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The neurobiology of canine distemper virus infection

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Abstract

Canine distemper virus (CDV) invades the nervous system and replicates in neurons and glial cell of the white matter during a period of severe viral induced immunosuppression. Demyelination occurs in infected white matter areas in the absence of inflammation. The mechanism of demyelination is not apparent because there is no ultrastructural evidence of viral replication in the oligodendrocytes, the myelin producing cells. However, brain tissue culture studies have shown that oligodendrocytes support transcription of all CDV genes and later on degenerate, although no viral proteins can be found in these cells. It remains to be shown how such a restricted infection leads to demyelination. Concomitant with immunologic recovery during the further course of the disease, inflammation occurs in the demyelinating lesions with progression of the lesions in some animals. A series of experiments in vitro suggested that chronic demyelination is due to a bystander mechanism associated with the virus-induced immune response in which antibody dependent cell-mediated reactions play an important role. The progressive, or even relapsing, course of the disease is associated with viral persistence in the nervous system. Persistence of CDV in the brain appears to be due to non-cytolytic selective spread of the virus with very limited budding. In this way CDV escapes immune surveillance.

Keywords: Canine distemper virus; Nervous system; Pathogenesis; Demyelination; Review

1. Canine distemper virus

Canine distemper virus (CDV) is a non-segmented, single stranded RNA virus and is a member of the morbilliviruses. The molecular biology, the different CDV strains and their host range are reviewed elsewhere in this issue.

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2. Entry of CDV into the central nervous system

The original studies on the pathogenesis of distemper were conducted by Appel and co-workers (Appel, 1969, 1970). CDV is generally transmitted as an aerosol infection to the upper respiratory tract. The primary virus replication takes place in the lymphoid tissues. Infection of these tissues is associated with severe long lasting immunosuppression, which has been investigated extensively by Krakowka and co-workers (Krakowka et al., 1980; Krakowka, 1982). At about 10 days post infection (p.i.), CDV starts to spread from the sites of primary replication to various epithelial tissues and the central nervous system (CNS).

The exact mechanism of entry of CDV into the CNS has not been entirely clarified. One study describes the presence of CDV infected lymphocytes in the perivascular spaces of the CNS at 10 days p.i., thus long before the first lesions occur (Summers et al., 1978, 1979). However, immunocytochemical studies of the brain lesions in distemper, do not support the notion of vascular or perivascular spread of CDV at the time of the lesion development (Vandevelde et al., 1985b; Mutinelli et al., 1989; Alldinger et al., 1993a, b). The frequent occurrence of periventricular and subpial lesions and the fact that CDV can easily be found in choroid plexus cells and ependyma suggest entry of the virus into the brain tissue by way of the cerebrospinal fluid (CSF) pathways, presumably by infected immune cells. In the CSF, virus can be found in mononuclear cells. Such infected mononuclear cells have been found to be fused with ependymal cells (Higgins et al., 1982).

3. Neuropathology of nervous distemper

The pathological anatomy of distemper has been extensively described by many pathologists over the past century (Innes and Saunders, 1962). Although the spectrum of the lesions appears to be wide, the neuropathology of spontaneous distemper is remarkably constant. The variability of the neuropathology is largely due to the evolution of the lesions when the disease progresses. Some variability may be due to strain differences, although there is little concrete evidence that these play a role in the natural disease in dogs. The polioencephalitis caused by the Snyder Hill CDV strain (Summers et al., 1984a) does not appear to occur in nature, and the so-called "old dog encephalitis" (Lincoln et al., 1971, 1973), a disease which differs from the chronic form of common nervous distemper (Vandevelde et al., 1980) and closely mimics measles virus-induced subacute sclerosing panencephalitis (SSPE) in people, is exceedingly rare. In the vast majority of spontaneous distemper as well as in experimental studies with so-called "demyelinating" strains such as R252 (McCullough et al., 1974) and A75/17 CDV (Summers et al., 1979), the virus causes multifocal lesions in the grey as well as in the white matter of the CNS (Innes and Saunders, 1962; Frauchiger and Fankhauser, 1957). In the grey matter, CDV infects neurons which can lead to neuronal necrosis and even polioencephalomalacia (Lisiak and Vandevelde, 1979; Krakowka et al., 1978). Neuronal infection can also be very widespread with remarkably little evidence of cytolysis. It has been known for more than a century that the white matter lesions in distemper are characterized by selective loss of myelin sheaths (Fankhauser, 1982). The demyelinating lesions are not only responsible for severe neuro-

