Review Article
Human Herpesvirus 6 and Neuroinflammation

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Human herpesvirus (HHV-) 6A and HHV-6B are two distinct β-herpesviruses which have been associated with various neurological diseases, including encephalitis, meningitis, epilepsy, and multiple sclerosis. Although the reactivation of both viruses is recognized as the cause of some neurological complications in conditions of immunosuppression, their involvement in neuroinflammatory diseases in immunocompetent people is still unclear, and the mechanisms involved have not been completely elucidated. Here, we review the available data providing evidence for the capacity of HHV-6A and -6B to infect the central nervous system and to induce proinflammatory responses by infected cells. We discuss the potential role of both viruses in neuroinflammatory pathologies and the mechanisms which could explain virus-induced neuropathogenesis.

1. Introduction

Human herpesvirus (HHV-) 6 was first isolated in 1986 by Salahuddin and colleagues [1]. This enveloped DNA virus belongs to the β-herpesvirus family and, together with its closest homologue HHV-7, forms the roseoloviruses subfamily. HHV-6 is widely spread in the population (seroprevalence > 90%) and can establish a persistent and most often asymptomatic infection in humans. Based on genetic, epidemiological, and functional features, the numerous isolated strains of HHV-6 were initially separated into two variants, HHV-6A and HHV-6B, which have recently been recognized as two distinct viruses. HHV-6A and -6B share an overall sequence identity of 90%, and several open reading frames are present in only one of the two viruses [2]. Primary infection with HHV-6B generally happens before the age of two; the virus is transmitted through saliva and close contacts with parents [3] and provokes exanthem subitum (or roseola), a benign febrile illness with skin rash. HHV-6A infection is thought to happen later in life and was not yet clearly identified as the causative agent for any disease.

To date, the only identified cellular receptor for both HHV-6A and -6B is the complement-regulatory transmembrane protein CD46 [4]. This protein is ubiquitously expressed in humans, allowing the viruses to infect a wide range of cells and tissues, including cells from the central nervous system (CNS). Both viruses have a high tropism towards T cells, which are the best virus producers in vitro, and can establish a persistent infection in different tissues, including the salivary glands (for HHV-6B only) and peripheral lymphocytes.

In immunocompromised patients, HHV-6A and -6B often reactivate and can provoke neurological pathologies. Moreover, many clinical studies have reported an association between HHV-6A and -6B and neuroinflammatory diseases, such as encephalitis or multiple sclerosis (MS), suggesting a role for both viruses in inflammatory processes. Indeed, although HHV-6A and -6B are generally considered as immunosuppressive agents, allowing them to evade the immune system, reports showing their proinflammatory properties are accumulating. Here, we review the available data providing evidence for HHV-6A and -6B infection in the human brain and their involvement in neurological diseases, and we discuss the potential mechanisms by which they could participate in neuroinflammation.

2. HHV-6A and HHV-6B Are Neurotropic Viruses

2.1. Evidence for the Presence of HHV-6A and -6B in the Brain.
Although HHV-6 was first identified as a lymphotropic virus,
it is now admitted that both HHV-6A and -B can also infect the brain. Indeed, several studies have reported the presence of HHV-6 DNA in different brain regions of healthy immunocompetent adults [5–11] as well as some viral transcripts, using in situ hybridization techniques [12]. However, in most of these studies, investigators failed to detect viral antigens, suggesting that HHV-6 may establish a latent infection in the brain in normal conditions. Overall, HHV-6B DNA was found more frequently in the brain than HHV-6A [7–9], in correlation with its higher prevalence, which indicates that both viruses have similar neuroinvasive properties. In contradiction, the analysis of the presence of HHV-6A and -6B DNA in the cerebrospinal fluid (CSF) of children with acute primary infection suggested that HHV-6A infection is more often restricted to the brain [13]. In some cases, both viruses can coexist in the brain, though their DNA was detected in different brain areas [9, 13]. Very little is known concerning the mechanisms of HHV-6 entry in the CNS. HHV-6B is thought to invade the brain and to establish persistent infection directly after primary infection [14]. Concerning HHV-6A, a recent study indicated that it might be able to travel through the olfactory pathway to reach the brain, thanks to its ability to infect specialized glial cells located in the nasal cavity [15].

