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Immune mechanisms in the pathogenesis of viral diseases: a review

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ABSTRACT

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Three immunopathological mechanisms may determine the pathogenesis of viral diseases in animals. (1) A variety of viruses causes transient or prolonged immunosuppression by infecting lymphoreticular tissues and interacting with components of the immune system. (2) In persistent viral infections effective immune responses may result in tissue damage. The mechanisms involved are T-cell-mediated destruction of infected cells and delayed-type hypersensitivity. (3) In a number of viral diseases pathogenic immune complexes are formed when antibodies are produced and react with viral antigen molecules persisting in the host. The selected examples of immune dysfunction are the focus of this review.

INTRODUCTION

In certain viral infections transient or prolonged dysfunction of the immune system is an important feature of pathogenesis, leading either to aggravation of the respective disease or ultimately causing death of the host. This review will focus on three examples of virus-associated immune dysfunction: immunosuppression, immunopathological mechanisms in persistent viral infections and immune complex disease.

VIRUS-INDUCED IMMUNOSUPPRESSION

A variety of viruses may cause transient or prolonged immunosuppression by infecting lymphoreticular tissues and interacting with cellular components of the immune system. The mechanism involved in the pathogenesis of immunosuppression may be quite obvious, as in the case of cellular destruction

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of lymphoid cells or may be highly sophisticated as in some non-lytic viral infections. In man and animals, there are several examples of temporary or permanent virus-induced immunosuppression (Sissons and Borysiewicz, 1985; Mims, 1986; Rouse and Horohov, 1986). In some viral diseases immunosuppression is due to direct destruction of lymphocytes resulting from virus replication. Viruses may also impair the function of all classes of lymphocytes or may cause dysfunction in subpopoulations of lymphocytes.

Certain viruses preferentially infect CD4-positive (helper/inducer) T lymphocytes, thus causing depletion of this cell subset and an imbalance in immune regulation, as seen in human, simian and possibly feline immunodeficiency virus infections (Fauci, 1988). The lytic infection of CD4 cells may have a number of consequences, because this cell has a central role in immune regulation. In another interesting immunopathological mechanism some viruses have effects on immunological mediators. They combine with interleukin-2 (IL-2) on CD4 lymphocytes, thus causing depression of IL-2 production and clonal proliferation of cytotoxic T cells. Lastly, viruses may replicate preferentially in macrophages and cause dysfunction of these cells.

Feline leukaemia virus.

Immune dysfunction associated with feline leukaemia virus (FeLV) infection has been reported repeatedly (Rojko and Olsen, 1984; Neil and Onions, 1985; Olsen et al., 1987; Pedersen, 1987c; Rojko et al., 1988; Lafrado et al., 1989; Lutz, 1990). Immunodeficiency associated with FeLV infection involves various components of the immune system. Abnormalities in cellular and humoral immunity, the phagocytic and complement system have been recognized (Olsen et al., 1981; Hardy, 1982; Olsen and Krakowka, 1984; Ogilvie et al., 1988). Thus, immunopathological manifestations in FeLV infections include immune-cell deficiencies due to lymphoid depletion, immune-cell dysfunctions, immune-mediated disease (i.e. glomerulonephritis), impairment of phagocytosis, and complement deficiencies. Based on experimental data so far accumulated, several mechanisms of FeLV-mediated immunosuppression have been considered. Any one mechanism may operate independently or in concert with others (Olsen et al., 1987).

FeLV-mediated cytotoxicity is closely associated with the presence of a variant viral DNA which is not integrated into the host's DNA. This unintegrated viral DNA, present in bone marrow, lymphoid tissues and intestine, appears with the onset of clinical disease and may persist for considerable time (Mullins et al., 1986,1989). Experimentally, the immunosuppressive isolate of FeLV (designated FeLV-FAIDS) induces a fatal immunodeficiency syndrome with drastic reduction of circulating T-lymphocyte progenitor cells in nearly 100% of infected cats. Survival periods range from 3 months (acute immunodeficiency syndrome) to longer than 1 year (chronic immunodeficiency syndrome), depending on the age of the cats at the time of infection.

These results support the hypothesis that the viral genome rather than the host or environmental factors plays the major role in FeLV-induced immunodeficiency disease (Hoover et al., 1990).