logical signs but are also thought to be a model for human demyelinating conditions such as multiple sclerosis (Dal Canto and Rabinowitz, 1982; Appel et al., 1981). Therefore, the pathogenesis of demyelination has been closely investigated. In the following sections, we will focus on what is known about the pathogenesis of the white matter lesions in distemper.

4. Acute and chronic demyelination

Pathogenetic studies have to consider an acute and a chronic stage in the development of CDV-induced demyelination. The initial demyelinating lesions occur around 3 weeks p.i. and evolve during a period of massive immunosuppression, thus in the absence of any local immune-inflammatory response (Vandevelde et al., 1982a). Depending on the degree and speed of immune recovery, animals may either become quickly moribund or may recover after developing a mild or even subclinical illness. An intermediate group of animals recovers slowly or partially and tends to develop a chronic or even relapsing disease with progression of the demyelinating lesions as a result of immunopathologic reactions (Vandevelde et al., 1982b; Vandevelde et al., 1981).

5. The pathogenesis of acute demyelination

5.1. Infection of the glial cells of the white matter

The initial myelin lesions develop during a period of severe immunosuppression and are not inflammatory (Vandevelde et al., 1982a). Several immunocytochemical studies and recent in situ hybridization work in spontaneous and experimental distemper have clearly shown that demyelination coincides with replication of CDV in the glial cells of the white matter (Vandevelde et al., 1985b; Zurbriggen et al., 1993a). Spatio-temporal studies leave no doubt that the initial white matter lesions result from viral activity and that their development is highly predictable (Vandevelde et al., 1985b; Higgins et al., 1982; Summers et al., 1979). There is no experimental evidence at all to support the notion (which can still be read in certain text books) that demyelination in distemper could be a "late" event occurring months to years after infection.

The obvious explanation for the phenomenon of demyelination would be infection of oligodendrocytes, the myelin producing cells. Therefore, research has focused on finding evidence of CDV in oligodendrocytes. Reliable techniques to demonstrate canine oligodendrocytes in histological sections are not yet available, but at the light microscopic level, it has been shown that the majority of infected cells are astrocytes (Mutinelli et al., 1989). Most electron microscopical studies agree that oligodendroglial infection is very rare in distemper (Raine, 1976; Wisniewski et al., 1972; Summers and Appel, 1987; Higgins et al., 1982; Blakemore et al., 1989). However, because of the limited number of cells that can be examined, ultrastructural techniques remain anecdotal. The question of viral tropism was studied extensively in primary canine brain cell cultures (DBCC) (Zurbriggen and Vandevelde, 1983). These cultures contain numerous astrocytes and oligodendrocytes, which can be unequivocally identified with antibodies against cell specific cell markers

(Zurbriggen et al., 1984). Similar to the in vivo situation, virulent CDV causes a slowly spreading non-cytolytic infection in these cultures. Despite considerable efforts using immunocytochemical and ultrastructural techniques, CDV proteins or viral nucleocapsids were only very rarely found in oligodendrocytes, in contrast to astrocytes and microglial cells which easily support CDV infection (Zurbriggen et al., 1986, 1987; Vandevelde et al., 1985a). Recently, using in situ hybridization techniques, we found that oligodendrocytes in CDV-infected brain cultures contain CDV mRNA corresponding to all viral genes, despite the fact that these cells do not produce viral protein (Zurbriggen et al., 1993b). Thus, we concluded from these studies that CDV causes a restricted infection of the oligodendrocyte, which is possibly responsible for the phenomenon of demyelination. Why the production of viral protein does not take place in these cells remains to be clarified.

