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# Latent viral infections of the nervous system: Role of the host immune response

## *Infections virales chroniques du système nerveux central : rôle de la réponse immune*

*M. Lafon*

*URA CNRS 3015, unité de neuro-immunologie virale, Institut Pasteur, 25, rue du Dr-Roux, 75724 Paris cedex 15, France*

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ABSTRACT

Viruses that infect the nervous system may cause acute, chronic or latent infections. Despite the so-called immunoprivileged status of the nervous system, immunosurveillance plays an important role in the fate of viral infection of the brain. Herpes simplex virus 1 (HSV-1) persists in the nervous system for the life of the host with periodic stress induced reactivation that produces progeny viruses. Prevention of reactivation requires a complex interplay between virus neurons, and immune response. New evidence supports the view that CD8+T cells employing both lytic granule- and IFN-gamma-dependent effectors are essential in setting up and maintaining HSV-1 latency. HSV-1 infection of the nervous system can be seen as a parasitic invasion which leaves the individual at risk for subsequent reactivation and disease. The recent observation that herpes virus latency may confer protection against experimental bacterial infection suggests that unexpected symbiosis may exist between latent viruses and the infected nervous system of its host.



RÉSUMÉ

En parasites obligatoires, les virus ont adopté des stratégies d'évitement des défenses cellulaires et des réactions immunitaires. Pendant la phase infection aiguë, les virus doivent se répliquer sans faire périr la cellule et l'hôte qui les hébergent et éviter de se faire éliminer trop rapidement par la réponse immunitaire de l'hôte infecté. Après quelques cycles et la dissémination des particules virales nouvellement formées, l'infection est généralement éliminée. Dans certains cas, toutefois, le virus disparaît sous sa forme infectieuse, mais son génome reste hébergé par les cellules de l'organisme. Ces cellules constituent un réservoir où le virus persiste à l'état latent pendant toute la durée de vie de l'hôte. Les virus de la famille des Herpes (virus de Herpes simplex, virus de la varicelle) sont des exemples bien documentés d'infection latente du système nerveux central. L'état de latence virale semble résulter d'un équilibre subtil entre le virus, la machinerie cellulaire et la réponse immunitaire. Certains stimuli – comme un affaiblissement de la réponse immune – peuvent causer des phases de réactivation qui se traduisent par éruption de boutons de fièvre ou de

E-mail address: Monique.lafon@pasteur.fr.
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zona. Les cellules infectées de façon latente sont souvent présentes dans les organes – comme le système nerveux – peu accessibles à la réponse immunitaire ce qui rend leur élimination difficile. L'infection par le virus du VIH réactive, à la faveur de l'immunodépression qu'il provoque, des infections virales du système nerveux responsables d'encéphalites (CMV, HSV) mais aussi de lymphomes (EBV). L'émergence de cas d'encéphalite leucocytaire causée par le polyoma virus JC après l'utilisation du Natalizumab (anticorps dirigé contre la chaine $\alpha$4 de l'intégrine 4 dans le traitement de la sclérose en plaques) a mis en lumière le rôle de la réponse immune dans le contrôle des infections virales latentes du système nerveux. De récentes données illustrent le rôle paradoxal des lymphocytes cytotoxiques de l'hôte dans le système nerveux ; leur présence serait requise pour que la latence virale s'établisse et persiste. Néanmoins, comme dans de nombreuses associations parasitaires, il se pourrait aussi que l'hôte infecté trouve quelques avantages à la présence de virus latents dans son système nerveux.



