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Invited Review

Morphological analysis of mouse hepatitis virus A59-induced pathology with regard to viral receptor expression

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Summary. Mouse hepatitis virus, strain A59 (MHV-A59), is a coronavirus that triggers in susceptible mice a wide variety of pathologies, including hepatitis, thymus involution, B lymphocyte polyclonal activation and, after intra-cerebral inoculation, transient demyelination. One receptor that mediates entry of the virus into target cells has been identified: it is a glycoprotein of the carcinoembryonic antigen family, called Bgp1a. The availability of antibodies recognizing this molecule permits the analysis of its cellular expression and of the relationship between receptor expression and pathology induced by the virus. Bgp1a is found on epithelial and endothelial cells as well as on B lymphocytes and macrophages. In the liver, Bgp1a expression correlates well with infection of hepatocytes and endothelial cells, leading to the development of hepatitis. However, other cells expressing this molecule, such as central nervous system endothelial cells, are not infected by the virus. This observation may explain how the blood-brain barrier prevents dissemination of MHV-A59 from the general circulation into the brain. Thymic atrophy results from apoptosis of immature double-positive T lymphocytes which might be caused indirectly by infection of a small proportion of thymus epithelial cells that express Bgp1a rather than by infection of T cells that do not express the receptor. Finally, polyclonal activation of B lymphocytes, leading to increased secretion of antibodies of the IgG2a isotype, involves a cascade of events, including cytokine secretion, that may result from the interaction of MHV-A59 with B cells and macrophages that express Bgp1a. Therefore, after viral infection, cellular expression of Bgp1a may have different results: cell lysis; alteration of cellular functions that may lead to indirect death of other cell types, or resistance to infection.

Key words: Viral receptor, Mouse hepatitis virus, Viral pathogenicity, Biliary glycoprotein, Carcinoembryonic antigen

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Introduction: viral tropism and cellular receptors

The pathogenicity induced by viral infections results from several factors that are sometimes difficult to distinguish. Some of these factors depend on the viral genome. It is well documented that virus strains that differ in one of their proteins, and often only by a few or even by a single amino acid, have widely different abilities to trigger diseases in an infected host. In addition, factors in the host itself may determine the outcome of an infection. Some host factors clearly determine the efficiency of the immune response to eliminate the invading microorganism. Others affect the initial interactions between the virus and the host, and particularly, the ability of the virus to infect host cells. Although considerable work remains to be done in order to elucidate the mechanisms that affect the host-virus relationship, it is clear that viral tropism, which is the ability of a virus to infect particular cell types, is a critical factor in viral pathogenicity.

Although the encounter of a potential host cell by a virus remains regulated by chance, the first event that will determine the tropism of this virus is usually its binding onto the cell. Therefore, many reports point to the expression of specific receptors, and even of co-receptors as key factors that explain at least partly the pathogenicity of a particular virus. However, in some circumstances, viruses may infect cells that do not express receptors specifically recognized by viral proteins. For instance, infection of a cell that expresses no specific virus receptor may result from close contact of an infected cell with another cell type (Gallagher et al., 1992). Several viruses, when coated with anti-viral antibodies (Halstead and O'Rourke, 1977; Cafruny and Plagemann, 1982; Inada and Mims, 1985; Ochiai et al., 1988; Robinson et al., 1989) and/or complement (Montefiori et al., 1990), can infect phagocytic cells by binding of the antibody- or complement-coated virus to Fc receptors or to receptors to complement components on these cells (reviewed by Halstead, 1994). However, the usual way for a virus to infect a cell is via binding to a specific component of the cell membrane via one or

more viral structural proteins.

Based on their biochemical nature, two types of virus receptors can be distinguished. Some of them are carbohydrate residues and others are proteins. Examples of carbohydrate receptors are the heparan sulfate-like glycosaminoglycans initially bound by herpes viruses including herpes simplex virus and human cytomegalovirus (WuDunn and Spear, 1989; Kari and Gehrz, 1992; Cooper, 1994), and sialic acid residues that are recognized by the hemagglutinin glycoprotein of influenza viruses and by parvoviruses (Paulson et al., 1979; Weis et al., 1988). Although carbohydrate moieties with virus receptor activity are expressed on many cell types and could therefore allow for a widespread dissemination of the virus, some restriction in viral tropism results from conformational differences in the saccharidic residues or from modifications of the viral attachment protein by proteolytic cleavage, which is sometimes required for viral infectivity (Naeve et al., 1984; Skehel et al., 1994; Tashiro and Rott, 1996).

