The role of CNS immunity in the clearance of rabies virus

Authors:

Aurore Lebrun[1]
Douglas Craig Hooper[1,2]

Authors' note:

Jefferson Center for Neurovirology, Department of Cancer Biology[1] and Neurological Surgery[2], Thomas Jefferson University, Philadelphia, PA, USA

Address correspondence to:

Drs. Aurore Lebrun or D. Craig Hooper, Department of Cancer Biology, Thomas Jefferson University, 1020 Locust Street, JAH Room 452, Philadelphia, PA 19107-6731;

E-mail:
aurore.lebrun@jefferson.edu;
E-mail:
DouglasC.Hooper@jefferson.edu

ABSTRACT

Rabies is a zoonotic disease caused by the neurotropic rabies virus (RABV). In the absence of treatment the infection is nearly always fatal for the host. Extensive research aimed at better understanding RABV pathogenicity and immunogenicity has led to the characterization of a wide array of RABV strains. Comparative studies between pathogenic and attenuated RABV strains have provided insights into the mechanism by which the virus can be cleared from CNS tissues. In this context, attenuated RABV represents a unique model in which the timely development of an unconventional non-inflammatory rabies-specific neuroimmune response is the key determinant of host survival. Highly pathogenic wild-type rabies viruses have evolved strategies to evade the host immune response and spread through the maintenance of blood-brain barrier integrity and an intact neuronal network. The focus of this review is to provide a synopsis of the differences in the CNS immune responses to pathogenic and attenuated RABV strains and their relevance for the development of new treatment strategies.

Keywords: rabies virus, CNS, immunology

Non standard abbreviations: RABV: rabies virus; BBB: blood-brain barrier, VNA: virus neutralizing antibody; Ab: antibody; Ag: antigen; Ig: immunoglobulin

1. Introduction

Rabies is an ancient disease with historical records going back to antiquity (Adamson, 1977; Maurya et al., 2015). It is one of the most highly lethal infectious diseases known to mankind with nearly a hundred percent mortality. To date, rabies still accounts for over 60,000 human deaths worldwide according to the World Health Organization (WHO), mostly in Asia and Africa, with 60% of registered cases in India ("WHO Expert Consultation on rabies," 2005; "WHO Expert Consultation on Rabies. Second report," 2013). Rabies is a zoonotic disease, transmitted to humans through a bite or a scratch from an infected animal (mammalian carnivores and bats). The causative agent is the neurotropic, single strand, negative sense RNA rabies virus (RABV) which taxonomically belongs to the *Lyssavirus* of the *Rhabdoviridae* family (Rupprecht, 1996). Its simple genome encodes the five proteins necessary for the virus replication and life cycle: the nucleoprotein (N), the phosphoprotein (P), the matrix protein (M), the glycoprotein (G) and finally the RNA-dependent-RNA polymerase (L) (Albertini, Ruigrok, & Blondel, 2011). Following virus entry into peripheral tissues, which is generally associated with trauma, the virus crosses neuromuscular junctions to gain entry into the nervous system and travels to the CNS by trans-axonal retrograde transport (Tsiang, 1979), therefore bypassing the blood-brain barrier (BBB).

The BBB is a specialization of the CNS vasculature composed of adjacent endothelial cells which form both a physical barrier that prevents the entry of toxins and pathogens and a dynamic structure that actively regulates the exchange of beneficial substances and waste products between blood and CNS to maintain brain tissue homeostasis (Gloor et al., 2001; Rubin & Staddon, 1999; Zlokovic, 2008). Endothelial cells (EC) of the BBB are characterized by a high mitochondrial content (Oldendorf, Cornford, & Brown, 1977), low levels of transendothelial pinocytosis (Sedlakova,