## 1. Introduction

Neurotropic viruses cause serious neurological diseases in humans. Development of the disease as an acute or latent infection results of several factors among which the strength of the viral load, the potency of the host immune response and the strategies of virus to escape from the immune response are important factors. In most experimental virus infections of the brain the rapid production of a local innate immune response, including the production of type I interferon (type I IFN) is paramount for host survival (Griffin, 2003). In other instances, the virus burden is so high that clearance of infection by the immune system from the brain fails. This is for example the case of fatal encephalitic cases of West Nile virus encephalitis in mouse model and in humans, where death occurs despite accumulation of inflammatory infiltrates consisting predominantly of nodules of activated microglia, T and B cells, macrophages (Agamanolis et al., 2003; Brehin et al., 2008; Kelley et al., 2003). Failure of the immune response to clear infection off the brain may also result of immunoevasive strategies selected by viruses to evade the host immune response. A well-characterized case is rabies. Rabies virus has developed sophisticated mechanisms to destroy or inactivate 'protective' T cells that migrate into the infected nervous system, as a result of the overexpression of immunosubversive molecules such as FasL, HLA-G or B7-H1 in the infected nervous system (Lafon et al., 2006; Lafon et al., 2008; Baloul et al., 2004). For other virus infection such as herpes simplex virus of type 1 (HSV-1) evasion from the immune response can be in some how incomplete. In HSV-1 brain infection, the host immune constraints are sufficient to contribute to latency but they are not strong enough to clear infection. Weakness of the immune response leads episodically to reactivation of the infection. Nevertheless, the immune response in the brain is not always beneficial and can cause immunopathological conditions. An obvious illustration is multiple sclerosis (MS) for which an infectious etiology has been suspected (Dolei and Perron, 2009; Lunemann and Munz, 2009; Perron et al., 2009; Perron et al., 2001; Tai et al., 2009) and where demyelination results both of inflammatory response and B cell activation. This could be also the case of the influenza-associated encephalopathy, where neurological complications of influenza virus infection have been attributed to the inflammatory reactions in the brain rather to the dysfunction of the infected neurons (Okumura et al., 2009).

## 2. Immune status of the nervous system

### 2.1. *Innate immune response*

Nervous parenchyma – as most tissues – has the capacity to sense viral infection. The innate immune response triggered in situ by the entry of pathogen into the brain is characterized by the production of type I IFN (predominantly IFN-β in the brain [Delhaye et al., 2006; Prehaud et al., 2005]), chimiokines and inflammatory cytokines. Beside intrinsic antiviral property, type I IFN also controls the expression of a large number of genes involved in chemo attractive, antiviral and inflammatory responses, which contribute to the host, defence against brain invasion. Microglia, astrocytes and now neurons have been identified as main innate keepers of the brain (Olson and Miller, 2004; Delhaye et al., 2006; Lafon et al., 2006; Yang et al., 2000; Zhou et al., 2009). Cells of the NS, mainly glial cells, express receptors such as Toll-like receptors (TLR) or RIG-like (RLR) which allow them to recognize and respond to the presence of danger signals and Pathogen Associated Molecular Patterns (PAMPS) encoded by pathogens (Furr et al., 2008; Olson and Miller, 2004). Only recently neurons were found to express TLRs and RLRs, (Lafon et al., 2006; Tang et al., 2007; Tang et al., 2008). TLR3 is strongly expressed by Purkinje neurons in the cerebellum of human brains affected by viral encephalitis, amyotrophic lateral sclerosis, stroke or Alzheimer disease (Jackson et al., 2006).

It is still unclear whether the innate immune responses of the brain are as efficient as those in periphery. Injection of the bacterial component LPS into the brain parenchyma elicits neutrophil and monocyte recruitment within 2 h postinjection into the skin, whereas monocyte recruitment is observed only after 2 days when LPS is injected into the brain parenchyma (Andersson et al., 1992). This reduced inflammatory response may result of the property of neurons to reduce inflammation and regulate microglial phenotype during infection or injury (Meuth et al., 2008). Control of local glial inflammation occurs

via the expression by neurons of receptors such as CD47, CD22, CD200 and by their ligands on glial cells (Griffiths et al., 2007; Hoek et al., 2000; Wright et al., 2000).

