Microreview

Borna disease virus: a unique pathogen and its interaction with intracellular signalling pathways

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Summary

Borna disease virus (BDV) is a neurotropic RNA virus that establishes non-cytolytic persistent infection in the central nervous system of warm-blooded animals. Depending on the host species and the route of infection, BDV persistence can modulate neuronal plasticity and animal behaviour and/or may provoke a T cell-mediated immunopathological reaction with high mortality. Therefore, BDV functions as a model pathogen to study persistent virus infection in the central nervous system. Here, we review recent evidence showing that BDV interferes with a spectrum of intracellular signalling pathways, which may be involved in viral spread, maintenance of persistence and modulation of neurotransmitter pathways.

Introduction

Borna disease virus (BDV) is a unique pathogen regarding its molecular biology, tropism, pathogenesis and the capacity to influence animal behaviour. Research in recent years has revealed multiple interactions of BDV with intracellular signalling pathways, including the prototypic mitogen-activated protein kinase (MAPK) cascade, the NF-κB system, the pleiotropic protein kinase C (PKC), the tumour suppressor p53 and the antiviral type I interferon (IFN) system, which may form the basis for some of the fascinating properties of this virus. For a better appreciation of these aspects, we will first summarize general findings on the history, the molecular biology and pathogenesis of the virus before we focus on signal transduction events.

Borna disease derives its name from the town of Borna in the state of Saxony, Germany, where an outbreak was recorded among farm animals and military horses around 1900 (Lipkin and Briese, 2007). Borna disease is a rare fatal neurological disease that affects primarily ungulates such as horses and sheep in central Europe, but many other warm-blooded animals including rodents and non-human primates are susceptible to experimental infection (Staeheli et al., 2000). BDV was characterized as an enveloped virus with a single negative-stranded RNA genome of about 8.9 kb (Lipkin and Briese, 2007). The virus transcribes and replicates its genome in the nucleus of infected cells and uses the splicing machinery to regulate the expression of viral genes. At least six viral proteins are synthesized in BDV-infected cells: the nucleoprotein (N), the X- or p10 protein, the phosphoprotein (P), a putative matrix protein (M), a single glycoprotein (GP) and a polymerase (L) (Fig. 1). The virus utilizes an unidentified receptor and enters the host cell by receptor-mediated endocytosis. It is assumed that infected cells release only a minimal amount of free virion particles and that the virus rather spreads through cell-to-cell contacts (Lipkin and Briese, 2007). Based on the analysis of the BDV genome and its terminal sequences (Pleschka et al., 2001), reverse genetic systems have only recently been established allowing genetic manipulation and investigation of BDV (Schneider et al., 2005; de la Torre, 2006).

Persistent, non-cytolytic BDV infection of the central nervous system (CNS) in the classical hosts causes delayed immunopathology. The virus primarily infects neurons of the limbic system, in particular the cortex and the hippocampus, which is thought to support cognitive functions, emotion, behaviour and long-term memory (Gosztonyi and Ludwig, 1995). The period between virus infection and onset of disease signs varies depending on the species and the age of the host from several days to years. During this phase, BDV can affect intracellular signalling pathways in the CNS and may cause molecular and cellular alterations prior to the onset of immunopathology. A wide spectrum of BDV-induced neurological
disorders has been described in animals that range from disturbances in cognitive functions, including deficits in learning and social behaviour to immune-mediated locomotor and sensory dysfunction (Lipkin and Briese, 2007).

BDV serves as an excellent model to study virus-induced immune-mediated pathogenesis in the CNS. The pathology found after intracerebral infection of Lewis rats is comparable to the immunopathology found in naturally infected horses and sheep. After intracerebral infection, rats develop an encephalomyelitis in which the infiltrating lesions can be found mainly in the cortex but also in the hippocampus in areas where the virus is present. The infiltrating cells have been characterized as CD4+ and CD8+ T cells and macrophages. BDV-specific CD8+ T cells represent the effector cell population. The immunodominant epitopes for rat and mice MHC class I molecules are present on the viral nucleoprotein. CD8+ T cells significantly contribute to the destruction of virus-infected brain cells in vivo (Stitz et al., 2002). No evidence has been presented that antibodies contribute to neuropathology, although neutralizing antibodies apparently control virus tropism and can prevent the spread of virus from peripheral infection sites to the CNS (Furrer et al., 2001; Stitz et al., 2002). Analysis of BDV-infected brain tissue revealed the presence of mRNA encoding for pro-inflammatory cytokines (e.g. IL-1β, IL-6, TGFβ and TNFα) and chemokines (e.g. IP-10 and CCL5) leading to activation of intracellular signalling pathways (reviewed in Stitz et al., 2002).