Most viral receptors identified so far are membrane proteins or glycoproteins. Interestingly, many of these viral receptors are adhesion molecules belonging to the immunoglobulin superfamily or to the integrin family, that are also either responsible for physiological recognition of various cell types, or receptors for functionally important soluble molecules of the host. The restriction of the expression of specific receptors to particular cell subpopulations may thus be an important determinant of virus tropism. For example, human immunodeficiency virus (HIV-1) can infect T helper lymphocytes, monocytes and brain cells that harbour the CD4 molecule, recognized by the viral gp120 envelope glycoprotein (Dalgleish et al., 1984; Klatzmann et al., 1984; Maddon et al., 1986; Harrison, 1994). Other types of membrane proteins, including transporter molecules and low-density lipoprotein receptor-related proteins, can serve as receptors for diverse retroviruses (Cunningham and Kim, 1994; Weiss, 1994; Young et al., 1994). Restriction of infection with Epstein-Barr virus to human B lymphocytes and epithelial cells relies on the selective expression on these cells of CD21, which is a receptor for both the C3d complement molecule and the virus (Fingeroth et al., 1984; Nemerow et al., 1986; Inghirami et al., 1988; Cooper, 1994). To bind to specific target cells, several picornaviruses use adhesion molecules and functional cell receptors, including intercellular adhesion molecule 1 (ICAM-1) and low-density lipoprotein receptor for rhinoviruses (Greve et al., 1989; Staunton et al., 1989; Tomassini et al., 1989; Blaas et al., 1994; Crowell and Tomko, 1994; Greve and Rossmann, 1994; Hofer et al., 1994), ICAM-1 and decay accelarating factor (DAF or CD55) for Coxsackie viruses (Crowell and Tomko, 1994), CD55 and the very late antigen-2 (VLA-2) integrin for echoviruses (Bergelson et al., 1992, 1994), a member of the immunoglobulin superfamily designated PVR, with several isoforms, for poliovirus (Mendelsohn et al., 1989; Wimmer et al., 1994), vascular cell adhesion molecule-1 (VCAM-1) for encephalomyocarditis virus (Huber, 1994), and an as yet unidentified 34 kD molecule for Theiler's virus (Kilpatrick and Lipton, 1991). Cellular expression of membrane cofactor protein (MCP or CD46), a receptor for measles virus, is correlated with susceptibility to infection by this virus (Dörig et al., 1993, 1994; Naniche et al., 1993). Antigens of the major histocompatibility complex (MHC) have been implicated in cellular binding of Semliki Forest virus and lactate dehydrogenase-elevating virus (Helenius et al., 1978; Inada and Mims, 1984, 1985), although this has not yet been conclusively proven (Oldstone et al., 1980; Buxton et al., 1988). Alphaviruses, including Sindbis virus and Venezuelan equine encephalitis virus apparently recognize several different receptors, one of which is the high-affinity laminin receptor (Ubol and Griffin, 1991; Wang et al., 1992; Strauss et al., 1994). Human coronavirus HCV-229E and transmissible gastroenteritis virus of swine can bind their target cells after recognition of amino-peptidase N (Delmas et al., 1992; Yeager et al., 1992, Holmes and Dveksler, 1994).

Therefore, on one hand a virus may use more than one cellular receptor. On the other hand, some molecules may act as receptors for viruses belonging to very different families. Other factors, in addition to the expression of a receptor expressed on the surface of potential target cells, also influence the tropism of a virus. Expression of molecules in addition to the specific virus receptor may be required for virus entry into the cell. Several proteins have been identified as cofactors, including chemokine receptors. Such cofactors also affect the cellular tropism observed for diverse HIV-1 isolates (Choe et al., 1996, Doranz et al., 1996, Feng et al., 1996). Similarly the lymphocyte homing receptor CD44 may possibly interact with PVR to promote binding of poliovirus onto cells and therefore modulate viral tropism (Shepley, 1994; Shepley and Racaniello, 1994). In addition to virus receptors and co-factors, intracellular host factors and the immune response may also affect susceptibility of cells to viral infection.