Nevertheless, the type I IFN in the infected nervous system is essential in controlling some neurotropic infections. This is the case for coronavirus clearance off the brain, for which type I IFN response is primordial irrespective of functional adaptive immune response (Ireland et al., 2008). Neuronal expression of TLR3 seems to play a major role in the control of neurotropic viral infection, either decreasing viral replication in the case of West Nile virus infections or more surprisingly by promoting virus neuronal infection as shown in the case of rabies virus (Daffis et al., 2008; Menager et al., 2009). Moreover, a role of TLR3 and the resulting innate immune response has been evoked in the susceptibility of children to encephalitis associated to HSV-1 infection (HSVE). When HSV-1 infects the temporal neurons, it causes severe HSVE, with 60% of fatality in absence of treatment. Origin of the tropism is not yet understood, nevertheless, inefficient innate immune response may play a role since HSVE development has been linked to TLR3 signalling deficiency, either through *TLR3* polymorphism (Zhang et al., 2007) or to UNC-93B deficiency (Casrouge et al., 2006). UNC-93B- and TLR3-deficient patients appear to be specifically prone to HSVE, although clinical penetrance is incomplete. Children with predisposition to HSVE carry an heterozygous mutation in *TLR3* at the crucial site for dsRNA binding to TLR3 and TLR3 multimerization. UNC93B1 binds the transmembrane domain of TLR3, 7/8 and 9. It is specifically involved in the trafficking of TLR3, 7/8 and 9. In its absence, TLR3, 7/8 and 9 cannot reach anymore the endolysosomes, and signalling is impaired (Brinkmann et al., 2007). Humans with homologous germline mutation show impaired cytokine production upon TLR3, 7/8 and 9 stimulation.

### 2.2. *Adaptive immune response in the brain*

If an allograft is implanted into the brain, rejection is delayed compared to grafts in other organs (Medawar, 1991). This phenomenon has given rise to the concept that general rules of the immune system are not applicable to the central nervous system and that the brain – an organ with poor regenerative capacity – enjoys immunological privilege. The 'immune privilege' of the central nervous system is a longstanding notion which, over time, has acquired several misconceptions and a lack of precision in its definition (Galea et al., 2007). Different compartments composed the nervous system: parenchyma, ventricles containing the choroid plexus and filled with cerebrospinal fluid CSF and the meninges. The immune privilege is solely applicable to the nervous parenchyma and not to the other tissues such as meninges, choroid plexus, circumventricular organs and ventricles nor to CSF. Experimentally, a virus infection confined to the parenchymal substance of the brain primed the immune system inefficiently or not at all (Byrnes et al., 1996a; Stevenson et al., 1997). In contrast, infection in the CSF elicits a comparable immune response to intranasal infection, with an antiviral proliferative response in the draining lymph nodes (Stevenson et al., 1997). These different situations result on the absence of lymphoid organs into the nervous system and the distinct capacities of antigens to be drained or not from the nervous system towards the cervical lymph nodes (Galea et al., 2007; Weller et al., 2009). Even if immune privilege of nervous parenchyma is well established, it is not a barrier for host defence, since all neurotropic viruses reach the brain after an initial entry in the peripheral tissues, such as muscle, skin or intestinal cells. In these conditions, detection of the pathogen by the peripheral immune system has already occurred and complete immune response has been triggered against the foreign pathogen. The so-called blood brain barrier is not a barrier either for access of T, B and macrophages into the brain from the periphery, since, once activated, immune expressing surface adhesion molecules have the capacity to enter the nervous system (Engelhardt, 2008). In contrast, it is well-documented that after there entry, the migratory immune cells faced unfavourable conditions for survival. This results of a series of parameters controlled by neurons that seriously dampen T cells activity. For example, secretion of several neuropeptides and neurotransmitters by neurons such as vasointestinal peptide, calcitonin gene related peptide, norepinephrin and alpha melanocyte stimulating hormone down regulate the activity of T cells (Niederkorn, 2006). T cells can be subjected to apoptosis by encountering FasL (Baloul et al., 2004). T cells can also be converted into regulatory T cells in presence of TGF-β secreted by neurons (Liu et al., 2006).