5.2. *Degeneration of oligodendrocytes*

Virulent CDV causes in DBCC a non-cytolytic infection, which reaches confluency at about 3 weeks p.i. Between 20 and 30 days p.i., the cultured oligodendrocytes, which grow superimposed on a layer of astrocytes, start to degenerate and disappear although the supporting culture remains a continuous cell sheet (Zurbriggen et al., 1987). Ultrastructural studies revealed microvacuolation and loss of organelles in such degenerating oligodendrocytes (Glaus et al., 1990). The morphological changes are preceded by metabolic dysfunction of these cells, because the activity of cerbroside sulpho-transferase (an oligodendrocyte specific enzyme) decreased markedly soon after infection (Glaus et al., 1990). Following these in vitro observations (Zurbriggen et al., 1987) similar changes of oligodendrocytes were also described in the demyelinating lesions in vivo (Blakemore et al., 1989; Summers and Appel, 1987). There is little doubt that degeneration of these cells lies at the base of the demyelinating process but its mechanism is not yet understood. It is possible that viral transcription taking place in these cells interferes with specialized functions necessary to maintain myelin membranes. Indeed, we found that transcription of myelin protein genes in these cells is markedly reduced following CDV infection (unpublished results). It cannot be excluded that these cells are killed as a result of virus-induced changes in other cell types. However, a series of experiments could not confirm this hypothesis. Supernatants derived from CDV infected DBCC did not induce oligodendroglial lesions in recipient dog or mouse brain cultures (Zurbriggen et al., 1987). We were unable to find evidence for toxic factors such as TNF alpha or reactive oxygen radicals in the supernatants of CDV infected DBCC (Brügger et al., 1992). Cocultivation of infected DBCC with mouse brain cultures, which are refractory to CDV, did not damage the mouse oligodendrocytes (unpublished results). Likewise, the mouse brain cells, which remained uninfected in these cocultivation experiments, did not provide protection for the canine oligodendrocytes (unpublished results).

In summary, the acute CDV infection of the white matter results in oligodendroglial degeneration which leads to demyelination. Whether the degeneration of the oligodendrocytes is the direct result of the restricted CDV infection, which has been shown in vitro in these cells, remains to be shown.

6. The pathogenesis of chronic demyelination

6.1. The intrathecal immune response in distemper

Coinciding with the recovery of the immune system, perivascular cuffing with lymphocytes, plasma cells and monocytes occurs in the initial virus-induced brain lesions (Vandevelde et al., 1981). The inflammatory reaction in the demyelinating lesions can lead to progression of the tissue damage (Vandevelde et al., 1982b; Wisniewski et al., 1972). There is often frank necrosis of the tissue in such lesions. Thus, the chronic stage of the disease is characterized by immunopathologic complications. The inflammation is associated with intrathecal immunoglobulin synthesis. Based on quantitation of this immunoglobulin in the CSF, which reflects the severity of the inflammatory response, we found that the intensity of the inflammatory response gradually decreased in several experimentally infected dogs (Vandevelde et al., 1986). These dogs improved clinically. In some dogs however, inflammation exhibited a progressive course with continuous worsening of the signs. Efforts have been made to characterize the nature of the intrathecal immune response.