Shivers, & Del Maestro, 1999), an absence of fenestration (Fenstermacher et al., 1988) and by the presence of specialized tight junctions (Wolburg & Lippoldt, 2002). To ensure proper CNS function, EC are involved in highly coordinated communications with multiple cell types, including pericytes (Armulik, Abramsson, & Betsholtz, 2005), astrocytes (Abbott, Ronnback, & Hansson, 2006), microglia and neurons, which are together designated the neurovascular unit (NVU) (Iadecola, 2004). While essential for reliable neuronal transmission, the BBB has long been considered a major impediment in the communication between the CNS and the immune system (Medawar, 1948). The presence of the BBB, together with the lack of a conventional lymphatic drainage system (Yamada, DePasquale, Patlak, & Cserr, 1991), the absence of dendritic cells (Matyszak & Perry, 1996) and low levels of expression of MHC class I and II (Perry, 1998) contribute to the immune privilege of CNS tissues, where foreign antigens do not readily induce an overt immune reaction. The recent discovery of a meningeal lymphatic system that drains cerebrospinal fluid (CSF) to deep cervical lymph nodes (Aspelund et al., 2015; Louveau et al., 2015) and evidence for CNS immune surveillance throughout the meninges and choroid plexus under physiological conditions (Ransohoff & Engelhardt, 2012) suggest that there is communication between the immune system and certain areas of the brain. Nevertheless, the brain parenchyma proper is immune privileged particularly with respect to the entry of immune cells and factors.

In that context, the wide variety of RABV strains that greatly differ in their levels of neurotropism and pathogenicity provide unique tools to study CNS immunology. Wild-type, or street, viruses isolated from naturally infected animals greatly differ genetically and phenotypically according to their reservoir source and can therefore be unpredictable in their pathogenicity. In addition, due to the high mutation rate, wild-type RNA viruses exist as quasispecies with a

dominant variant within a heterogeneous pool of viruses (Morimoto et al., 1998). To minimize the difficulties in experimental reproducibility, laboratory-adapted fixed strains were developed by passaging rabies virus isolates in animals or cell culture. Propagation of a laboratory-adapted rabies virus in cultures containing a monoclonal virus-neutralizing antibody led to the discovery of a virus with a mutation that renders it relatively apathogenic and therefore highly suited for studies of rabies immunity (Dietzschold et al., 1983). Finally, the development of cloned RABV and the application of reverse genetic engineering technology to generate stable RABV strains with defined properties have provided unique tools to study the inherent pathogenicity of RABV and the contribution of immunity to this feature (Morimoto et al., 2001; Schnell, Mebatsion, & Conzelmann, 1994). The purpose of this review is to provide a critical summary of the use of these RABV variants to better understand the role played by the immune system in the pathogenesis of RABV infection.

2. Rabies, an unconventional non-inflammatory disease.

Inflammation is characterized by signs of heat, redness, pain, swelling and loss of tissue function which are manifestations of blood vessel dilatation, increased microvascular permeability and local immune cell infiltration (Lawrence, Willoughby, & Gilroy, 2002). Inflammation can be beneficial, when acute, or detrimental, depending on its location, the cells and factors involved, as well as its magnitude and persistence. In the context of a brain viral infection, acute inflammation involving neutrophils and monocytes is most often a key element of the entry of immune cells into CNS tissues and often associated with pathogenesis (e.g. Borna disease) but can contribute to virus containment and clearance. When the recruitment of immune effectors induces the release of pro-inflammatory cytokines and the production of reactive oxygen species (ROS), often by infiltrating monocytes, neuronal function can be greatly impaired over time (Terry et al.,

2012). In this regard, much of our understanding of the CNS-immune system communication comes from pathological inflammatory conditions, notably multiple sclerosis (MS) and its animal model correlate experimental autoimmune encephalomyelitis (EAE), in which the massive infiltration of autoreactive immune cells and monocytes into the brain and spinal cord leads to neural tissue destruction and therefore cognitive and motor function impairment (Greenwood et al., 2011).

Infection with wild-type RABV is unique in the sense that very little histopathological changes are observed (Murphy, 1977). Of particular interest is the lack of evidence for neuronal apoptosis in human cases of rabies (Jackson, Randle, Lawrance, & Rossiter, 2008) as well as in the experimental infection of bats (Reid & Jackson, 2001), mice (Scott, Rossiter, Andrew, & Jackson, 2008) and dogs (Suja, Mahadevan, Madhusudhana, Vijayasarathi, & Shankar, 2009) with street viruses. On the other hand, infection with attenuated RABV strains trigger neuronal apoptosis, which correlates with the level of glycoprotein expression and with RABV clearance from CNS tissue (Faber et al., 2002; Jackson, Rasalingam, & Weli, 2006; Morimoto, Hooper, Spitsin, Koprowski, & Dietzschold, 1999; Sarmento, Li, Howerth, Jackson, & Fu, 2005; Yan et al., 2001). In addition to its level of expression, the structure of the G protein itself actively participates in either the activation or the repression of neuronal apoptosis. Indeed, the PDZ binding domain from pathogenic RABV G binds to the microtubule-associated serine and threonine kinase 2 (MAST2), a pro-apoptotic kinase, therefore promoting neuronal survival whereas the G from attenuated RABV bind to the tyrosine-phosphatase PTPN4, an inhibitor of cell apoptosis, therefore promoting neuronal death (Caillet-Saguy et al., 2015). While infection-associated neuronal death is generally regarded as detrimental, the release of viral antigen and stimulatory factors from apoptotic neurons following infection with attenuated RABV strains drives immunity and virus