The behavioural disturbances caused by BDV in animal models and sero-epidemiological studies in humans raised the question, whether patients suffering from depression or schizophrenia had been exposed to BDV or a related pathogen (Rott et al., 1985; Lipkin et al., 2001). However, there are considerable technical challenges to establish validated diagnostic procedures for this neurotropic virus that is released from infected cells only in very low amounts and for which the intra vitam detection is difficult even in naturally infected animals. Thus, the available data indicate that BDV is a natural pathogen of animal species, but there is currently not sufficient evidence to conclude that this virus is the causative agent for human mental diseases (Wolff et al., 2006; Durrwald et al., 2007).

**Interactions of BDV with cellular signalling pathways**

**BDV-induced neuronal changes: viral interactions with PKC and the Raf/MEK/ERK pathway affect synaptic plasticity**

BDV-associated behavioural and neurodevelopmental abnormalities were proposed to be in part due to viral interference with signalling pathways important for neuron functions such as the synaptic vesicle (SV) recycling and neuronal outgrowth (reviewed in Gonzalez-Dunia et al., 2005). These conclusions were based on observations that BDV impairs expression of proteins involved in synaptic plasticity and the neuronal neurotrophine response (Gonzalez-Dunia et al., 2000; Hans et al., 2004). Synaptic plasticity describes the functional and morphological adaptation of neurons to external influences. PKC as well as the MAPK signalling pathway play a pivotal role in
these processes as they modulate presynaptic neurotransmitter release (Turner et al., 1999; Gonzalez-Dunia et al., 2005).

Functional interactions of BDV with cellular kinases were suggested when the viral P protein, a cofactor of the viral polymerase, was found to be phosphorylated by the epsilon isoform of PKC and to a lesser extent also by the casein kinase II (Schwemmle et al., 1997; Schmid et al., 2007). The high concentration of PKCε in the limbic system coincides with the limbic distribution of BDV and this tropism may have significant implications for pathological virus-induced changes (reviewed in Gonzalez-Dunia et al., 2005). An ex vivo analysis of BDV’s impact on the rate of SV recycling in primary neurons, which reflects synaptic activity, indicated a functional involvement of PKC activity for BDV-induced changes (Volmer et al., 2006). Here it was found that BDV infection does not affect basic presynaptic functioning of neurons. Rather, BDV infection blocked the increase in SV recycling, suggesting defects in long-term potentiation and it was concluded that this blockade is due to reduced PKC-dependent phosphorylation of proteins that regulate SV recycling. The interference of BDV with PKC-dependent phosphorylation appeared to involve a competition of the BDV P protein with PKC-dependent phosphorylation of endogenous cellular PKC substrates (Volmer et al., 2006). This resembles the suggested decoy mechanism of how the BDV P protein inhibits activation of the kinase TBK1 (see below).

The regulation of PKC signalling by BDV was further deduced from a study of an in vitro model of neuronal communication involving neurons cultured on multielectrode arrays (Volmer et al., 2007). Here, BDV infection did not affect spontaneous neuronal activity, but modulated synaptic plasticity important for learning and memory by a selective blockade of activity-dependent enhancement of neuronal network activity (Volmer et al., 2007). Interestingly, the solitary expression of the BDV P protein in astrocytes of transgenic mice was sufficient to cause distinct behavioural and neurological changes, emphasizing that this protein plays an important pathological role in BDV infection (Kamitani et al., 2003). Taken together, these findings elucidate possible mechanisms of viral interference with neuronal function and provide an explanation of how BDV could cause synaptic dysfunction and contribute to neurobehavioural disorders (Volmer et al., 2006).

An additional aspect of how BDV infection could affect neuronal network connections and brain development comes from the observation that the BDV P protein interacts and interferes with signalling by amphoterin (HMGB1), a nuclear protein implicated in the transcription regulation and DNA repair through interaction with factors like RAG1, p53 and Hox (Kamitani et al., 2001). HMGB1 is also functionally involved in processes of neurite outgrowth and cell migration (for review: Gonzalez-Dunia et al., 2005). The P/HMGB1 interaction was shown to repress p53-mediated transcription activity (Zhang et al., 2003). As p53 is involved in cell cycle regulation and apoptosis, the indirect modification of p53 activity by the viral P protein may be linked to the persistence and unique neuropathogenesis of the virus in the CNS (Zhang et al., 2003). It should also be noted that BDV manipulates the cell cycle by interaction of the viral nucleoprotein (N) with the Cdc2-cyclin B1 complex. Persistently infected rat fibroblast cells show decelerated proliferation due to delayed G(2)-to-M transition, a cell cycle checkpoint, regulated by the Cdc2-cyclin B1 complex. Interestingly, this effect is N- but not P-dependent (Planz et al., 2003).