Recently, it was shown by molecular cloning that the original FeLV-FAIDS isolate consists of two major genomes: a highly replication-competent but minimally pathogenic FeLV, designated the common form virus (clone 61E) and a replication-defective but highly pathogenic form virus (clone 61C). Clone 61E is non-cytopathogenic for T cells and fails to induce an immunodeficiency syndrome. By contrast, the FeLV-FAIDS variant virus (clone 61C) is highly T-cell cytotropic and cytopathogenic and capable of consistently inducing a fatal immunodeficiency syndrome in cats (Overbaugh et al., 1988). From these studies in the FeLV-FAIDS system it was concluded that the acutely pathogenic retrovirus may itself be replication-defective but may be complemented by a coexistent replication-competent retrovirus.

All of the in vitro immunosuppressive effects of FeLV can be produced by the low molecular envelope protein p15E. In recent studies new insight has been gained into the mechanism by which FeLV or the p15E protein causes immunosuppression. The impairment or loss of T-cell function suggests a specific inhibition of a T-cell factor. It has been shown that the structural protein p15E binds, among other cells, to CD4 lymphocytes and suppresses the production and response to IL-2 (Copelan et al., 1983). The IL-1 production by accessory monocytes is not affected. In more detailed in vitro studies it was shown that in the presence of FeLV, lymphocytes cannot be stimulated by Con A to produce IL-2. FeLV inhibits the IL-2 signal from entering into the cell, and gamma interferon production is inhibited (Orosz et al., 1985). Further observations suggest that p15E may be effective by interfering directly with the passage of the IL-2 signal through the cellular surface membrane of lymphocytes. Most likely, FeLV-p15E interferes with the production of cAMP, a central component of the second messenger system used for signal transfer across the cell surface membrane (Olsen et al., 1987).

Feline immunodeficiency virus

Feline immunodeficiency virus (FIV), formerly designated feline T-lymphotropic lentivirus is a typical lentivirus of type D morphology which was first isolated from a group of cats in California (Pedersen et al., 1987,1989; Pedersen, 1990). Although in FIV infection a number of clinical manifestations, due to secondary infections, are suggestive of an immunodeficiency syndrome, the precise pathomechanisms of immunosuppression have not yet been fully elucidated. Important effects of FIV may be inhibition of T- and B-cell cooperation and granulocytopoiesis resulting in neutropenia. Experimentally FIV-infected SPF cats have been kept in disease-free quarters and observed for 3 years (Yamamoto et al., 1988). About one-third of the infected cats had intermittent or persistent leukopenia and/or depression of the

absolute CD4-lymphocyte count or inversion of the CD4:CD8 ratio (Sparger et al., 1989). The CD4:CD8 ratio for normal cat lymphocytes appears to be around 1.5. Cats with naturally acquired FIV infection and AIDS-like disease may have CD4:CD8 ratios below 0.8 and as low as 0.3, indicating depletion of helper/inducer cells and decrease in certain cellular immune functions. Similar to the human immunodeficiency virus, FIV may have a selective tropism for CD4-positive lymphocytes that express the receptor for the virus. Recently, it has been demonstrated that the CD4 homologue occurs on feline CD4-positive lymphocytes (Ackley et al., 1990). It remains to be shown whether FIV has the same high affinity to this molecule as HIV.

Immunosuppression in parvovirus infections

In feline panleukopenia, immunosuppression is thought to be due to destruction of lymphoid cells in lymphatic tissues by the parvovirus (Pedersen, 1987a). Similarly, canine parvovirus type 2 causes depletion of lymphocytes in lymphatic tissues (Appel and Parrish, 1987).

Canine distemper virus

Canine distemper virus (CDV) is the cause of a systemic disease in dogs that involves several organ systems (Appel, 1987a). In dogs that succumb to acute distemper between 2–4 weeks post infection, there is clear evidence of immunosuppression. They are lymphopenic, have minimal neutralizing antibodies and the cell-mediated immune responses are absent or the onset is delayed (Appel et al., 1982,1984). CDV-infected and immunosuppressed dogs are not able to generate effective in vitro immune responses. The in vitro blastogenic responses to phytohaemagglutinin and pokeweed mitogen may be diminished for months. It is not known whether this suppressed phytomitogen response is mediated by infectious virus or viral envelope glycoproteins (Krakowka, 1982). Dogs that have recovered from CDV infection retain subtle CDV-associated immune dysfunctions, as demonstrated by a poor response to non-viral antigens such as keyhole limpet hemocyanin (Krakowka et al., 1980). There is evidence that this prolonged immunosuppression may be mediated by suppressor cells that are activated by he presence of CDV (Olsen and Krakowka, 1984). It has been shown in vitro that CDV modulates monocyte functions by inhibiting IL-1 production and by enhancing PGE_2 release (Krakowka et al., 1987).

