-Rol et al., 1999). The Clements group at Johns Hopkins has shown increased CCL2 mRNA in brain extracts using a highly accelerated encephalitis model (Witwer et al., 2009), although mRNA does not always equate with secreted protein. Additionally, the Berman group at Einstein College of Medicine has shown numerous effects of CCL2 on HIV-infected macrophages (Eugenin et al., 2003, Eugenin et al., 2006). CCL2 was among several chemokines in CSF that was not upregulated in one study using humans infected with HIV (Kolb et al., 1999), although IP-10 was upregulated. In contrast, CCL2 was increased in pigtail macaques that develop encephalitis (Mankowski et al., 2004).

The precise cell types producing these chemokines were not identified in these studies. CCL2 mRNA was upregulated in cultured astrocytes, but remained at low levels compared to CCL7, suggesting a role for CCL7 in HIV-related encephalitis (Renner et al., 2011).

Even under noninflamed conditions CCL7 is expressed in the brain (Renner et al., 2011, Sasseville et al., 1996), which could contribute to basal levels of monocyte migration into the brain for “routine surveillance” (Williams and Hickey, 1995). That CCL7 is upregulated by astrocytes in response to cytokines present in encephalitic brains gives a potential role for controlling monocyte migration during encephalitis as well (Sasseville et al., 1996, Renner et al., 2011).

5. Microglia

Microglia are the resident macrophages in brain. These cells are believed to be derived from bone marrow, and present in brain from birth with no replenishment of these cells during the life of an individual (Williams and Hickey, 1995). In normal, healthy brain, microglia play a surveillance role. The high surface area to volume ratio is indicative of a cell “sampling” its environment (Figure 2). On activation, fine processes are no longer visible, with the microglia taking on a more amoeboid morphology. In SIV infection microglia can be recruited and productively-infected themselves (Gonzalez-Scarano and Martin-Garcia, 2005). These cells can also be induced to upregulate CD163 (Roberts et al., 2004b, Borda et al., 2008) which can be quite prominent in areas of BBB breakdown.

5.1 Summary of gliosis

The overall response to SIV or HIV infection of the CNS which primarily involves infected monocyte/macrophages is pro-inflammatory. Neuroinvasion by monocyte/macrophages initiates a positive feedback loop stimulating glial cells to respond further. Glial involvement increases not only the intensity but the area affected by inflammation, damaging local neural circuitry, and recruiting monocytes into the parenchyma. While the glial inflammatory response may seem detrimental, ablation of monocytes led to increased tissue damage in a model of retinal inflammation, implicating lesion formation as a partially neuroprotective response (London et al., 2011). Although the initial monocytes entering the brain carrying HIV/SIV may not be recruited by glial signaling, later neuroinvasion is likely driven, at least in part, by gliosis.

6. Modeling HIVE *in vitro*

6.1 Simple models – single cell type

Numerous groups have used *in vitro* models for determining the cellular and molecular events occurring during the development of HIVE. These have ranged from utilizing single cell types including astrocytes (Renner et al., 2011, Eugenin and Berman, 2007), or endothelial cells (MacLean et al., 2001, Oshima et al., 2000) to tease out initial activation steps. An *ex vivo* single cell type model has also been used recently to examine BBB disruption whereby intact microvessels are extracted and incubated with the lentiviral-infected macrophages (Ivey et al., 2009b). This method has an advantage of maintaining original tight junction orientations. However, the downside is that this technique is only suitable for assessing interactions for the first couple of hours due to viability issues with the microvessels.

6.2 2.5D model of BBB *in vitro*

More complex models involve monolayers of endothelial cells cultured above astrocytes, either on top of a collagen matrix (Biegel and Pachter, 1994, Biegel et al., 1995) or on opposite sides of a membrane (Lu et al., 2008, Persidsky et al., 1997, Eugenin et al., 2006). The coculture allows tight junction formation to occur. The endothelial cells are still a single monolayer, and for this reason, the model is referred to as 2.5D, rather than 3D. These models have been used to examine mechanisms of encephalitis.

6.3 3D model of BBB *in vitro*

A further refinement involved the growth of endothelial cells in tubes (Stanness et al., 1999), or of culturing the endothelial cells within a matrix surrounded by glial cells allowing the

endothelial cells to form tubes with astrocytes extending processes to induce tight junction proteins (Al Ahmad et al., 2010). Collagen gels were used to create 3D cultures with BMEC and astrocytes. Al Ahmad et al. showed that BMEC alone were unable to localize tight junction proteins to the cell border. Coculture with astrocytes corrected this, with Claudin5 and ZO1 localized to functionally relevant positions. This clearly demonstrates the necessity for including astrocytes in BBB culture models. As of yet, these models have not been applied to encephalitis studies.

A further model that has been utilized is slice cultures (Renner et al., 2011, Norberg, 2004). These *ex vivo* models are essentially a complex co-culture that preserves cell:cell ratios, and functional spatial relationships. This model allows one to determine precise cell types secreting chemokines in response to viral-infected cells. It will also prove useful for mechanistic studies of neuropathogenesis.

7. Summary of SIV model of encephalitis

Under normal conditions the brain allows only limited access by immune cells. Early in HIV infection the virus enters the brain through normal trafficking. This leads to a transient increase in BBB permeability, and a localized immune response. As the disease progresses to encephalitis the immune response is dramatically increased, marked by a loss of tight junction integrity, gliosis, and formation of multinucleated giant cells in the parenchyma.

The parallel between the neuropathogenesis of HIV in humans, and SIV in the rhesus macaque has led to the establishment of rhesus macaque as the predominant *in vivo* model for HIV. The use of *in vitro* models allows for precise control for investigating pathways of lentiviral neuropathogenesis.

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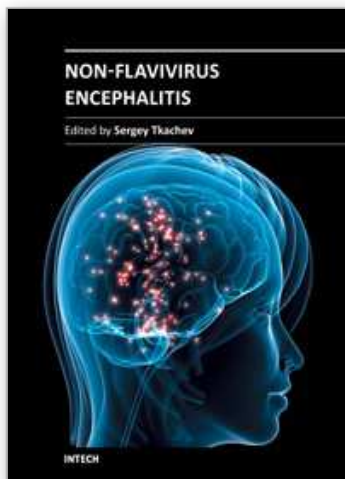
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This book covers the different aspects of non-flavivirus encephalitis of different etiology. The first section of the book considers general problems of epidemiology such as study of zoonotic and animal vectors of encephalitis causative agents and methods and approaches for encephalitis zoonoses investigations. The members of different virus species are known to be the causative agents of encephalitis, so the second section of the book is devoted to these viral pathogens, their epidemiology, pathology, diagnostics and molecular mechanisms of encephalitis development by such viruses as HIV/SIV, herpes simplex virus type 1 and equine herpesvirus 9, measles virus, coronaviruses, alphaviruses and rabies virus. The next section of the book concerns the study of protozoan pathogens such as toxoplasma and amoebae. The last section of the book is devoted to multicellular pathogen as human *Filaria Loa Loa* - a filarial worm restricted to the West Africa.

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