The Raf/MEK/ERK cascade transmits signals by consecutive phosphorylation from the serine/threonine kinase Raf via the kinase MEK (MAP kinase kinase/ERK kinase) to ERK (extracellular signal regulated kinase) and is the prototype of the MAPK signalling pathway family. MAPK signalling has been implicated in a variety of cellular functions and is also activated by many viruses (Pleschka et al., 2008). In the CNS, this pathway plays a crucial role for control of long-lasting forms of synaptic plasticity and memory (Thomas and Huganir, 2004). In neuronal cells, the Raf/MEK/ERK pathway is stimulated, among others, by neurotrophins, a family of neuronal growth factors including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF). Neurotrophins and their specific receptors are expressed at high levels in areas of the brain, where intense neuronal plasticity is found (reviewed in Gonzalez-Dunia et al., 2005). BDV was in fact one of the first RNA viruses shown to activate the Raf/MEK/ERK signalling pathway (Planz et al., 2001). Already 1 h after experimental infection, ERK activation was detected in non-neuronal cells. In addition, ERK is constitutively activated to distinct levels in various persistently BDV-infected cell lines (Planz et al., 2001). Even though the exact mechanism of ERK activation and its requirements for BDV replication are unknown, the very early time point of activation suggested that viral gene expression is not involved in this first onset of cascade activation.

Later studies revealed further interactions of BDV with ERK-dependent signalling, which were first studied in PC12 cells that normally undergo neuronal differentiation after stimulation with NGF. A persistent BDV infection caused constitutive activation of the Raf/MEK/ERK pathway in PC12 cells (Hans et al., 2001). However, the activated ERK failed to translocate into the nucleus efficiently and NGF treatment failed to induce neuronal differentiation, suggesting that BDV blocks ERK-dependent gene expression required for neuronal outgrowth. Furthermore, the analysis of primary hippocampal pyramidal neurons demonstrated that a persistent BDV infection

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also blocked phosphorylation of ERK in response to the neurotrophin BDNF (Hans et al., 2004). In BDV-infected cells, the BDNF-dependent expression of SV proteins was suppressed, which resulted in severely impaired synapticogenesis and defects in synaptic organization. Hence, BDV infection appears capable to block the responses of neuronal cells to exogenous stimuli via MAPK signalling and may lead to disturbances of neuronal functions including synaptic plasticity. Interestingly, inhibition of the cascade by the MEK inhibitor U0126 resulted in a block of BDV spread and reduced virus yields up to 99%. Inhibition was observed in non-neuronal cells and in human oligodendrocytes, showing that the effect is not restricted to a particular cell type (Planz et al., 2001). Treatment of persistently BDV-infected cells did not result in reduction of viral titer, indicating that U0126 treatment does not affect viral replication but rather inhibits viral cell-to-cell spread.

The influence of BDV infection on NF-κB signalling

The transcription factor NF-κB is involved in the regulation of many cellular processes including apoptosis and host defence. A variety of stimuli initiate different signalling pathways leading to NF-κB activation. Most of these pathways converge on the IkB kinase (IKK) signalling complex that plays a major role in NF-κB activation (Israel, 2000). NF-κB is activated by multiple viral pathogens and it is a general belief that NF-κB exerts an antiviral function upon infection with RNA viruses (reviewed in Hiscott et al., 2001; Ludwig et al., 2003). In the brain, the target tissue of BDV, NF-κB is an important regulator of biochemical and molecular cascades that can either prevent cell death and support neuronal plasticity or induce apoptosis. NF-κB is activated by various intercellular signals including cytokines, neurotrophic factors and neurotransmitters. NF-κB was proposed to protect neurons temporarily from the amyloid β-mediated apoptosis leading to neurodegeneration during Alzheimer's disease (Kaitschmidt et al., 1999). On the other hand, NF-κB activation enhanced neuronal death in a mouse model of stroke (Herrmann et al., 2005). Thus, activated NF-κB can participate in different ways in the neuronal functions depending on the specific state of neuronal activity or differentiation (Kaitschmidt et al., 1994).