2.2. Cell Tropism within the Human Brain. Histology analyses suggest that HHV-6A and -6B infect oligodendrocytes in vivo [7, 12], especially in case of productive infection (characterized by mRNA expression and production of viral proteins). In vitro experiments confirmed the capacity of the virus to infect oligodendrogial cell lines [16–18], as well as primary adult oligodendrocytes [19] and primary oligodendrocyte precursors, in which both HHV-6A and HHV-6B were able to induce syncytia formation, cell cycle arrest, and cell differentiation [20]. By histology analysis, Donati et al. found HHV-6 antigens in cells expressing the astrocyte marker glial fibrillary acidic protein (GFAP) in the brain of patients with temporal lobe epilepsy, indicating that HHV-6 can also infect astrocytes in vivo [21]. HHV-6A inoculation resulted in productive infection in primary fetal astrocytes [22–24] and induced apoptosis in both primary cells and astroglialoma cell lines [17, 25] with syncytia formation (Figure 1). On the contrary, infection of astrocytes with HHV-6B seems to be less efficient, leading to decreasing viral DNA load and fewer


### Table 1: Modulation of the immune response by HHV-6A and HHV-6B in different cell types.

<table>
<thead>
<tr>
<th>Cell type</th>
<th>HHV-6A</th>
<th>HHV-6B</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoid cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBMC</td>
<td>↑ IL-1β, TNFα, IFNα, IL-10, IL-15</td>
<td>↘ IL-12, IFNγ, IL-2</td>
<td>[29, 41–43]</td>
</tr>
<tr>
<td>T cells (primary and cell lines)</td>
<td>↑ IL-18, IL-2R, IFNγ R, CCL-2</td>
<td>↓ IL-10, IL-14, IL-10R, IL-13R, IL-2</td>
<td>[29, 44, 45]</td>
</tr>
<tr>
<td>NK cells</td>
<td>↑ IL-15, cytotoxicity</td>
<td></td>
<td>[46]</td>
</tr>
<tr>
<td>Monocytes (primary and cell lines)</td>
<td>↑ TNFα, IL-10, IL-12, IL-15</td>
<td></td>
<td>[47, 48, 126]</td>
</tr>
<tr>
<td>Tonsillar cells (ex vivo)</td>
<td>↑ CCL-5, IL-6, IL-12, IL-12, GM-CSF, CXCL-6, IL-10, TNFα, IL-7R</td>
<td>↑ IL-6, IL-10, IL-12β</td>
<td>[45, 127]</td>
</tr>
<tr>
<td>Dendritic cells</td>
<td>↑ maturation, IL-12</td>
<td>↓ IFNα-1, maturation, IL-12</td>
<td>[40, 49]</td>
</tr>
<tr>
<td>Macrophages</td>
<td></td>
<td></td>
<td>[39]</td>
</tr>
<tr>
<td>Brain cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astrocytes (primary and cell line)</td>
<td>↑ CCL-5, CCL-2</td>
<td>↑ IL-6, IL-10, IL-12β</td>
<td>[45, 127]</td>
</tr>
<tr>
<td>Other cell types</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelial cells</td>
<td>↑ CCL-5, CXCL-8, CCL-2</td>
<td></td>
<td>[52, 53]</td>
</tr>
<tr>
<td>Hepatoma cells</td>
<td>↑ CXCL-8</td>
<td></td>
<td>[54]</td>
</tr>
</tbody>
</table>

↑: enhanced production; ↓: inhibited production.

*Replication-dependent effect; †replication-independent effect.

morphological changes, which indicates that the two HHV-6 viruses may have different infection patterns within the brain. Fewer data concerning the infection of neurons and microglial cells are available; yet, some studies suggested that both cell types may be susceptible to HHV-6A and/or -6B infection in vitro [16, 17, 19, 24]. HHV-6A seems to be able to induce the formation of syncytia in neuroblastoma cell lines (Figure 1), and infected neurons were detected by immunostaining in patients who succumbed to HHV-6 encephalitis [26]. Both HHV-6A and -6B are then able to invade the central nervous system and to establish a persistent infection. However, HHV-6A seems to infect astrocytes and neurons more efficiently than HHV-6B, which may lead to the induction of different CNS pathologies.