clearance from the CNS. Moreover, rapid neuronal death paradoxically impairs the cell-to-cell spread of the virus. By actively repressing neuronal apoptosis, pathogenic RABV strains promote viral spread throughout CNS tissues by preserving the neuronal network and minimizing immune sensitization.

The adverse effect on the innate immune response between pathogenic and attenuated RABV strains is highlighted by differences in the levels of CNS chemokine/cytokine gene expression. Overall, infection with pathogenic RABV strains is associated with the downregulation of CNS gene expression, with the exception of genes involved in cell metabolism and synaptic activity, whereas attenuated strains promote the expression of pro-inflammatory genes in CNS tissues (Prosniak, Hooper, Dietzschold, & Koprowski, 2001; Prosniak et al., 2003; Z. W. Wang et al., 2005). Of particular interest is the ability of pathogenic RABV strains to inhibit the interferon (IFN) system. Type I IFN (IFN-α/-β) generally exerts strong antiviral effects. Pathogenic strains of RABV can counteract type I IFN at both the production level (Brzozka, Finke, & Conzelmann, 2005; Masatani et al., 2010; Rieder et al., 2011), and at the level of downstream signaling (Blondel, Maarifi, Nisole, & Chelbi-Alix, 2015).

Finally, another unconventional feature of rabies virus infection concerns macrophages. Macrophages are a major component of the inflammatory response during viral infection where they can play an important role in phagocytosis of virus particles and proinflammatory mediator release (Glass, Rosenberg, & Murphy, 2003). While studies have reported the presence of macrophages at the peripheral site of RABV infection due to tissue damage (Charlton & Casey, 1979), and possibly the perivascular cuff, they do not infiltrate deep within the brain parenchyma. Overall, infection with either pathogenic or attenuated RABV fails to induce the infiltration of monocytes into the brain parenchyma. $CD8^+$ T cells enter

brain tissues following infection with either pathogenic or attenuated rabies virus while only the latter induces the infiltration of the $CD4^+$ T cells and B cells that are required for virus clearance (Phares, Fabis, Brimer, Kean, & Hooper, 2007; Phares, Kean, Mikheeva, & Hooper, 2006; Roy & Hooper, 2007; Roy, Phares, Koprowski, & Hooper, 2007).

3. The cross-talk between immune effectors and the neurovascular unit is the primary determinant of rabies pathogenesis.

The prognosis for individuals who do not promptly receive postexposure prophylaxis (PEP) treatment is very poor. To date, there is no report of survivors infected by a dog-derived RABV and only few reports of patients surviving without receiving PEP treatment. One survived a bat-associated virus infection ("Recovery of a patient from clinical rabies--Wisconsin, 2004," 2004; Willoughby et al., 2005) and the other an infection by an unknown RABV strain transmitted by a free roaming cat ("Recovery of a patient from clinical rabies--California, 2011," 2012). Naturally infected individuals, who do not receive PEP treatment, generally mount a weak rabies-specific antibody response only at the end stage of the disease ("Human rabies--Minnesota, 2007," 2008; "Human rabies--Mississippi, 2005," 2006; Johnson, Cunningham, & Fooks, 2010). However, the fact that certain RABV strains can elicit an immune response and that proper PEP management can prevent rabies development indicates that the pathogenicity of a given RABV strain depends upon its ability to either outrace the immune system or to spread outside of the reach of a protective immune response.