Various NF-κB activating cytokines are induced during BDV infection in the CNS. In the normal, uninfected rat brain, activated NF-κB was predominantly found in the cortex and in the cerebellum (Bourteele et al., 2005). Interestingly, at early time points after BDV infection (13 days), the virus was primarily detectable in the hippocampus, a region in which NF-κB was not activated. The amounts of BDV-positive cells in the cortex and cerebellum were limited early after infection and the activation status of NF-κB was not altered compared with uninfected rat brain (Bourteele et al., 2005). However, during the peak of BDV infection around days 17–25 post infection, activation of NF-κB was increased in infected cells in different areas of the brain, which was most probably due to the presence of various cytokines in the BDV-infected rat brain (Shankar et al., 1992; Stitz et al., 2002).

The inhibitory interaction of BDV with the NF-κB signalling pathway in the rat brain was supported by in vitro findings as highly susceptible neuronal cells did not induce the transcription factor upon infection (Bourteele et al., 2005). The inhibition of NF-κB activation during BDV infection may involve a viral interference with the regulatory TBK-1/IKKe complex. The available data support the hypothesis that BDV infection inhibits NF-κB functions in the brain leading to disturbances in synaptic plasticity and induction of apoptosis already at time points when immunopathology is absent. Moreover, one might argue that the neuronal alterations are not due to the effect of a single signalling pathway. Beside the fact that NF-κB activation is reduced in the hippocampus, which may lead to a preferential tropism of BDV for this region, strong neurotrophin expression and PKC activity in the hippocampus was suggested to further support BDV replication in this region (Hans et al., 2004).
with long dsRNA, a by-product of viral replication (Kato et al., 2008). In the endosomal compartment, viral dsRNA is detected by TLR-3 (Fig. 2), whereas TLR-7/-8 respond to single-stranded RNA (Kawai and Akira, 2007). Some pathogens such as neurotropic West Nile virus are sensed by both receptor families, depending on the specific cell type (Daffis et al., 2008). The RLRs trigger a signalling module controlling the activation of the latent transcription factors IRF-3/-7, NF-kB and ATF-2/c-jun that activate IFN gene promoters (Takeuchi and Akira, 2008). Key components of this module include the mitochondrial IPS-1 protein that is contacted by activated RLR, and the Iκ-B kinase family members TBK1 and/or IKKε that activate IRF-3/-7 by phosphorylation (Hiscott, 2007). Phosphorylated IRF-3 migrates to the nucleus and engages in transcriptional activation of target genes. Activation of IRF-3 through TLR3 is mediated by the TRIF adapter protein that recruits TBK1. The secreted IFNs stimulate the JAK-STAT signalling pathway through the IFN-α/β receptor in para- and autocrine manners, thereby inducing the expression of cellular proteins with potent antiviral activity (Randall and Goodbourn, 2008).

BDV replication is susceptible to treatment with exogenous IFN, suggesting that the virus does not inhibit the JAK-STAT pathway or IFN-inducible proteins (von Rheinbaben et al., 1985; Hallensleben and Staeheli, 1999). However, BDV infection did not upregulate IFN-α mRNA levels or IRF-3 in the rat brain (Shankar et al., 1992; Unterstab et al., 2005) and genetic ablation of the type I IFN receptor did not influence viral titers or spread in infected mice, indicating that IFN is not sufficiently activated to contain the virus in vivo (Staeheli et al., 2001). Interestingly, the BDV P protein was identified to interact with the kinase TBK1 in the RIG-I-dependent signalling module and to inhibit virus-stimulated IFN-β induction (Unterstab et al., 2005). Moreover, the P protein was phosphorylated by TBK1 and competed with IRF-3/-7 as a kinase substrate, suggesting that the viral protein serves as a decoy to reduce activation of IFN genes (Unterstab et al., 2005). The interference of the P protein with TBK1 may also contribute to the suppression of NF-kB activity. Recent in vitro analysis confirmed the repressive activity of the P protein on transcription factors involved in IFN induction (Peng et al., 2007).