Surprisingly despite this rigorous regulation, T cells can still participate to the immunosurveillance against brain infection as illustrated by the side effect attributed to the use of natalizumab. Natalizumab is a humanized recombinant monoclonal antibody that efficiently reduces inflammation of nervous system in MS patients. This mAb targeting the α4 subunit of α4β1 integrin expressed by T cells inhibits alpha (4) integrin-mediated adhesion of human T cells to the inflamed BBB (Bauer et al., 2009; Coisne et al., 2009). Nevertheless, a few MS patients treated with Natalizumab in clinical trials developed a progressive multifocal leukoencephalopathy caused by the polyomavirus JC, an opportunistic viral infection of the NS (Stuve, 2008). This might be related to the property of Natalizumab to decrease the entry into the brain of protective lymphocytes allowing the infection of the nervous system by the JC virus a human neuroropic poyomavirus, a virus requiring strong suppression of the immune system in order to thrive. This opportunity occurs after Natalizmab treatment and as told by Igor Koralnik "*Bad things* may happen when *rescuers* are turned back *at the gates*" (Berger and Koralnik, 2005). This side effect illustrates the critical role of immuneresponse – despite the immunosuppressive neuronal local environement – in protecting the brain against viral infection. Role of immune response in brain protection against invading pathogens, is also illustrated by HIV-infected subjects progressing into symptomatic AIDS and concomitantly their immune response deteriorating, they become vulnerable to opportunistic infections such as *Cryptococcus neoformans* (2–30% of cases), human cytomegalovirus, HCMV (9%), toxoplasmosis (4%), HSV-1 (4%) as well as Epstein-Barr virus infection (5–10%) the latest causing primary central nervous system lymphoma (Anthony et al., 2008). Indeed T cells, are major actors in the clearance of viral infections (Baloul et al., 2004; Bantug et al., 2008; Byrnes et al., 1996b; Galelli et al., 2000; Lafon et al., 2008). Nevertheless, in

some cases, as illustrated below, T cells may have dual role in the fight against infection in the nervous system.

## 3. Dual role of immune response in HSV-1 latency

HSV-1 establishes a lifelong persistent infection of human peripheral nervous system. During primary infection, virus enters the nervous termini located in mouth-pharyngeal area, and then travels by retrograde axonal transport up to the bodies of the sensory nerves in sensory ganglia. Acute infection is replaced by a latent infection where viral genomes persist without viral particles production. Reactivation from latency can occur sporadically upon different triggering such as UV irradiation or stress. Reactivation results most of the times in benign cold sores and rarely in severe blinding immunopathological herpes stromal keratitis. The role of the immune responses in the control of acute HSV infection, the establishment of the latency and reactivation have been studied in a mouse model of infection, where corneal scarification in presence of virus result in the infection of trigeminal ganglia mimicking human infection.

### 3.1. *Acute infection*

In the first 2–3 days after infection, an innate immune response is quickly triggered as soon as the virus starts replication in the ganglia. Both cellular arm of the innate immune response consisting in the triggering of IFN-γ secreting γδ TCR$^+$ T cells or macrophages producing nitric oxide (NO) and tumour necrosis factor alpha (TNF-α) and humoral arm (type 1 IFN, chemokines, cytokines) are rapidly triggered. The recognition of HSV components is both TLRs (2 and 9) and RLRs-dependent(Krug et al., 2004; Kurt-Jones et al., 2004; Lund et al., 2003; Rasmussen et al., 2007; Sorensen et al., 2008). Despite the capacity of HSV-1 to impede the IFN response later in the virus cycle (Randall and Goodbourn, 2008), this early competent innate immune response is sufficient to eliminate most – but not all – replicating virus from the infected ganglia. Plasmacytoid and conventional DCs are also triggered to produce type I IFN which is essential for the activation of CD8$^+$ T cells and expansion of memory population (Garcia-Sastre and Biron, 2006). Indeed memory CD8$^+$ T cells infiltrate the ganglion by day 6 post-infection, expand and settle in the trigeminal ganglion for the rest of life of the infected animals. In this period, CD8$^+$ T cells participate to the clearance of virus.