PEP treatment consists of proper wound cleaning, active vaccination and the passive administration of virus neutralizing antibodies (VNA) ("Rabies vaccines: WHO position paper--recommendations," 2010). Rabies VNA are essential for virus clearance (Dietzschold, 1993; Hooper et al., 1998), yet they lose their utility once the virus reaches the CNS due to their

limited capacity to cross the intact BBB. Therefore, strategies to artificially enhance BBB permeability with hypertonic shock or RABV-producing immune stimulating molecules have been developed to improve VNA accumulation in the CNS (Huang et al., 2014; Liao et al., 2012; Roy & Hooper, 2007; H. Wang et al., 2011). However, although these approaches can prevent clinical rabies development in animal models, they are very unlikely to be transferable into human anti-rabies therapy as BBB leakage itself is likely pathological and is involved in many neurological diseases (Daneman, 2012). Under normal circumstances the local production of antibodies (Ab) within the CNS rather than an Ab leakage plays an important role in RABV clearance (Hooper, Phares, Fabis, & Roy, 2009). Thus, the active vaccination component of PEP, which can elicit T and B cells capable of infiltrating CNS tissues, is likely essential for the induction of therapeutic CNS immunity against RABV.

In animal models of RABV infection, the most striking difference between pathogenic and attenuated strains is manifested at the BBB. The former evade immune clearance through the maintenance of BBB integrity while infection with the latter is associated with enhanced BBB fluid-phase permeability and immune effector infiltration into the CNS (Roy & Hooper, 2008). Thus, the clearance of attenuated virus seems to be a sequential process involving an inside-out (CNS to immune system) followed by an outside-in (immune system to CNS) cross-talk between the NVU and immune effectors (Figure 1). Initial support for the concept of inside-out communication comes from the observation that the production of TNF-α by CNS resident cells during attenuated RABV infection, while not directly enhancing BBB permeability but triggers the expression of ICAM-1(Phares et al., 2007; Phares et al., 2006), a key adhesion molecule in lymphocyte recruitment (Dietrich, 2002).