At present, no information is available on a cellular receptor that recognizes BDV RNA. The nuclear replication of BDV is a conceptual benefit as the intracellular innate immune receptors reside in the cytosolic or endosomal compartment. However, the viral genome may become detectable to cellular sensors when it is transferred to the cytosol for budding or when the virus enters a new host cell via endosomes. Interestingly, replication of the BDV genome involves trimming of four 5′-terminal nucleotides, which also removes the 5′-triphosphate group present on the genomes of many other negative strand RNA viruses (Schneider et al., 2005; Habjan et al., 2008). This processing event was suggested to be not only important for genome replication, but also to reduce recognition by the RIG-I receptor (Habjan et al., 2008). Still, the antagonistic activity of the BDV P protein on
TBK1 that is crucial for IFN induction in response to both RLRs and the TLR-3 and -4 receptors indicates a necessity for active IFN suppression during the virus life cycle. Recent studies showed that not only BDV but also some paramyxov- and rabies virus have evolved an antagonistic protein for TBK1 (Brzozka et al., 2005; Lu et al., 2008).

**BDV infection modulates caspase activation and apoptotic processes**

In order to fight viral infection multicellular organisms employ many defences including the cell autonomous process of apoptosis that is a morphologically and biochemically defined form of cell death (Razvi and Welsh, 1995). Apoptosis induction in the CNS is a delicate process as the elimination of infected cells may pay off if the dying cells can be easily substituted, but the damage of irreplaceable highly specialized neurons might have fatal consequences (Allsopp et al., 1998). Therefore, apoptosis in the CNS has to be well controlled to prevent a loss of essential vital functions. The central component of the apoptotic machinery is a proteolytic system consisting of a family of cysteinyl proteases, termed caspases (for review, see Thornberry and Lazebnik, 1998).

BDV infection can lead to the activation of cellular apoptosis, which results in detrimental effects in the host. Intra-cerebrally BDV-infected newborn Lewis rats showed prolonged cell loss in the hippocampus and cerebellum with reduction in granule and Purkinje cell numbers, which seemed to be related to neurodevelopmental damages. Remarkably, those animals showed behavioural disorders that resemble abnormalities observed in some autistic children (Hornig et al., 1999). This included abnormal reflexes, hyperactivity, inhibition of open-field exploration and stereotypic behaviours (Hornig et al., 1999). Neurons were lost predominantly by apoptosis, as supported by increased mRNA levels for pro-apoptotic or -pyroptotic gene products (Fas, caspase-1), decreased mRNA levels for the antiapoptotic bcl-x protein and fragmentation of DNA. Hornig and colleagues suggested that BDV-infected newborn rats may be useful as a model to study neuropathologic abnormalities and human neurodevelopmental disorders (e.g. autism) (Hornig et al., 1999).

A direct indication for a functional role of caspases in BDV-mediated apoptosis of neuronal cells was demonstrated by a study of poly (ADP-ribose) polymerase 1 (PARP-1) and caspase-3 in neonatal BDV infection (Williams et al., 2008). PARP-1 is not only a target of caspase activity and thereby an apoptosis marker, but also participates in DNA damage repair and cell proliferation (Kauppinen and Swanson, 2005). PARP-1 can also influence the inflammatory response in the brain by regulating the activation and proliferation of microglia, the resident immune cells of the CNS, which can contribute to CNS injury by cytokine secretion at the site of neuronal damage (Kauppinen and Swanson, 2005). Enhanced PARP-1 expression and the activation of PARP-1 and caspase-3 contributed to hippocampal neurodegeneration and the glial response to persistent BDV infection in the CNS (Williams et al., 2008). These findings support the conclusion that BDV-induced cellular apoptotic reactions lead to neuronal tissue destruction and disease.

**Conclusions and open questions**

The neurotropic BDV has been described as a ‘mood virus’ that is able to persist in the CNS of a variety of host species and alter their behaviour even in the absence of neuroinflammatory responses. We summarized the current knowledge of how modulation of cellular signalling by this pathogen may contribute to various pathologic changes. Clearly, there is heterogeneity in different cell types and cross-talk between some of the discussed signalling pathways (such as MAPK and NF-kB), but due to the infancy of this field there is currently limited understanding about how those aspects are involved in virus infection. There is also a lot to be learned about this unique virus in other areas. Thus, it is barely understood, whether high susceptibility of some species for BDV is related to enhanced viral replication and spread possibly involving distinct interactions with the host’s signalling components or is rather due to different immunological responses. This is interesting in particular in the context of the still to be solved question whether humans are generally susceptible to BDV infection. Further, will it be feasible to tackle interactions of the virus with signalling cascades in order to possibly modulate: (i) viral replication, or (ii) behavioural changes or (iii) immunopathogenesis in animal hosts in a beneficial direction? A novel Bornavirus was recently isolated from parrots suffering from a frequently deadly disease involving the loss of neurons in the avian gastrointestinal tract, raising the question about further reservoirs for Bornaviruses in nature (Kistler et al., 2008). Finally, BDV was one of the last Mononegaviruses that was engineered for the expression of a foreign gene (Schneider et al., 2007). Thus, could BDV be useful in the development of a persisting neurotropic vector for stable expression of transgenes? Investigating and solving these topics will not only lead to a better understanding of BDV biology, but may also shed light on our understanding of the consequences when a viral infection persists in the CNS.