### 3. Evidence for Proinflammatory Effects of HHV-6

HHV-6 was initially identified as an immunosuppressive virus. Primary infection with HHV-6B is indeed often associated with a decrease in leukocyte numbers [3], and both HHV-6A and -6B preferentially infect T lymphocytes in vivo and in vitro, reducing their proliferation [27–29] and inducing their apoptosis [30, 31]. Nevertheless, HHV-6A and -6B have also been demonstrated to exhibit proinflammatory properties in different contexts and have been suggested as potential agents in several inflammatory diseases, such as hepatitis [32], Sjögren's syndrome [33, 34], rheumatoid arthritis [35, 36], systemic lupus erythematosus [35, 37], and more recently Hashimoto’s thyroiditis [38]. While these associations remain hypothetical, extensive in vitro studies provide evidence for HHV-6A and -6B proinflammatory effects on a variety of cell types and tissues (summarized in Table 1).

The effects of HHV-6A and -6B on the cytokine expression profile in different types of immune cells have been widely investigated. Some studies have suggested that both viruses can induce a Th2 profile in T cells through the inhibition of IL-12 secretion by dendritic cells (DCs) and macrophages [39, 40] and through the induction of IL-10 production by peripheral blood mononuclear cells (PBMCs) [41]. In contradiction, other reports have shown that HHV-6 infection upregulates the expression of proinflammatory cytokines, including IL-1β, TNFα, and IFNα in PBMCs [42, 43], induces IL-18 and IFNγ receptor, and reduces IL-10 and IL-14 expression in T cells [44, 45], thus directing T cells towards a Th1 phenotype.

HHV-6A was also shown to exacerbate the cytotoxicity and IL-15 production in NK cells [46], as well as TNFα and IL-15 expression in monocytes [47, 48]. In plasmacytoid DC, HHV-6B was recently shown to induce type III IFN production, which has similar antiviral properties as type I IFN but had no effect on the Th1/Th2 balance [49].

In addition, studies on ex vivo cultures of lymphoid tissue showed that both HHV-6A and -6B can induce the secretion of chemokines in infected cells. Grivel et al. cultured freshly excised human tonsils and demonstrated that HHV-6A and -6B productive infection could be achieved, inducing
an upregulation of CCL-5 and CCL-3 expression [50, 51]. Meeuwsen et al. performed a transcriptional microarray analysis on infected astrocytes and showed that HHV-6A infection increased the expression of many proinflammatory cytokines upon stimulation with TNFa, IL-1β, and IFNy, including several chemokines (e.g., CCL-2, CCL-5, and CXCL-2) [45]. Moreover, HHV-6A was found to up-regulate the production of chemokines in primary endothelial cells [52, 53] and in a hepatoma cell line [54], indicating that the infection can promote the recruitment of leukocytes to different targeted tissues.

Altogether, these studies indicate that HHV-6A and -6B both have diverse proinflammatory effects on a variety of cell types. Although they could exhibit anti-inflammatory effects on some cell types, they are also able to increase the production of proinflammatory cytokines by some other cell types (Table 1) and to induce the development of a Th1 phenotype in T cells, thus eliciting the immune response. Moreover, they participate in the establishment of the inflammation in infected tissues by inducing the production of chemokines by resident cells. There is an apparent contradiction in the observed effects of HHV-6 infection, which include both the induction of immunosuppression and the promotion of inflammation. These differences may depend on the analyzed cell types or on infection kinetics representing different stages of infection and would require additional studies to be better understood.

4. HHV-6 and Neurological Diseases

HHV-6A and HHV-6B have both been directly or indirectly associated with neurological diseases [55–57], in cases of primary infection in immunocompetent young children, reactivation in otherwise healthy adults [3], or in immunosuppressed patients [58].

4.1. Infection in the “Immunocompetent” Population. HHV-6B was long ago conclusively identified as the etiologic agent for exanthem subitum (ES), a common infant febrile illness with skin rash [59]. Although ES is generally benign, it can be associated with various neurological complications, including convulsions, seizures, and encephalitis [60–62], often resulting in ataxia and epilepsy [63–66]. The most severe forms of encephalitis associated with ES can even lead to fatal outcome [67, 68].