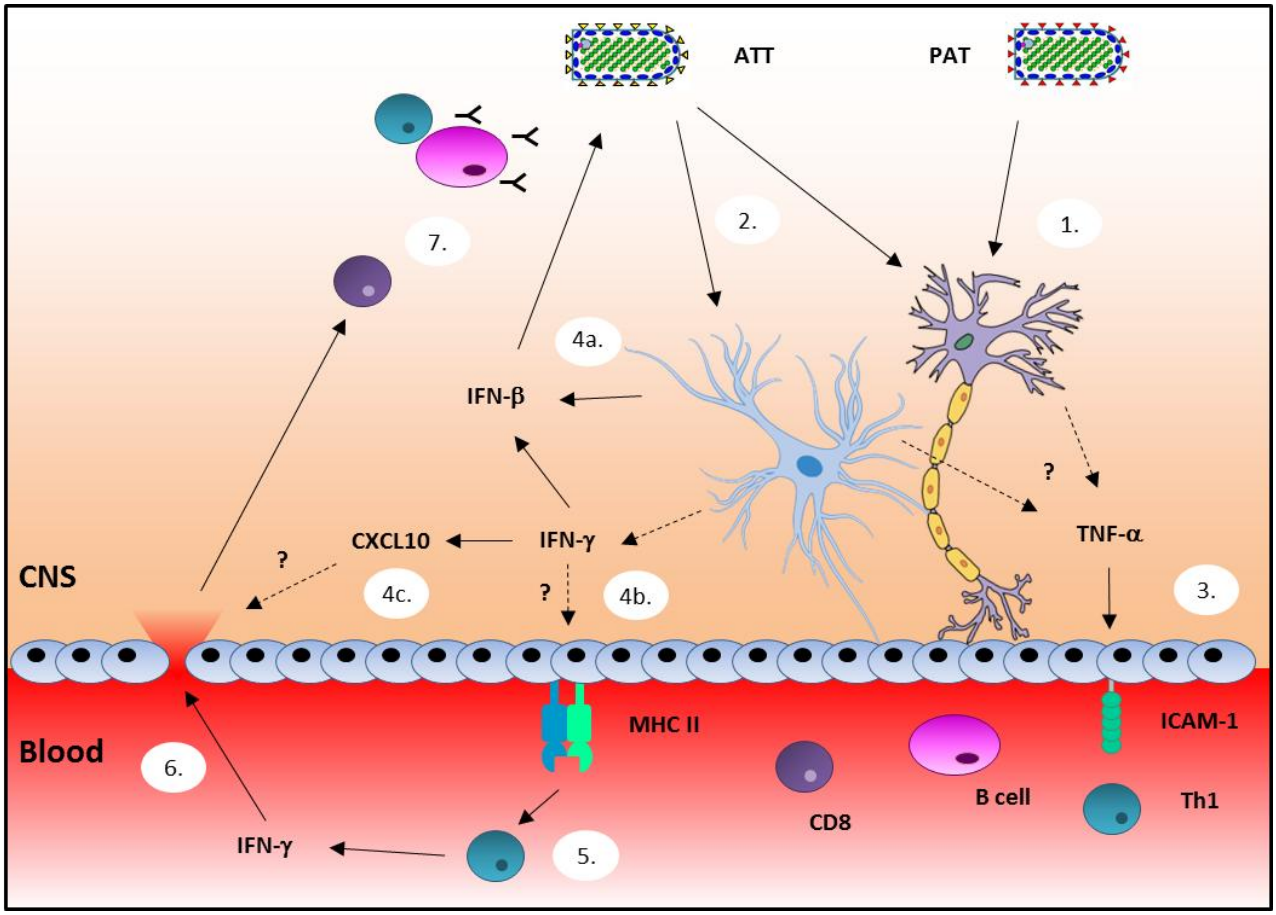

Figure 1: Illustration depicting the hypothetical mechanism of attenuated RABV clearance

1. Pathogenic (PAT) RABV do not infect astrocytes. 2. Attenuated (ATT) RABV can infect astrocytes. 3. Production of TNF-α by resident CNS cells enhances endothelial ICAM-1 expression and lymphocyte recruitment. 4a. Infected astrocytes produce antiviral IFN-β. 4b. IFN-γ enhances the IFN-β response and may enhance vascular MHC II expression. 4c. IFN-γ induces CXCL10 expression which may play a role in tight junction disruption. 5. ICAM-1 and MHC II participate in the recruitment of Th1 cells 6. IFN-γ enhances BBB permeability and immune effector infiltration into the CNS. 7. Th1 and B cells collaborate for the local IgG2a production and clear RABV.

Our group has demonstrated a central role for IFN-γ in CNS immunity against RABV through enhancement of both type I IFN secretion (Barkhouse et al., 2015) and BBB permeability (Phares et al., 2007). Interestingly, the main source of antiviral IFN-β during RABV infection may be abortively infected astrocytes (Pfefferkorn et al., 2016). Although pathogenic strains are neuronotropic,

several reports have shown that attenuated RABV strains can infect astrocytes both *in vivo* (Fekadu, Chandler, & Harrison, 1982; Prosniak et al., 2003; Suja et al., 2009) and *in vitro* (Ray, Power, Lynch, Ewalt, & Lodmell, 1997; Tsiang, Koulakoff, Bizzini, & Berwald-Netter, 1983). Astrocytes are essential for the NVU structure and function (Abbott et al., 2006), therefore infection of these cells by attenuated RABV strains may cause alterations in the BBB. Nevertheless attenuated RABV infection may establish an immune permissive state of the BBB but does directly trigger enhanced BBB permeability as BBB integrity is maintained in T and B cell deficient mice infected with attenuated RABV (Phares et al., 2007). In addition to the prior studies associating IFN-γ production with the loss of BBB integrity during attenuated RABV (Phares et al., 2007), recent studies have shown a loss of the TJ proteins Occludin, Claudin-5 and *zonula occludens* 1 (ZO-1) and enhanced BBB permeability in association with production of the IFN-γ response chemokine CXCL10 during attenuated RABV infection (Chai, He, Zhou, Lu, & Fu, 2014; Chai, She, Huang, & Fu, 2015). The establishment of an immune permissive state of the BBB is associated with the expression of MHC class II at the BBB level which most likely plays an additional role in RABV antigen presentation and lymphocyte recruitment (Hooper, Roy, Barkhouse, Li, & Kean, 2011; Hooper, Roy, Kean, Phares, & Barkhouse, 2011). The importance of the establishment of an immune permissive BBB as a first step in RABV clearance is further supported by studies showing that the defect during pathogenic RABV infection is at the BBB rather than in the RABV-specific immune cells: The adoptive transfer of $CD4^+$ T and B cells from mice lethally infected with the pathogenic silver-haired bat virus (SHBRV) can clear the attenuated CVS-F3 virus in immunocompromised mice but the reciprocal transfer does not clear SHBRV (Roy et al., 2007). The dominant therapeutic effect of attenuated strains in