**Note**

We apologize to the many colleagues whose works could not be cited as a result of space limitations.
References
Allsopp, T.E., Scallan, M.F., Williams, A., and Fazakerley, J.K. (1998) Virus infection induces neuronal apoptosis: a comparison with trophic factor withdrawal. Cell Death Differ 5: 50–59.
Bourteele, S., Oesterle, K., Pleschka, S., Ehrhardt, C., Wolff, T., Ludwig, S., and Planz, O. (2005) Constitutive activation of the transcription factor NF-kB results in impaired Borna disease virus replication. J Virol 79: 6043–6051.
Brozok, K., Finke, S., and Conzelmann, K.K. (2005) Identification of the rabies virus alpha/beta interferon antagonist: phosphoprotein P interferes with phosphorylation of interferon regulatory factor 3. J Virol 79: 7673–7681.
Daffis, S., Samuel, M.A., Suthar, M.S., Gale, M., Jr and Diamond, M.S. (2008) Toll-like receptor 3 has a protective role against West Nile virus infection. J Virol 82: 10349–10358.
de la Torre, J.C. (2006) Reverse-genetic approaches to the study of Borna disease virus. Nat Rev Microbiol 4: 777–783.
Durrwald, R., Kolodziejek, J., Herzog, S., and Nowotny, N. (2007) Meta-analysis of putative human bornavirus sequences fails to provide evidence implicating Borna disease virus in mental illness. Rev Med Virol 17: 181–203.
Furrer, E., Bilzer, T., Stitz, L., and Planz, O. (2001) Neutralizing antibodies in persistent borna disease virus infection: prophylactic effect of gp94-specific monoclonal antibodies in preventing encephalitis. J Virol 75: 943–951.
Gonzalez-Dunia, D., Watanabe, M., Syan, S., Mallory, M., Masliah, E., and De La Torre, J.C. (2000) Synaptic pathology in Borna disease virus persistent infection. J Virol 74: 3441–3448.
Gonzalez-Dunia, D., Volmer, R., Mayer, D., and Schwemmle, M. (2005) Borna disease virus interference with neuronal plasticity. Virus Res 111: 224–234.
Gosztongyi, G., and Ludwig, H. (1995) Borna disease – neuropathology and pathogenesis. Curr Top Microbiol Immunol 190: 39–73.
Habjan, M., Andersson, I., Klingstrom, J., Schumann, M., Martin, A., Zimmermann, P., et al. (2008) Processing of genome 5′-termini as a strategy of negative-strand RNA viruses to avoid RIG-I-dependent interferon induction. PLoS ONE 3: e2032.
Hallensleben, W., and Staeheli, P. (1999) Inhibition of Borna disease virus multiplication by interferon: cell line differences in susceptibility. Arch Virol 144: 1209–1216.
Hans, A., Syan, S., Crosio, C., Sassone-Corsi, P., Brahic, M., and Gonzalez-Dunia, D. (2001) Borna disease virus persistent infection activates mitogen-activated protein kinase and blocks neuronal differentiation of PC12 cells. J Biol Chem 276: 7258–7265.
Hans, A., Bajramovic, J.J., Syan, S., Perret, E., Dunia, I., Brahic, M., and Gonzalez-Dunia, D. (2004) Persistent, non-cytolytic infection of neurons by Borna disease virus interferes with ERK 1/2 signaling and abrogates BDNF-induced synapticogenesis. Faseb J 18: 863–865.
Hermann, O., Baumann, B., de Lorenzi, R., Muhammad, S., Zhang, W., Klesiej, J., et al. (2005) IKK mediates ischemia-induced neuronal death. Nat Med 11: 1322–1329.