Bovine viral diarrhoea virus

In both acute and chronic persistent bovine viral diarrhoea virus (BVDV) infections transient phases of immunosuppression with increased susceptibility to secondary microbial infections may occur. In an experimental infection with non-cytopathogenic BVDV, transient leukopenia occurred on days 3–7 post infection. Using cytofluorimetric analyses leukopenia was characterized

by decreases in the absolue numbers of circulating T lymphocytes, including CD4 and CD8 subsets, B lymphocytes and neutrophils (Ellis et al., 1988). The exact mechanism involved in BVDV-induced immunosuppression is not sufficiently clear. Recent in vitro studies have revealed that BVDV inhibits the production of IL-2 of lymphocytes (Atluru et al., 1990).

Infectious bursal disease virus

Infectious bursal disease of chicken, originally described as Gumboro disease, is caused by a double-stranded RNA virus (IBDV) which belongs to the new family of Birnaviridae (Becht, 1980; Becht and Müller, 1991; Müller, 1991). The main target organ with extensive IBDV replication and lymphoid cell destruction is the bursa of Fabricius. The importance of the latter in the pathogenesis of IBD has been clearly shown (Käufer and Weiss, 1980). While the highly virulent IBDV strain Cu-1 caused 100% mortality in 4-week-old SPF chickens, surgically bursectomized birds survived the lethal infection. Destruction of bursal follicles is associated with suppression of the humoral immune response. Chickens become susceptible to opportunistic secondary infections and respond poorly to immunization against other pathogens.

IMMUNOPATHOLOGICAL ASPECTS OF PERSISTENT VIRAL INFECTIONS

In several acute infections with cytopathogenic viruses destruction of cells is followed by transient infiltration with neutrophilic granulocytes and subsequently by perivascular accumulation of lymphocytes and macrophages. The mononuclear inflammatory response is considered an expression of specific cell-mediated immunity. Cell-mediated, together with humoral immune responses eventually lead to the elimination of virus from the tissue.

In a number of persistent viral infections, particularly when the viral agent is relatively non-cytopathogenic, effective immune responses may result in tissue damage. One important mechanism is T-cell-mediated destruction of infected cells (Sissons and Borysiewicz, 1985). Another principal effector mechanism, mediated by T cells, is delayed-type hypersensitivity. Experimental studies with T cell clones have revealed that both helper T cells and cytotoxic T cells have the potential to produce delayed-type hypersensitivity reactions by secreting factors which recruit macrophages to sites of local virus replication (Morris et al., 1982). In several viral infections of animals the cellular immune response has been shown to be the cause of tissue damage. This notion was further supported by adoptive transfer of specific T cells into virus-infected but experimentally immunosuppressed recipient animals.

Lentivirus infections

Lentiviruses, a subfamily of retroviruses, derive their name from the unusually long incubation periods and slow clinical course of the disease in man

and various animal species (Cheevers and McGuire, 1985; Haase, 1986a,b; Dawson, 1988; Narayan and Zink, 1988; Perk, 1988; Narayan and Cork, 1990). Lentiviruses cause maedi-visna, adenomatosis in sheep, arthritis-encephalitis in goats, infectious anaemia in horses and acquired immunodeficiency syndromes. All lentiviruses are highly successful in evading the defense mechanisms of their hosts and cause persistent infections. Lentiviruses show marked tropism for cells of the monocyte/macrophage lineage. Characteristically, virus gene expression occurs at a low level in the precursor cells, the monocyte, but is increased when these cells become differentiated and immunologically activated (Narayan and Clements, 1989). All lentivirus infections are considered examples of immunopathological diseases, that is, the pathological changes in tissues are for the most part indirectly mediated by the immune and inflammatory response of the host.