6.2. Virus-induced autoimmunity in distemper

Evidence of autoimmunity is not unusual in virus infections in different organ systems, including the brain. In most of these instances, autoimmune reactions such as antibodies against tissue antigens do not correlate with the clinical course of the disease, lesion development or both. It has been repeatedly postulated that viruses could induce autoimmune demyelination (Zurbriggen and Fujinami, 1989; Zurbriggen and Fujinami, 1990). However, until the present day, there is no conclusive evidence in any of the animal models of viral demyelination for the induction of an experimental allergic encephalitis (EAE)-like disease with demyelination after the virus has been completely cleared from the tissue. Antimyelin antibodies in serum have been known for a long time to occur in distemper (Krakowka et al., 1973). We found such antibodies also in the CSF of dogs with distemper and that these antibodies are locally produced in the inflammatory brain lesions (Vandevelde et al., 1986). It was also recognized that neither occurrence nor titre of these antibodies correlated with the course of the disease (Vandevelde et al., 1986; Krakowka et al., 1973). A cell-mediated response against myelin basic protein (MBP) was found in 4 of 11 dogs experimentally infected with CDV (Cerruti Sola et al., 1983). However, two of these animals had not developed any demyelination at all. Comparative morphologic studies in canine experimental allergic encephalitis and distemper did not reveal resemblance between the two diseases (Summers et al., 1984b). One mechanism by which anti-myelin antibodies could induce demyelination would be antibody-dependent cytotoxicity (ADCC). In chemoluminescence experiments in brain cell cultures, sera and CSF samples of dogs with inflammatory distemper failed to elicit ADCC-like reactions in contrast to canine EAE sera and defined anti-myelin antibodies (Griot et al., 1989a). We can conclude from all these studies that the autoimmune reactions in distemper are probably epiphenomena which are not primarily involved in the chronic demyelinating process.

6.3. The intrathecal antiviral immune response

Both the antibody- as well as the cell-mediated aspects of the systemic immune response against CDV have been studied (Appel et al., 1982; Krakowka et al., 1975b). It has been known for a long time that antiviral antibodies play a dominant role in immunity against CDV. In the CNS, only the humoral immune response against CDV has been investigated (Johnson et al., 1988; Vandevelde et al., 1986). The intrathecal immune response in distemper is characterized by infiltration of large numbers of plasma cells and strong antibody synthesis (Vandevelde et al., 1986; Vandevelde et al., 1981). The titres of CDV neutralizing antibodies in the CSF often exceed those in the serum (Bollo et al., 1986). Binding studies show that antibodies are made against all proteins of CDV (Johnson et al., 1988). We found that the occurrence of anti-CDV antibodies in the CSF coincided with clearance of CDV and CDV containing cells from the inflammatory lesions (Bollo et al., 1986). Immunocytochemical studies from others support this finding (Alldinger et al., 1993b; Baumgärtner et al., 1989). Since oligodendrocytes do not express viral proteins, progression of demyelination could hardly be explained by an antiviral cytotoxic reaction killing infected oligodendrocytes. We postulated that other types of antiviral immune response could be responsible for the inflammatory tissue damage seen in distemper.

6.4. Bystander demyelination associated with the antiviral immune response

One early ultrastructural study postulated that demyelination in distemper results from so-called bystander demyelination (Wisniewski et al., 1972). Macrophages, which are very numerous in distemper lesions, would play an important role. The hypothesis of bystander demyelination was investigated in CDV infected DBCC, which also contain numerous macrophages (Bürge et al., 1989). We used a chemoluminescence technique detecting the production of reactive oxygen radicals by stimulated macrophages (Bürge et al., 1989; Griot et al., 1989b; Griot et al., 1989a). We found that sera and CSF of dogs with inflammatory distemper were capable of stimulating macrophages in infected but not in uninfected cultures. It was shown in subsequent experiments that antiviral antibodies bound to the surface of CDV infected cells interacted with the Fc receptors of neighbouring macrophages by way of their Fc portions (Bürge et al., 1989; Griot et al., 1989b; Griot et al., 1989a). This interaction resulted in a respiratory burst of the macrophages with release of reactive oxygen radicals. We could also show that stimulation of macrophages by way of their Fc receptors or other means led to selective destruction of oligodendrocytes in their vicinity (Griot-Wenk et al., 1991). Likewise, treatment of mouse brain cell cultures, which are resistant to CDV infection, with immune complexes made from purified CDV and defined anti-CDV monoclonal antibodies killed oligodendrocytes (Botteron et al., 1992). Thus, these experiments showed how the humoral antiviral immune response could lead to destruction of oligodendrocytes as "innocent bystander" cells.