Hiscott, J. (2007) Convergence of the NF-kappaB and IRF pathways in the regulation of the innate antiviral response. Cytokine Growth Factor Rev 18: 483–490.
Hiscott, J., Kwon, H., and Genin, P. (2001) Hostile takeovers: viral appropriation of the NF-kappaB pathway. J Clin Invest 107: 143–151.
Hornig, M., Weissenbock, H., Horscroft, N., and Lipkin, W.I. (1999) An infection-based model of neurodevelopmental damage. Proc Natl Acad Sci USA 96: 12102–12107.
Israel, A. (2000) The IKK complex: an integrator of all signals that activate NF-kappaB? Trends Cell Biol 10: 129–133.
Kaltschmidt, B., Uherek, M., Wellmann, H., Volk, B., and Kaltschmidt, C. (1999) Inhibition of NF-kappaB potentiates amyloid beta-mediated neuronal apoptosis. Proc Natl Acad Sci USA 96: 9409–9414.
Kaltschmidt, C., Kaltschmidt, B., Neumann, H., Wekerle, H., and Baueuerle, P.A. (1994) Constitutive NF-kappaB activity in neurons. Mol Cell Biol 14: 3981–3992.
Kamitani, W., Shoya, Y., Kobayashi, T., Watanabe, M., Lee, B.J., Zhang, G., et al. (2001) Borna disease virus phosphoprotein binds a neurite outgrowth factor, amphoterin/HMG-1. J Virol 75: 8742–8751.
Kamitani, W., Ono, E., Yoshino, S., Kobayashi, T., Taharaguchi, S., Lee, B.J., et al. (2003) Glial expression of Borna disease virus phosphoprotein induces behavioral and neurological abnormalities in transgenic mice. Proc Natl Acad Sci USA 100: 8969–8974.
Kato, H., Takeuchi, O., Mikamo-Satoh, E., Hirai, R., Kawai, T., Matsushita, K., et al. (2008) Length-dependent recognition of double-stranded ribonucleic acids by retinoic acid-inducible gene-I and melanoma differentiation-associated gene 5. J Exp Med 205: 1601–1610.
Kauppinen, T.M., and Swanson, R.A. (2005) Poly (ADP-ribose) polymerase-1 promotes microglial activation, proliferation, and matrix metalloproteinase-9-mediated neuron death. J Immunol 174: 2288–2296.
Kawai, T., and Akira, S. (2007) Antiviral signaling through pattern recognition receptors. J Biochem 141: 137–145.
Kistler, A.L., Gancz, A., Clubb, S., Skewes-Cox, P., Fischer, K., Sorber, K., et al. (2008) Recovery of divergent avian bornaviruses from cases of proventricular dilatation disease: identification of a candidate etiologic agent. Virol J 5: 88.
Lipkin, W., and Briese, T. (2007) Bornaviridae. Philadelphia: Lippincott, Williams and Wilkins.
Lipkin, W., Hornig, M., and Briese, T. (2001) Borna disease virus and neuropsychiatric disease – a reappraisal. Trends Microbiol 9: 295–298.
Lu, L.L., Puri, M., Horvath, C.M., and Sen, G.C. (2008) Select paramyxoviral V proteins inhibit IRF3 activation by acting as alternative substrates for inhibitor of kappaB kinase epsilon (IKKe)/TBK1. J Biol Chem 283: 14269–14276.
Ludwig, S., Planz, O., Pleschka, S., and Wolff, T. (2003) Influenza-virus-induced signaling cascades: targets for antiviral therapy? Trends Mol Med 9: 46–52.
Peng, G., Zhang, F., Zhang, Q., Wu, K., Zhu, F., and Wu, J. (2007) Borna disease virus P protein inhibits nitric oxide synthase gene expression in astrocytes. Virology 366: 446–452.
Planz, O., Pleschka, S., and Ludwig, S. (2001) MEK-specific inhibitor U0126 blocks spread of Borna disease virus in cultured cells. J Virol 75: 4871–4877.