In immunocompetent adults, evidence for the direct implication of HHV-6A or -6B in neurological diseases is more difficult to provide. Viral DNA loads in the serum and CSF, as well as IgM levels, are commonly used to detect HHV-6 infection. Based on these data, some cases of probable HHV-6-related encephalitis or meningoencephalitis have been reported in otherwise healthy adults and sometimes successfully treated with antiviral drugs [69–71]. Furthermore, studies of patients with encephalitis of unknown etiology strongly suggested that HHV-6 could be involved in disease establishment in certain cases [72–74].

4.2. Reactivation in Immunosuppressed Patients. As for other latent human herpesviruses, immunological defects are able to trigger HHV-6 reactivation from latency. Indeed, HHV-6A and -6B have been suggested to reactivate in immunocompromised patients, which received chemotherapy treatments or were diagnosed with AIDS. In hematopoietic stem cell transplant recipients especially, HHV-6 DNA (mostly -6B) was detected in the serum or PBMC in around 50% of the cases [58, 75, 76], indicating that viral reactivation has occurred. In several case reports, where no other possible cause was found, neurological complications in immunosuppressed people have been attributed to HHV-6 reactivation [56, 58]. Its involvement in encephalitis development was generally supported by the detection of viral DNA in the CSF and more rarely by the presence of viral proteins in affected areas of the brain at autopsy [26, 77, 78]. Moreover, several epidemiological studies have suggested a correlation between the risk of developing neurological symptoms and HHV-6 reactivation [79–81].

4.3. Association with Multiple Sclerosis. HHV-6 has long been cited as a potential candidate virus for the etiology of multiple sclerosis (MS). The importance of this inflammatory neurological disease, which represents the first cause of nontraumatic handicap in young adults, particularly inspired the research in this area. Abundant clinical studies have highlighted a correlation between MS and several parameters assessing for HHV-6 infection. For instance, the levels of HHV-6 DNA in the serum, which are characteristic of ongoing infection, are significantly increased in MS patients when compared to healthy donors or with patients with other diseases [82–85]. HHV-6 DNA was also detected at higher frequencies in the CSF and in the peripheral blood mononuclear cells of MS patients [82, 84, 86]. Moreover, the levels of HHV-6-specific IgG and IgM in the serum and in the CSF were reported to be higher in MS patients in several studies [83, 86, 87], although this phenomenon does not appear to be specific for HHV-6. Indeed, some groups have reported similar increases in the titers of antibodies against other viruses including Epstein-Barr virus or varicella-zoster virus. Soldan et al. also showed that lymphoproliferative responses against HHV-6 antigens were increased in MS patients [88]. The analysis of brain biopsies and postmortem tissues indicated that HHV-6 DNA was present more frequently in the brain of MS patients than in control brains, and that it was also more frequent in MS lesions than in normal areas of the same brains. Immunohistochemistry analyses confirmed the presence of viral proteins in oligodendrocytes and astrocytes in the brain from MS patients, with a higher frequency in demyelinating plaques [7, 12, 87, 89, 90]. Most interestingly, viral loads were detected more frequently, and levels of HHV-6-specific IgG were increased in MS patients experiencing disease exacerbation [84, 91–93], thus suggesting a correlation between HHV-6 infection and MS relapses.

As the distinction of HHV-6A and -6B as two different viruses was only recently adopted, many of the initial studies do not discriminate between the two variants. However, based on few reports, it appears that HHV-6A is found more
frequently than -6B in the serum of MS patients [94]. Especially in case of active infection, Alvarez-Lafuente et al. have found only HHV-6A [92]. In contrast, in one study, intrathecal HHV-6B IgG levels were more abundant than HHV-6A IgG in MS patients, and only HHV-6B-specific IgM levels were found [95].

The potential association between HHV-6A and HHV-6B infection and MS has often been discussed and remains controversial. Some studies provided contradictory results [96–98], raising methodological and technical questions, especially concerning the choice of control groups and the immunological state of the included patients, who often receive immunosuppressive treatments, that may provoke latent herpesvirus reactivation by itself. Some studies have taken these matters into account and therefore provide solid data supporting the existence of a correlation between HHV-6 infection and MS pathology. Yet, whether HHV-6 infection is the etiologic cause, a factor for disease progression, or a consequence of MS remains unclear and would need further investigation.