Maedi-visna virus (MVV) is considered a prototypic lentivirus which causes pulmonary, neurological-paralytic and, rarely, arthritic disease in sheep (Zink et al., 1987; Cutlip et al., 1988; Dawson, 1988; Narayan and Zink, 1988; Perk, 1988). Considerable progress has been made in understanding how MVV spreads and persists in spite of a sustained immune response by the host and how it causes tissue destruction. The long persistence of MVV may be explained by the fact that in vivo most infected cells harbor the virus in a latent state in which viral antigens are not produced in sufficient quantities for detection and subsequent destruction of the infected cells by immunological mechanisms (Haase, 1986a,b). The "Trojan horse" hypothesis explains how MVV succeeds in evading immune cells and antibody in the blood stream, cerebrospinal fluid and body fluids (Haase, 1986a,b). In the "Trojan horse" mechanism, mobile cells, predominantly monocytes, conceal the viral genome and convey it to other body sites (Narayan et al., 1982; Peluso et al., 1985).

Cells of the mononuclear phagocyte system are the targets of MVV replication which is dependent on the maturation and differentiation of monocytes and macrophages (Narayan and Zink, 1988). The effect of in vitro maturation of monocytes to macrophages on the virus life cycle was shown in a series of experiments (Gendelman et al., 1986). In vitro, only 7% of monocytes can be infected, and the production of viral RNA transcripts but not of virus polypeptide can be detected. In contrast, 50% of the mature macrophages carrying the acid phosphatase marker can be infected to produce greater numbers of viral transcripts and virus polypeptides. Thus, maturation of monocytes is clearly associated with increased permissiveness of the cells for replication of MVV (Narayan and Zink, 1988).

Recently, a novel interferon (LV-IFN) has been characterized which may play a significant role in maintaining lymphoproliferation associated with MVV infection. This interferon is produced by T cells responding to MVV-infected macrophages. It delays maturation of monocytes and thus indirectly

inhibits virus replication. It also induces class II MHC antigens and Ia antigens on the cellular membranes of macrophages (Kennedy et al., 1985; Narayan et al., 1985).

Borna disease

Borna disease (BD) is a natural disease of horses and sheep with the clinical manifestation of progressive encephalopathy, caused by a highly neurotropic, only partially characterized single-stranded RNA virus. In the brain of infected animals and in cell cultures three virus-specific antigens with molecular weights of 38/39 kDa, 24 kDa and 14.5 kDa can be detected (Ludwig et al., 1988; Rott et al., 1988; Richt et al., 1991). Considerable progress in understanding the pathogenesis of BD in the natural host has been made by establishing experimental BD in the rat. These studies have clearly shown that a virus-induced cell-mediated immune mechanism plays an important role in the pathogenesis of experimental BD virus-induced encephalitis which follows the pattern of a delayed-type hypersensitvity reaction. The development of neurological signs and inflammatory brain lesions can be prevented when immunoincompetent newborn or athymic rats are infected with BD virus and when rats are immunosuppressed by cyclophosphamide (Narayan et al., 1983a,b; Herzog et al., 1985; Stitz et al., 1991a). The results of these experimental studies suggest that the replicating BD virus alone does not cause clinical disease and brain lesions, but that a cell-mediated immune response plays an important role in the pathogenesis. This hypothesis was further supported by experiments with adoptive transfer of lymphoid cells from infected donor rats (Narayan et al., 1983a). Effective T cells predominantly carry the CD4 marker (Richt et al., 1989; Stitz et al., 1991a,b). Immunohistological examination of cells involved in perivascular inflammatory brain infiltrates in BD-virus-infected rats revealed predominantly CD4 cells, few CD8 cells and inflammatory cells expressing MHC class II antigens. Transfer of BD virus-specific CD4 T cells into non-infected recipients did not induce disease, demonstrating that the immunopathological effect is triggered only by specific viral antigen present in the CNS (Richt et al., 1989,1990; Stitz et al., 1991a,b).