Obviously, several products secreted by stimulated macrophages, including reactive oxygen radicals, can be held responsible for damage to the oligodendrocyte/myelin compartment. Chemically produced reactive oxygen radicals in the xanthine/xanthine-oxidase system, which was added to the culture supernatant, selectively damaged cultured oligodendrocytes (Griot et al., 1990). Based on experiments with radical scavengers, highly

toxic hydroxyl radicals were thought to be the immediate cause of the cell damage in these experiments. Hydroxyl radicals are produced in a Fenton type reaction in which iron ions play a catalytic role (Griot et al., 1990). We believe that the fact that oligodendrocytes are rich in iron compounds, in particular transferrin, could make these cells particularly vulnerable to oxygen radical attacks (Griot and Vandevelde, 1988).

The experimental conditions in the antibody experiments in vitro closely mimic the situation in vivo in which CDV infected glial cells in the white matter are in close contact with macrophages and antiviral antibody producing cells. Therefore, it is not unreasonable to conclude that a bystander mechanism associated with the antiviral immune response can be held responsible for the progression of demyelinating lesions in the chronic stage of CDV infection.

6.5. Virus-induced modifications of macrophage functions

In recent years, viruses have been shown to alter the function of immune cells resulting in modification of the immune response, presumably leading to destruction of the tissue (Zurbriggen and Fujinami, 1989; 1990). It has been shown that CDV causes a marked suppression of lymphocyte function (Krakowka et al., 1975a) but it is not known whether this results in an imbalance of the immune function favoring immunopathological reactions. We have not found evidence for upregulation of class II antigens or TNF alpha in glial cells in distemper in vitro and in vivo (unpublished results), such as has been described in other viral systems (Massa et al., 1987). However, there is some experimental evidence for virus-induced alterations at the level of macrophage functions. The production of interleukin I by macrophages in vitro was decreased and of prostaglandin E increased as a result of CDV infection in vitro. We found that Fc-dependent or independent phagocytosis as well as the ability to release reactive oxygen radicals by macrophages remained unaltered after CDV infection in vitro. The procoagulant activity of macrophages was even markedly enhanced after CDV infection (Brügger et al., 1992). Considering the relation between the coagulation system and inflammatory functions, these observations show that CDV infection may enhance the destructive potential of macrophages and provide further support for the hypothesis that bystander demyelination occurs in chronic distemper.

6.6. Virus persistence

Correlation between immunohistological studies to demonstrate CDV antigen and intrathecally produced anti-CDV antibodies showed virus clearance in inflammatory demyelinating lesions (Bollo et al., 1986). The antiviral immune response should therefore be beneficial to the host in that CDV is removed from the tissue. However, our studies also showed that CDV can persist in white matter areas outside of the inflammatory demyelinating lesions or even in the immediate periphery of such lesions (Bollo et al., 1986). It appears that a chronic progressive disease develops if the intrathecal immune response keeps lagging behind viral replication. Thus viral persistence is the key to the pathogenesis of the chronic lesions. The mechanism of persistence of CDV is not yet understood. It has been suggested that CDV surface proteins may be modified in chronic distemper lesions rendering CDV less detectable by the immune system (Alldinger et al., 1993a). Our studies with

virulent CDV in DBCC showed that virulent CDV spreads in a non-cytolytic manner by way of cell processes with very limited budding and release of infectious virus. This particular type of spread is related to differences in viral assembly as compared to attenuated distemper viruses, which do spread by budding and cytolysis. Viral assembly depends on molecular properties of a particular strain. Sequencing studies have shown differences between virulent and attenuated CDV at the level of the NP gene (Stettler et al., 1994). Persistence of CDV appears to be related to a non-cytolytic spread of virulent CDV in which release of cell debris and virus particles in the extracellular space are very limited. As a result, macrophage stimulation attracting the antiviral immune response in the area of active viral replication is avoided.

7. Outlook

At the level of the acute virus-induced lesion, current studies focus on the effect of restricted CDV infection on oligodendroglial metabolism and function. In the chronic lesion, our efforts concentrate on mechanisms of virus persistence. In particular, we are in the process of isolating the molecular determinants of virulence and persistence.

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