5. Potential Mechanisms for HHV-6-Induced Neuroinflammation

Although the potential role of HHV-6A and -6B in MS has not been completely elucidated, both viruses have been conclusively involved in some cases of encephalitis in immunocompromised patients and in neurological complications of exanthem subitum. Several observations may provide explanations on how HHV-6 could trigger or participate in the establishment of neuroinflammation.

5.1. Molecular Mimicry. Among the mechanisms proposed for virus-induced autoimmunity, molecular mimicry is one of the most popular ones. Based on the similarity in peptide sequence between viral proteins and self-proteins, it has been postulated that viral infections could activate cross-reactive T cells, able to recognize both viral and self-antigens, which could then trigger an autoimmune response and cause tissue damage. Several studies suggest that such a mechanism could be involved in HHV-6-induced neuroinflammation. A first study reported that 15%–25% of HHV-6-specific T cell clones obtained from healthy donors or MS patients were cross-reactive to myelin basic protein (MBP), one of the autoantigens implicated in MS pathology [99]. In fact, MBP and the U24 protein from HHV-6 were later shown to share an identical amino acid sequence of 7 residues. Moreover, T cells directed against an MBP peptide also recognized an HHV-6 peptide, both peptides containing the identical sequence. Interestingly, cross-reactive cells were more frequent in MS patients than in controls [100]. These data were further confirmed by a more recent study, in which the presence of cross-reactive CD8+ cytotoxic T cells was found [101]. Altogether, these studies suggest that HHV-6 infection can activate T cell responses which can simultaneously be directed against myelin sheaths, thus strongly supporting the potential role for HHV-6 in autoimmune diseases affecting the CNS (Figure 2(a)).

5.2. Infection of CNS Cells and Creation of a Proinflammatory Environment. As mentioned earlier, HHV-6A and HHV-6B are able to infect several CNS cell types, both in vitro and in vivo, and to trigger proinflammatory responses in a variety of infected cells. In particular, HHV-6A can infect primary astrocytes and induce the expression of several proinflammatory genes, especially when the cells have been pre-treated with proinflammatory cytokines [45]. This suggests that HHV-6A could enhance the proinflammatory response of astrocytes, thus increasing leukocyte infiltration, in patients who already suffer from neuroinflammatory diseases (Figure 2(b)).

Recently, one study on dendritic cells demonstrated that HHV-6B can induce IFNα-1 production via TLR-9 signaling [49]. Moreover, TLR-9 has been shown to be expressed in human astrocytes [102]. It is then likely that HHV-6A can alter astrocyte cytokine expression profile through TLR-9 signaling.

Another consequence of HHV-6 infection of CNS cells could be the unmasking of autoantigens. HHV-6A was shown to induce cell death in oligodendrocytes and astrocytes either directly [25] or indirectly, via the production of soluble factors by productively infected T cells [17, 105]. Therefore, HHV-6A productive infection of CNS cells or the presence of productively infected lymphocytes in the brain could provoke the death of glial cells and release previously unrecognized self-antigens, thus initiating an autoimmune response directed to the brain.

5.3. Leukocyte Chemotraction via Virokin Expression. The genome of HHV-6 encodes two G protein-coupled receptors, U22 and U51, similar to human chemokine receptors [106, 107] and one single chemokine-like protein, U83. The U83 gene from HHV-6B encodes a functionally active, highly specific agonist of the chemokine receptor CCR-2 [108, 109], which is expressed on monocytes and macrophages. Similarly, the U83 gene from HHV-6A encodes a homologous protein which can bind with high potency to several receptors, including CCR-1, -4, -5, and -8 [110], expressed by a variety of leukocytes. U83 is one of the few genes which are not present in the genome of Human Herpesvirus 7 (HHV-7), the closest homologue of HHV-6A and -6B. Interestingly, this other roseolovirus has not yet been associated with neuroinflammatory diseases.

Therefore, the productive infection of resident cells by both HHV-6A and -6B and the production of the U83 protein in the brain could then promote leukocyte infiltration in the CNS by chemotraction (Figure 2(b)).

