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Review paper

Pathogenesis and immunopathology of systemic and nervous canine distemper

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ABSTRACT

Canine distemper is a worldwide occurring infectious disease of dogs, caused by a morbillivirus, closely related to measles and rinderpest virus. The natural host range comprises predominantly carnivores. Canine distemper virus (CDV), an enveloped, negative-sense RNA virus, infects different cell types, including epithelial, mesenchymal, neuroendocrine and hematopoietic cells of various organs and tissues. CDV infection of dogs is characterized by a systemic and/or nervous clinical course and viral persistence in selected organs including the central nervous system (CNS) and lymphoid tissue. Main manifestations include respiratory and gastrointestinal signs, immunosuppression and demyelinating leukoencephalomyelitis (DL). Impaired immune function, associated with depletion of lymphoid organs, consists of a viremia-associated loss of lymphocytes, especially of CD4+ T cells, due to lymphoid cell apoptosis in the early phase. After clearance of the virus from the peripheral blood an assumed diminished antigen presentation and altered lymphocyte maturation cause an ongoing immunosuppression despite repopulation of lymphoid organs. The early phase of DL is a sequel of a direct virus-mediated damage and infiltrating CD8+ cytotoxic T cells associated with an up-regulation of pro-inflammatory cytokines such as interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α and IL-12 and a lacking response of immunomodulatory cytokines such as IL-10 and transforming growth factor (TGF)-β. A CD4+-mediated delayed type hypersensitivity and cytotoxic CD8+ T cells contribute to myelin loss in the chronic phase. Additionally, up-regulation of interferon-γ and IL-1 may occur in advanced lesions. Moreover, an altered balance between matrix metalloproteinases and their inhibitors seems to play a pivotal role for the pathogenesis of DL. Summarized, DL represents a biphasic disease process consisting of an initial direct virus-mediated process and immune-mediated plaque progression. Immunosuppression is due to early virus-mediated lymphocytolysis followed by still poorly understood mechanisms affecting antigen presentation and lymphocyte maturation.

Contents

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1. Introduction

Canine distemper is a worldwide occurring infectious disease, caused by a morbillivirus of the family *Paramyxoviridae*. The natural host spectrum of canine distemper virus (CDV) comprises all families of the order Carnivora (Deem et al., 2000). Clinical and morbid anatomical signs of canine distemper were already described in detail at the beginning of the 19th century by Jenner (Lauder et al., 1954). He also commented on the high incidence of nervous complications in affected dogs.

Recent canine distemper epidemics have been observed in France, Germany, USA, Japan and Finland demonstrating the importance of regular vaccination as a highly efficient and protective tool (Adelus-Neveu et al., 1991; Mori et al., 1994; Johnson et al., 1995; Gemma et al., 1996; Ek-Kommonen et al., 1997; Moritz et al., 2000). Furthermore, occasional disease outbreaks can be observed in vaccinated dog cohorts, possible due to the introduction of genetically different CDV strains (Mori et al., 1994; Mochizuki et al., 1999; Simon-Martínez et al., 2007).

Though infection of dogs may result in a variety of clinical forms affecting the respiratory and gastrointestinal tract, skin and other organs and tissues, immunosuppression and demyelinating leukoencephalitis (DL) represent the main sequel in this species (Krakowka et al., 1985; Appel, 1987). Due to the morphological similarities of neuropathological changes between DL and human demyelinating diseases, such as multiple sclerosis (MS), the canine disease represents one of the few spontaneously occurring animal models to study the pathogenesis of myelin loss associated with immune-mediated mechanisms (Baumgärtner and Alldinger, 2005). Furthermore, lymphoid depletion and long-lasting impaired immune functions in distemper are comparable with those described for measles virus (MV) infection, a closely related morbillivirus in humans. It is the aim of the present communication to provide an overview about the different manifestation forms of distemper, the pathogenesis of demyelination in the central nervous system (CNS) and mechanisms of immunosuppression in CDV infected dogs. In addition, the perpetuating role of the misdirected immune response especially for the development of nervous white matter lesions is detailed.

2. Viral properties

CDV belongs to the family *Paramyxoviridae* (Lamb and Kolakofsky, 2001). Beside CDV, the genus morbillivirus comprises measles virus, dolphin morbillivirus, peste-des-petits-ruminants virus, rinderpest virus, porpoise morbillivirus, and phocine distemper virus (Pringle, 1999; Lamb and Kolakofsky, 2001).

CDV is an enveloped, negative-sense, single-stranded RNA virus (Lamb and Kolakofsky, 2001), which contains six structural proteins, the nucleocapsid (N), the phospho- (P), the large (L), the matrix- (M), the hemagglutinin (H), and the fusion (F) protein (Hall et al., 1980; Örvell, 1980; Diallo, 1990; Lamb and Kolakofsky, 2001). Additional accessory genes, the C and V protein, are found mostly as extra transcriptional units within the P gene (Lamb and Kolakofsky, 2001). The lipid envelope, surrounding the virion, contains the two surface glycoproteins F and H, which mediate viral entry and exit from the host cell. Furthermore, the helical nucleocapsid core, containing the N, P and L protein, initiates intracellular replication and is located within the envelope (Lamb and Kolakofsky, 2001). The viral M protein connects the surface glycoproteins and nucleocapsid during viral maturation.

3. Natural host range and different strains of CDV

The host spectrum of CDV, which traditionally included numerous families within the order of Carnivora like *Canidae* (dogs, dingos, foxes), *Procyonidae* (raccoons, kinkajous, lesser panda), *Mustelidae* (ferret, mink, badger),