pathogenic RABV superinfection models suggests that a deficit in the induction of an immune permissive state of the BBB rather than an active inhibitory mechanism allows pathogenic viruses to evade immune clearance (Faber et al., 2007) but this concept remains to be validated.

Finally, adoptive transfer experiments provide compelling support for the concept that elements of adaptive immunity are required to trigger the fluid-phase BBB permeability associated with virus clearance following the development of the BBB permissive state (outside-in communication). Indeed, while BBB integrity is maintained in infected immunodeficient $Rag2^{-/-}$ mice, which lack functional B and T cells (Shinkai et al., 1992), and animals will eventually succumb to the infection, adoptive transfer of $CD4^+$ T cells and B cells but not $CD8^+$ T cells results in RABV clearance from CNS tissues and the survival of $Rag2^{-/-}$ recipients (Phares et al., 2007). The central role of $CD4^+$ T cells in secondary cross-talk with the BBB is further supported by the fact that $JHD^{-/-}$ mice, which only lack functional B cells, display enhanced BBB permeability and CD4 T cell accumulation in CNS tissues following infection with attenuated RABV (Hooper et al., 2009; Hooper, Roy, Barkhouse, et al., 2011).

4. Immune bias is a key determinant of timely RABV clearance from the CNS

As highlighted in the previous paragraph, the cross-talk between the BBB and immune effectors is essential for the therapeutic clearance of attenuated RABV from CNS tissues. However, the capacity of immune effectors to reach CNS tissues is not the only limiting factor in RABV clearance; the bias of the immune response generated upon RABV infection is also a key determinant of this process. $CD4^+$ T helper (Th) cells differentiate into the following subsets: Th1, Th2, Th17, Tfh and T-reg, each characterized by the expression of a master regulator transcription factor and by the production of a signature cytokine (O'Shea & Paul,

2010). T-bet, encoded by the *Tbx21* gene, belongs to the T-box family of transcription factors and acts as the master regulator of the Th1 cell lineage by inducing Th1 signature genes (IFN-γ) and by repressing genes (GATA3, RORγT and Foxp3) specific for alternative T helper cell fates (Th2, Th17 and Treg) (Djuretic et al., 2007; Hwang, Szabo, Schwartzberg, & Glimcher, 2005; Oestreich, Huang, & Weinmann, 2011; Szabo et al., 2000). The role of Th1 biased $CD4^+$ T cells in attenuated RABV clearance is supported by the absence of protection against pathogenic RABV challenge after immunization with an attenuated strain in T-bet deficient (T-$bet^{-/-}$) mice (Hooper, Roy, Barkhouse, et al., 2011). In addition, while T-$bet^{-/-}$ mice and their congenic controls have comparable T lymphocyte accumulation within the CNS following attenuated RABV infection, they greatly differ in terms of cell bias and activation. Early in the course of infection wild-type mice show enhanced T cell activation (CD69 upregulation) and the rapid development of a type 1 immune response (IgG2a antibody production) whereas T-$bet^{-/-}$ mice exhibit a relatively slow development of a type 2 immune response (no CD69 upregulation and low initial IgG1 production) resulting in delayed RABV clearance from the CNS (Lebrun et al., 2015). Surprisingly, T-$bet^{-/-}$ mice show an increased production of IFN-γ, despite the absence of the Th1 subset, likely due to the presence of $CD8^+$ T or natural killer (NK) cells (Lebrun et al., 2015). Nevertheless, the level of IFN-γ mRNA in the CNS tissues of these animals correlates with increased BBB permeability (Figure 2), which is consistent with previous data on the pivotal role of IFN-γ in the regulation of the BBB during attenuated RABV infection (Phares et al., 2007).