5.4. Infection of Endothelial Cells and Recruitment of Immune Cells to the CNS. Several studies have shown that HHV-6A can infect endothelial cells obtained from different...
Figure 2: Potential mechanisms for HHV-6-induced neuroinflammation. (a) Based on similarities between viral proteins and brain proteins, HHV-6A or -6B infection in the periphery could lead to the activation of cross-reactive T and B cells, able to recognize both viral antigens and brain antigens, and to the development of an autoimmune response directed to the brain (molecular mimicry). This would promote lymphocyte infiltration in the CNS, where they could have cytotoxic activities against resident cells, especially oligodendrocytes which express myelin antigens (1). Peripheral infection could also increase the inflammation by inducing IL-17 and inhibiting IL-10 production by T cells through CD46 binding (2). (b) Infection of astrocytes in the brain can lead to the release of proinflammatory cytokines and chemokines, which promote the infiltration of leukocytes expressing the corresponding chemokine receptor (3). Productive infection of CNS cells can result in the production of the viral chemokine U83, which can also attract leukocytes to the brain (4). Finally, infection of endothelial cells can induce the secretion of chemokines, thus attracting circulating leukocytes and facilitating their transmigration through the blood-brain barrier (5).

5.5. CD46 Engagement. The transmembrane protein CD46 is the only known entry receptor for both HHV-6A and -6B entry. This complement regulatory protein also plays an important role in the adaptive immune response as it can modulate T cell responses depending on which cytoplasmic tail is expressed [113] and can induce CD4+ T cells toward a Th1 phenotype, with high IL-10 production [114]. One could then hypothesize that HHV-6A and -6B, by binding to their receptor, could modulate its functions. In support to this theory, a clinical study indicated that increase in HHV-6 viral load was correlated to enhanced CD46 expression in MS patients [115], and several alterations in CD46 functions were described; the CD46-induced IL-10 secretion by T cells was strongly decreased [116], whereas the CD46-dependant IL-23 production by DC and IL-17 expression by T cells were
enhanced [117, 118]. This suggests that HHV-6 could participate in neuroinflammation in the context of MS, by promoting inflammatory processes through CD46 binding (Figure 2(a)).

5.6. Interaction with Other Infectious Agents. In the field of MS, many different genetic and environmental factors have been proposed as potential etiological agents. Yet, if considered separately, none of these candidates could be directly linked to the onset of the disease. Therefore, efforts are now focusing on combinations of factors, including both exogenous agents, such as living conditions or viral and bacterial infections, and endogenous factors, like genetic predispositions. One good example of these potential combinations is the interaction between herpesvirus infections and human endogenous retroviruses (HERVs) [119]. HERVs, which represent around 8% of the human genome, have been related to MS pathology since fully mature virions were isolated from leptomeningeal cells of an MS patient [120]. These viruses, and especially their envelope proteins, have strong inflammatory properties [121, 122]. HHV-6 infection seems to have direct transactivating properties on HERV, as it is able to increase their reverse transcriptase activity [123] and to stimulate the transcription of envelope genes [124, 125]. HHV-6 infection could then increase neuroinflammation by inducing HERV proteins, thus linking exogenous infections to endogenous factors.

6. Conclusion

HHV-6A and HHV-6B both exhibit neuroinvasive and proinflammatory properties. Moreover, both viruses are closely associated with neurological diseases involving inflammatory processes, which strongly supports the hypothesis that they can induce neuroinflammation.

The rare cases of encephalitis following primary HHV-6B infection, in which the virus is the only possible pathogenic cause of disease, provide evidence that HHV-6B has the ability to trigger inflammation in the brain. Whether this is a direct or indirect consequence of viral infection and whether the virus can induce such complications alone or in synergy with other factors remain to be clarified.

However, in other contexts, it is still difficult to bring solid proof of a decisive role for either HHV-6A or HHV-6B in the establishment of neuroinflammatory diseases. As HHV-6A appears to be more neurotropic and was more closely associated with multiple sclerosis, it may have more important implication in neurological diseases in adults. Yet, further investigations are still needed to better understand how these two viruses may participate in neuroinflammatory processes. The development of new tools, such as more complex in vitro systems or novel animal models in monkeys and humanized mice, could be of great help for the research in this field.

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