Canine distemper encephalitis

In recent years considerable progress has been made in elucidating the pathogenesis of distemper encephalomyelitis, especially the mechanism of demyelination associated with CDV infection of the brain (Appel, 1987a). In the advanced areas of demyelination CDV-infected macrophages (microglial cells) occur in close proximity to myelin sheaths. On the basis of this finding it has been suggested that infected macrophages may fuse with the myelin sheath and initiate, in a so-called "bystander reaction", the process of demyelination. The results of brain-cell culture studies indicate that in the

antiviral immune response brain macrophages are important effector cells and may contribute to the inflammatory demyelinating process. A new hypothesis suggests that tissue damage in chronic CD demyelinating encephalomyelitis may result from an "innocent bystander mechanism" rather than directly from the antiviral immune response (Bürge et al., 1989; Griot et al., 1989). It was reported that cultured canine brain cells contain a population of macrophages that are capable of producing reactive oxygen species as measured by luminol-dependent chemiluminescene. The burst of reactive oxygen species is triggered by serum and cerebrospinal fluid antibody directed against CDV antigen on infected brain cells. The reaction is mediated by the interaction of CD antigen-bound antibody with Fc receptors on brain macrophages. This mechanism, triggered by antiviral antibody, may lead to degeneration of myelin-producing and -maintaining oligodendrocytes, degradation of phospholipids, damage to myelin membrane proteins and ultimately to severe demyelination.

VIRUS-INDUCED IMMUNE COMPLEX DISEASE

In certain viral diseases immune complexes (IC) are formed when antibodies are produced and react with viral antigen molecules which persist in the host or are released from infected cells into extracellular fluids. In a second pathogenic pathway, viruses induce a polyclonal B-cell proliferation with production of antibodies with a broad spectrum of specificity including autoantibodies, thus leading to formation of IC which involve both viral and self antigens (Theofilopoulos and Dixon, 1980; Trautwein, 1982; Casali and Oldstone, 1983; Sissons and Borysiewicz, 1985). Some of the persistent viral infections are associated with virus-induced IC deposits and IC-mediated tissue injury. Evidence for IC disease is based both on the demonstration of IC circulating in the blood or in extravascular fluid and its presence at the site of tissue injury, e.g., renal glomeruli, small blood vessels, synovial membranes, uvea of the eye, and choroid plexus in the brain. Subsequently, the most pertinent examples of immune complex disease will be reviewed.

Aleutian disease of mink

Aleutian disease (AD) of mink is a persistent viral infection caused by an autonomous parvovirus (ADV). Its genome consists of a single-stranded DNA molecule. The capsid is composed of two structural proteins of 85 kDa (VP1) and 75 kDa (VP2). The non-structural proteins of 71 kDa (NS1) and 14 kDa (NS2) have been identified in lysates of infected cells (Bloom et al., 1980; Aasted, 1985; Porter, 1986; Alexandersen, 1990; Kaaden et al., 1990; Porter et al., 1990). Mink homozygous for the recessive Aleutian coat color gene (a) are particularly susceptible, but severity and outcome of the disease are also influenced by the virus strain. ADV replicates predominantly in B or pre-B

lymphocytes of lymphatic tissues and in bone marrow cells (Roth et al., 1984; Kaaden et al., 1986,1990; Alexandersen et al., 1987; Haas et al., 1990; Wohlsein et al., 1990). Except in newborn mink, virus replication does not directly damage host cells.

The result of the interference of ADV with cells of the immune system is marked polyclonal B cell stimulation and plasma cell proliferation in lymphatic and non-lymphatic tissues. Tissue injury and death of the infected animal are caused by a marked immune response to viral antigens with subsequent deposition of pathogenic IC in certain target tissues. In contrast, ADV-infected newborn mink from antibody-free mothers develop an acute and fatal interstitial pneumonia, and the type II pneumocyte in the lung is the major target cell of virus replication (Alexandersen, 1986; Alexandersen et al., 1987).

It is now clear that a considerable part of the hypergammaglobulinaemia in diseased mink consists of specific antibodies to ADV. Up to 81% of the gammaglobulin may be virus-specific antibodies, directed to both ADV structural and non-structural polypeptides (Porter et al., 1984). Recently, a myeloma-like hypergammaglobulinaemia was detected in single ADV-infected mink. The monoclonal IgG had antibody activity to ADV proteins (Aasted and Leslie, 1991). The steady increase in serum immunoglobulin is followed by immune complex formation. Using the ^{125}IC1q binding assay, IC become first detectable 4 weeks post infection (Müller-Peddinghaus et al., 1980; Müller-Peddinghaus and Trautwein, 1983a,b). Antibodies from infected mink have high antigen affinity (Aasted and Bloom, 1984). Continuous formation of IC eventually causes serious tissue injury, e.g., glomerulonephritis, necrotizing arteritis and iridocyclitis. With immunohistological methods IgG, IgM and C3 can be demonstrated in the lesions (Müller-Peddinghaus and Trautwein, 1983a,b). However, the nature of the antigen(s) is uncertain. Monoclonal antibodies against structural ADV proteins p85 and p75 (VP1, VP2) detected little antigen in glomerular cells of the kidney, and monoclonal antibodies against the virus-induced non-structural polypeptide p71 (NS1) were unreactive (Wohlsein et al., 1990).