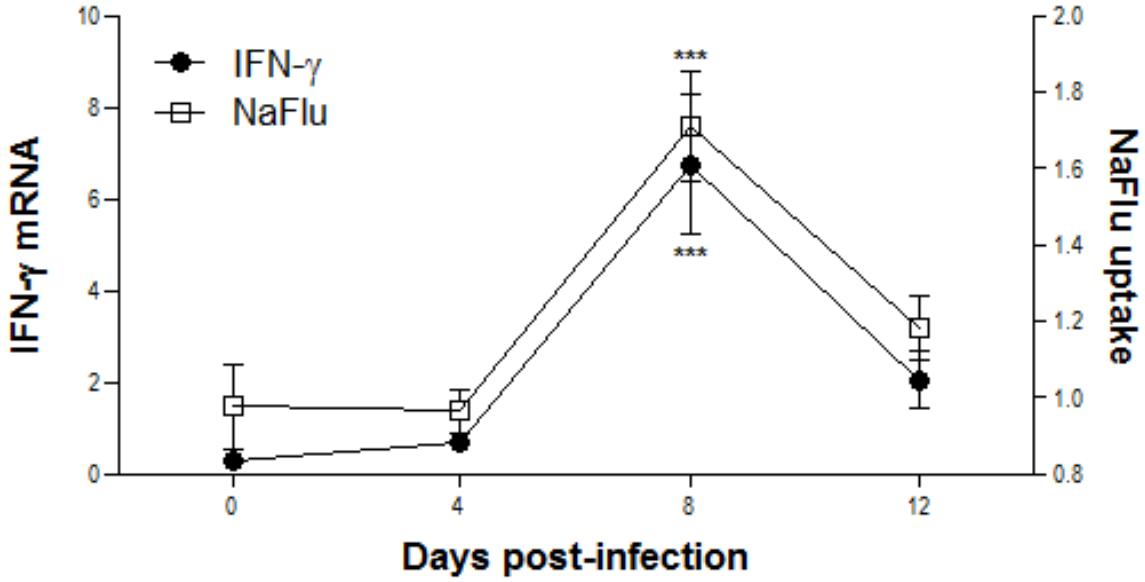

Figure 2: The level of BBB permeability correlates with IFN-γ production in T-bet$^{-/-}$ mice

T-bet$^{-/-}$ mice were infected intranasally with 10^5 F.F.U. of SPBN-GAS. The level of BBB permeability was evaluated by measuring sodium fluorescein uptake (NaFlu, right axis) which correlates with the level of IFN-γ production, measured by Q-RT-PCR, in the cortex of T-bet$^{-/-}$ mice (N=10). Statistically significant differences between controls and infected mice are denoted as follow: *** $p \leq 0.001$.

The bias of the immune response to RABV is of primary importance with regards to PEP. The current available vaccines for human use, for pre- and postexposure prophylaxis, consist of inactivated RABV prepared in human diploid cells, purified from Vero cell culture or purified from chick-embryos ("Rabies vaccines: WHO position paper--recommendations," 2010). However, the inactivation of RABV, either by UV light or with β-propriolactone, results in a vaccine that preferentially induces a type 2 immune response (Hooper, Roy, Barkhouse, et al., 2011). Because of their strong capacity to safely induce a long-lasting type 1 immune response capable of clearing RABV from CNS tissues with a single immunization, the use of novel, live-rabies vaccine, viruses containing

multiple copies of an attenuating glycoprotein, may provide for the induction of a more appropriate RABV immune state (Faber et al., 2009).

5. Concluding remarks

Rabies remains a public health problem primarily in developing countries where dogs still represent the main vector of the disease. Although vaccines for pre- and postexposure prophylaxis are currently available, cases of true PEP failure, despite timely management, are still reported. This may in part be due to the inability of the type 2 responses elicited by inactivated vaccines to clear RABV from neural tissues. Pathogenic RABV strains, by maintaining an intact neuronal network and avoiding the induction of an immune permissive state of the BBB, efficiently spread through the CNS with deadly consequences for the host. At the other end of the spectrum, the study of infection with attenuated RABV strains has provided unique insight into the key mechanisms necessary for the non-inflammatory clearance of virus from CNS tissues. Nevertheless, several questions remain unanswered. For instance, the precise mechanisms through which attenuated RABV strains promote, and pathogenic strains avoid, the induction of the immune permissive state of the BBB remain to be established.

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