To analyze the correlation of viral tropism with expression of a specific virus receptor, it is possible to use either cell lines or primary cell cultures. However, these *in vitro* techniques do not permit the study of the pathogenicity of the virus. Moreover, many differences can be observed between the *in vitro* and *in vivo* expression of a membrane cellular protein. The *in vitro* permissiveness of a particular cell type to infection by a virus does not necessarily reflect exactly the *in vivo* susceptibility of the same cell type to the same virus. It is therefore preferable to use animal models of infection to study the role of receptor expression in the viral pathogenesis. In addition, although molecular biology techniques provide important information on the progression of a viral infection and its consequences for the infected host, a morphological approach remains unrivalled in order to correlate cell types that express the viral receptor, virus dissemination and the development of disease. Recent technical progress has markedly

increased the accuracy of morphological analysis and its potential to provide valuable information about pathophysiological mechanisms. The availability of polyclonal and monoclonal antibodies for membrane glycoproteins permits immunohistochemical analysis by light or electron microscopy of the expression of many virus receptors, such as adhesion molecules in organs composed of numerous cell subpopulations, like the lymphoid organs and the brain (Godfraind et al., 1988). Advances in the processing and antigenic preservation of tissue sections have dramatically enhanced the ability to identify cells labelled with these techniques (Tokuyasu, 1980, 1989). The application of molecular biology methods to morphology and the development of new techniques like the use of biotinylated thyramine (Merz et al., 1995) have also increased their sensitivity.

Here, we review the recent progress, using morphological techniques, in the understanding of the relationship between expression of a particular viral receptor and the pathogenesis of the corresponding infectious agent, namely mouse hepatitis virus.

Mouse hepatitis viruses

Together with etiological agents of human common cold, transmissible gastroenteritis virus of swine, hemagglutinating encephalomyelitis virus of swine, feline infectious peritonitis virus, turkey bluecomb virus and infectious bronchitis virus of fowl, mouse hepatitis viruses (MHV) belong to the coronaviridae family (Almeida et al., 1968; Wege et al., 1982; Murphy, 1985). Based on their pathogenic properties and antigenic differences many strains of MHV have been distinguished, including the hepatotropic MHV-3 and MHV-A59 strains, enterotropic MHV-Y and MHV-RI strains, and the neurotropic MHV-JHM strain (Barthold et al., 1993).

The structure and replication strategy of MHV are similar to those of other members of the coronavirus family. With a diameter of approximately 100-150 nm, MHV are pleiomorphic virions, with surface projections called peplomers that give the virus family its name by reference to the corona around the sun (Almeida et al., 1968; reviewed by Kraft, 1982; McIntosh, 1985). A 30 kilobase long, single strand, positive sense genomic RNA encapsidated by numerous molecules of the 50-60 KDa phosphorylated protein forms the flexible helicoidal viral nucleocapsid (Holmes, 1985; Holmes and Lai, 1996). This nucleocapsid is enclosed within a lipoprotein envelope. Two structural glycoproteins, M and S, with molecular weights of 20-30 KDa and 180-200 KDa, respectively, are inserted into the envelope (Sturman and Holmes, 1977; Sturman et al., 1980; Holmes and Lai, 1996). The matrix glycoprotein M together with the S glycoprotein apparently mediate binding of the nucleocapsid to the viral envelope. The spike protein S forms the viral peplomers that bind to Bgp-related specific virus receptors on murine target cells and to human CEA as well as biliary glycoprotein (Chen et al., 1997). This viral protein also causes membrane fusion. Many neutralizing antibodies produced by infected animals react with this spike protein (Collins et al., 1982). After binding to and entering target cells, MHV replication involves synthesis of virus-encoded RNA-dependent RNA polymerase. This enzyme permits transcription of a minus-strand RNA which is followed by new positive-strand genomic RNA and mRNAs synthesis (Lai et al., 1982). Those mRNAs serve as templates for the synthesis of structural and non structural viral proteins. This synthesis is followed by the assembly of new virions in intracellular membranes and release of virions from infected cells (Dubois-Dalcq et al., 1982; Holmes and Lai, 1996).

In vitro, MHV strains replicate in several cell types, derived from different murine organs, including kidney, liver, macrophages, fibroblasts, neuronal cells, etc (David-Ferreira and Manaker, 1965; Mallucci, 1965; Shif and Bang, 1966). The ability of MHV to grow *in vitro* in macrophages derived from different mouse strains correlates with observed differences in susceptibility of these mouse strains to MHV infection *in vivo* (Bang and Warwick, 1960; Knobler et al., 1984b).