Feline leukaemia

A number of immune-mediated diseases are associated with FeLV infection: immune complex glomerulonephritis, autoimmune haemolytic anaemia, thrombocytopenia and chronic progressive polyarthritis (Pedersen, 1987c). The pathogenesis of glomerulonephritis has been clarified in experimental studies (Hardy, 1982). The long persistence of FeLV in chronically infected cats provides ideal conditions for the development of viral antigen–antibody complexes. As a result of viral lysis or cell lysis several FeLV structural components may become soluble antigens and potential antigenic components of IC. Thus, IC may contain intact virions, the envelope components gp70 and p15E, the internal viral structural components p27, p15, p12, and

p10 and after transformation of cells the tumor-specific antigen "FOCMA" (Hardy, 1982; Snyder et al., 1982).

Feline infectious peritonitis

Feline infectious peritonitis (FIP) is caused by a coronavirus (FIPV) and is known to occur with two clinical manifestations, the effusive and the granulomatous form (Pedersen, 1987b). Compelling evidence that circulating IC are involved in the pathogenesis of effusive FIP was presented in an experimental study (Jacobse-Geels et al., 1982). Using a haemolytic complement assay, these workers demonstrated initial complement activation followed by depletion in moribund cats. With a C1q binding assay a marked increase in circulating IC was shown to be associated with the appearance of humoral antibody and the onset of clinical signs. The analysis of IC purified from sera and ascitic fluids of FIP-infected cats revealed as antigen components proteolytic fragments (p83) of the peplomer p195, the main nucleocapsid protein p43 and three major envelope proteins. The antibodies had specificities against all classes of the virion peptides (Horzinek et al., 1986). It was shown that circulating IC were deposited in renal glomeruli (Jacobse-Geels et al., 1980,1982).

Miscellaneous virus-induced immune complex diseases

Infections with canine adenovirus, type 1, may be associated with inflammation of the anterior uveal tract of the eye ("blue eye") and glomerulonephritis (Appel, 1987b). One of the numerous aspects of bovine viral diarrhoea is the occurrence of IC glomerulonephritis both in cattle with mucosal disease and in persistently infected animals (Prager and Liess, 1976; Hewicker et al., 1987). Certain manifestations of African swine fever are considered due to immunopathological mechanisms, e.g., necrotizing pneumonia, glomerulonephritis and thrombocytopenia (Slauson and Sanchez-Vizcaino, 1981; Edwards et al., 1985a,b).

CONCLUSIONS

In the present review it was attempted to discuss the progress that has been made in understanding the complex immunological mechanisms underlying the pathogenesis of certain viral diseases. Transient or prolonged immunosuppression may result from the interaction of some viruses with single or multiple components of the immune system. The recent unravelling of the pathogenic mechanism in FeLV infection and the discovery of a new lentivirus (FIV) causing immunodeficiency in cats are important advancements. Both feline models will undoubtedly be of great value in further exploring the pathogenesis of acquired immunodeficiency in man and animals. Other important new findings were made in the field of persistent viral diseases. In

typical lentivirus infections of animals, e.g., maedi-visna and caprine encephalitis-arthritis, the essential role of monocytes/macrophages in virus distribution and disease development has now been clarified. New insight has been gained into the pathogenesis of Borna disease. Using the rat model, it was shown that the replicating virus alone does not cause tissue injury, but that an effective cell-mediated immune response plays an important role in the pathogenesis of the brain lesions. In canine distemper, a new hypothesis suggests that demyelinating encephalomyelitis may result from an "innocent bystander" mechanism which involves brain macrophages. Lastly, progress has been made in understanding the pathogenesis of virus-induced immune complex disease. In the prototype of IC-mediated diseases, Aleutian disease of mink, possible antigenic components have been identified. However, further studies are necessary to clarify the precise composition of IC circulating in the blood and IC deposited in critical target tissues.

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