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Planz, O., Pleschka, S., Oesterle, K., Berberich-Siebelt, F., Ehrhardt, C., Stitz, L., and Ludwig, S. (2003) Borna disease virus nucleoprotein interacts with the CDC2-cyclin B1 complex. J Virol 77: 11186–11192.

Pleschka, S. (2008) RNA viruses and the mitogenic Raf/MEK/ERK signal transduction cascade. Biol Chem 389: 1273–1282.

Pleschka, S., Staeheli, P., Kolodziejek, J., Richt, J.A., Nowotny, N., and Schwemmle, M. (2001) Conservation of coding potential and terminal sequences in four different isolates of Borna disease virus. J Gen Virol 82: 2681–2690.

Randall, R.E., and Goodbourn, S. (2008) Interferons and viruses: an interplay between induction, signalling, antiviral responses and virus countermeasures. J Gen Virol 89: 1–47.

Razvi, E.S., and Welsh, R.M. (1995) Apoptosis in viral infections. Adv Virus Res 45: 1–60.

von Rheinbaben, F., Sitz, L., and Rott, R. (1985) Influence of interferon on persistent infection caused by Borna disease virus in vitro. J Gen Virol 66 (Part 12): 2777–2780.

Rott, R., Herzog, S., Fleischer, B., Winokur, A., Amsterdam, J., Dyson, W., and Koprowski, H. (1985) Detection of serum antibodies to Borna disease virus in patients with psychiatric disorders. Science 228: 755–756.

Schmid, S., Mayer, D., Schneider, U., and Schwemmle, M. (2007) Functional characterization of the major and minor phosphorylation sites of the P protein of Borna disease virus. J Virol 81: 5497–5507. Science 228.

Schneider, U., Schwemmle, M., and Staeheli, P. (2005) Genome trimming: a unique strategy for replication control employed by Borna disease virus. Proc Natl Acad Sci USA 102: 3441–3446.

Schneider, U., Ackermann, A., and Staeheli, P. (2007) A Borna disease virus vector for expression of foreign genes in neurons of rodents. J Virol 81: 7293–7296.

Schwemmle, M., De, B., Shi, L., Banerjee, A., and Lipkin, W.I. (1997) Borna disease virus P-protein is phosphorylated by protein kinase C epsilon and casein kinase II. J Biol Chem 272: 21818–21823.

Shankar, V., Kao, M., Hamir, A.N., Sheng, H., Koprowski, H., and Dietzschold, B. (1992) Kinetics of virus spread and changes in levels of several cytokine mRNAs in the brain after intranasal infection of rats with Borna disease virus. J Virol 66: 992–998.

Staeheli, P., Sauder, C., Hausmann, J., Ehrensperger, F., and Schwemmle, M. (2000) Epidemiology of Borna disease virus. J Gen Virol 81: 2123–2135.

Staeheli, P., Sentandreu, M., Pagenstecher, A., and Hausmann, J. (2001) Alpha/beta interferon promotes transcription and inhibits replication of borna disease virus in persistently infected cells. J Virol 75: 8216–8223.

Stitz, L., Bilzer, T., and Planz, O. (2002) The immunopathogenesis of Borna disease virus infection. Front Biosci 7: d541–555.

Takeuchi, O., and Akira, S. (2008) MDA5/RIG-I and virus recognition. Curr Opin Immunol 20: 17–22.

Thomas, G.M., and Huganir, R.L. (2004) MAPK cascade signalling and synaptic plasticity. Nat Rev Neurosci 5: 173–183.

Thornberry, N.A., and Lazebnik, Y. (1998) Caspases: enemies within. Science 281: 1312–1316.

Turner, K.M., Burgoyne, R.D., and Morgan, A. (1999) Protein phosphorylation and the regulation of synaptic membrane traffic. Trends Neurosci 22: 459–464.

Unterstab, G., Ludwig, S., Anton, A., Planz, O., Dauber, B., Krappmann, D., et al. (2005) Viral targeting of the interferon-[(beta)-inducing Traf family member-associated NF-[(kappa)]B activator (TANK)-binding kinase-1. Proc Natl Acad Sci USA 102: 13640–13645.

Volmer, R., Monnet, C., and Gonzalez-Dunia, D. (2006) Borna disease virus blocks potentiation of presynaptic activity through inhibition of protein kinase C signaling. PLoS Pathog 2: e19.

Volmer, R., Prat, C.M., Le Masson, G., Garenne, A., and Gonzalez-Dunia, D. (2007) Borna disease virus infection impairs synaptic plasticity. J Virol 81: 8833–8837.

Wang, J., and Campbell, I.L. (2005) Innate STAT1-dependent genomic response of neurons to the antiviral cytokine NF-[(kappa)]B alpha interferon. J Virol 79: 8295–8302.

Williams, B.L., Hornig, M., Yaddanapudi, K., and Lipkin, W.I. (2008) Hippocampal poly (ADP-Ribose) polymerase 1 and caspase 3 activation in neonatal bornavirus infection. J Virol 82: 1748–1758.

Wolff, T., Heins, G., Pauli, G., Burger, R., and Kurth, R. (2006) Failure to detect Borna disease virus antigen and RNA in human blood. J Clin Virol 36: 309–311.

Zhang, G., Kobayashi, T., Kamitani, W., Komoto, S., Yamashita, M., Baba, S., et al. (2003) Borna disease virus phosphoprotein represses p53-mediated transcriptional activity by interference with HMGB1. J Virol 77: 12243–12251.