### 3.2. *Establishment of latency*

Six days after corneal infection, latency was established in some sensory neurons which do not produce replicating viruses anymore. Molecular events that switch an acute HSV infection into a latent infection are not completely understood. Latency is characterized by circularization of the viral genome and the expression of latency associated transcripts (LATs) and viral transcripts corresponding to immediate early (α) early (β) and even late (γ1) viral genes (Feldman et al., 2002; Stevens, 1987). It is not excluded that the cell type provides a critical environment for establishment of latency; in the experimental ocular infection of mice, HSV-1 establishes latency preferentially within A5 neurons, a subset of sensory neurons expressing Galβ1-4GlcNAc-R epitopes (Yang et al., 2000). This subset of neurons could correspond to neurons where expression of lytic viral genes such as ICP0 a gene which prevents circularization of viral genome, is impaired (Jackson and DeLuca, 2003; Margolis et al., 1992). Intriguingly enough, establishment of latency may also require CD8$^+$T cells since mice genetically deficient in CD8$^+$T cells or depleted in CD8$^+$T cells failed to establish uniform latency (Gesser et al., 1994; Simmons and Tscharke, 1992). Resident CD8$^+$T cells located in the latently-infected ganglia are specific for the glycoprotein B and since they expressed the marker of activation CD69 they should result of recent viral antigen encountering and activation. Indeed transcripts and viral proteins can be detected in latently-infected mouse neurons (Sawtell, 2003). This observation challenges the concept that HSV-1 latency represents a silent infection that should be ignored by the host immune response and suggests instead the antigen direct retention of memory CD8$^+$T cells (Khanna et al., 2003).

CD8$^+$ T lymphocytes play a critical role in preventing virus reactivation – a phenomenon which can occur in a small number of cells harbouring latent genomes, (1–5%) only, but sufficient enough to cause disease. It has been shown the reactivation is blocked by CD8$^+$ T cells which produced IFN−γ (Khanna et al., 2003). The CD8$^+$ T cells produce IFN-γ which inhibits the expression of the viral gene, *ICP0* that prevents genome circularisation (Halford and Schaffer, 2001; Knickelbein et al., 2008; Steed et al., 2006). The IFN-γ receptor is constitutively expressed in many neuronal populations (Robertson et al., 2000; Vikman et al., 1998), nevertheless, not all the neurons expressed receptor for IFN-γ, prevention of reactivation by IFN-γ would be restricted to IFN-γ receptor positive cells only. In neurons lacking IFN-γ receptor, it is thought that some virus-mediated latency mechanisms operate.

The CD8$^+$ T cells also polarize their T cell receptor (TCR) to the junction with neurons forming immunological synapses where the lytic granules of perforine and granzymes accumulated (Knickelbein et al., 2008). The function of lytic granules is not to trigger death of the surrounding HSV-infected neurons. Instead, lytic granules inhibit the expression of *ICP4*, a viral gene essential for further viral gene expression. Prevention of reactivation is controlled both by lytic granules and by IFN-γ. Thus, it has been proposed that altogether the virus, the neurons and CD8$^+$T cells are complementary actors in maintaining HSV1 latency (Divito et al., 2006).

In addition, HSV latency may confer a surprising benefit to the host. It appears that symbiotic protection could be offered form bacterial infection to the host harbouring HSV infection. Mice latently infected with a murine gamma herpes virus 68, were more resistant to bacterial infections than the non-latently virally infected mice. This effect is mediated by the prolonged production of the antiviral IFN-γ and the resulting systemic activation of macrophages (Barton et al., 2007). Thus, viral latency could be seen as a symbiotic relationship with immune benefit for the host. It remains to be shown whether this symbiotic protection do work in humans too.

## 4. Conclusion

Neurotropic virus and host immune responses can build intricate and complex interactions controlling viral pathology. Viral infections of the nervous system are powerful models to better understand how the nervous system controls inflammation and invading immune cells. Viral neuroimmunology studies may contribute to a better understanding of the harmful mechanisms leading to neurodegenerative diseases.

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