In vivo, MHV infection has been reported only in rodents (Kraft, 1982). Natural MHV transmission between mice occurs mainly through the feces, nasopharyngeal secretions, and possibly urine. After MHV inoculation, the lesions that can be observed in infected animals depend on the virus strain, the genetic background of the mouse, the age of the host and the route of viral administration. A common feature of MHV-induced pathology is the development of hepatitis, which is an important cause of death of the infected animals (Hirano et al., 1981; Wege et al., 1982). Infection of enterocytes can cause acute intestinal disease resulting in death, especially in infant mice (Kraft, 1962; Rowe et al., 1963; Barthold et al., 1982). With many MHV strains, infection may begin in the respiratory tract, with subsequent dissemination to other target organs (Barthold and Smith, 1984).

One of the most striking differences between various MHV strains is whether or not, and following which viral inoculation route, they can infect the central nervous system. Neurotropic strains like MHV-JHM induce severe neurological lesions, including meningitis, necrosis of various specific brain regions such as the hippocampus and the olfactory bulbs, and demyelination, mainly in the brain stem and the spinal cord (Bailey et al., 1949; Weiner, 1973; Kraft, 1982; Wege et al., 1982; Wang et al., 1990; Perlman et al., 1990). Sucklings are more severely affected than adult mice. In the brain, the major cellular targets of the virus are the oligodendrocytes although neurons can also be infected (Lampert et al., 1973; Powell and Lampert, 1975; Fleury et al., 1980). Inoculation with other strains of MHV causes less severe diseases of the central nervous system. MHV-3 induces chronic neurological disease characterized by meningitis, encephalitis and vasculitis, but with only minor involvement of the white matter

(Tardieu et al., 1982). Accordingly, *in vitro* tropism of this virus strain has been reported for neurons, ependymal cells and meningeal cells, but not for astrocytes or oligodendrocytes (Dubois-Dalcq et al., 1982; Tardieu et al., 1987, 1988). Interestingly, although it increased the acute lethality of MHV infection, treatment of mice with cyclosporin A reduced the frequency of chronic neurological changes, suggesting a role for the immune system in the pathogenicity of the disease (Boespflug et al., 1987, 1989). In contrast to what has been reported for MHV-3, intracerebral or intranasal inoculation of MHV-A59 causes a central nervous system disease mainly characterized by transient demyelinating lesions (Robb et al., 1979; Lavi et al., 1984a,b, 1995; Woyciechowska et al., 1984). Replication of this virus occurs mainly in glial cells of the spinal cord gray and white matter (Jordan et al., 1989). This viral infection has been used as an experimental model to analyze the cell subpopulations involved in remyelination processes and to show that O-2A$^+$ progenitor cells can give rise to both oligodendrocytes and type 2 astrocytes in these events (Godfraind et al., 1989).

Lymphotropism is a common feature of MHV infections, and these viruses induce a wide variety of acute and chronic immunological dysfunctions. Outbreaks of MHV in mouse colonies or experimental MHV inoculation can trigger alterations in macrophage functions, impair antigen presentation, inhibit T lymphocyte responses, and modify immunoglobulin secretion by B cells (Boorman et al., 1982; Casebolt et al., 1987; de Souza and Smith, 1991; Cook-Mills et al., 1992). Some of these alterations of immune parameters may modify susceptibility to unrelated infectious agents such as encephalomyocarditis virus or lactate dehydrogenase-elevating virus (Dempsey et al., 1986, Even et al., 1995).

After MHV infection, the antiviral immune responses appear to be rather weak. Like most antiviral antibodies elicited by inoculation of live viruses, anti-MHV antibodies belong mainly to the IgG2a subclass (Coutelier et al., 1987). Neutralizing anti-MHV antibodies are produced, most of which react with the viral spike protein S, although some anti-M antibodies may also neutralize MHV *in vitro*, but only in the presence of complement (Collins et al., 1982; Fleming et al., 1983). Even if its relevance to *in vitro* antiviral defence remains to be clarified, *in vivo* cytotoxicity of normal B lymphocytes towards target cells expressing the viral S glycoprotein has been demonstrated (Holmes et al., 1986; Welsh et al., 1986; Wysocka et al., 1989). This lytic activity, which can also be mediated by fixed B lymphocytes, is due to induction of apoptosis in the infected target cells (Nishioka and Welsh, 1993). Similarly, apoptosis of infected J774.1 target cells has been reported to be induced by CD8$^+$ cytolytic T lymphocytes specific for MHV, that can protect mice from lethal infection (Shibata et al., 1994; Stohlman et al., 1995). However, the most active anti-MHV response detected after infection is mediated by CD4$^+$ T lymphocytes that proliferate in response to viral glycoproteins and exert a strong cytolytic activity against cells

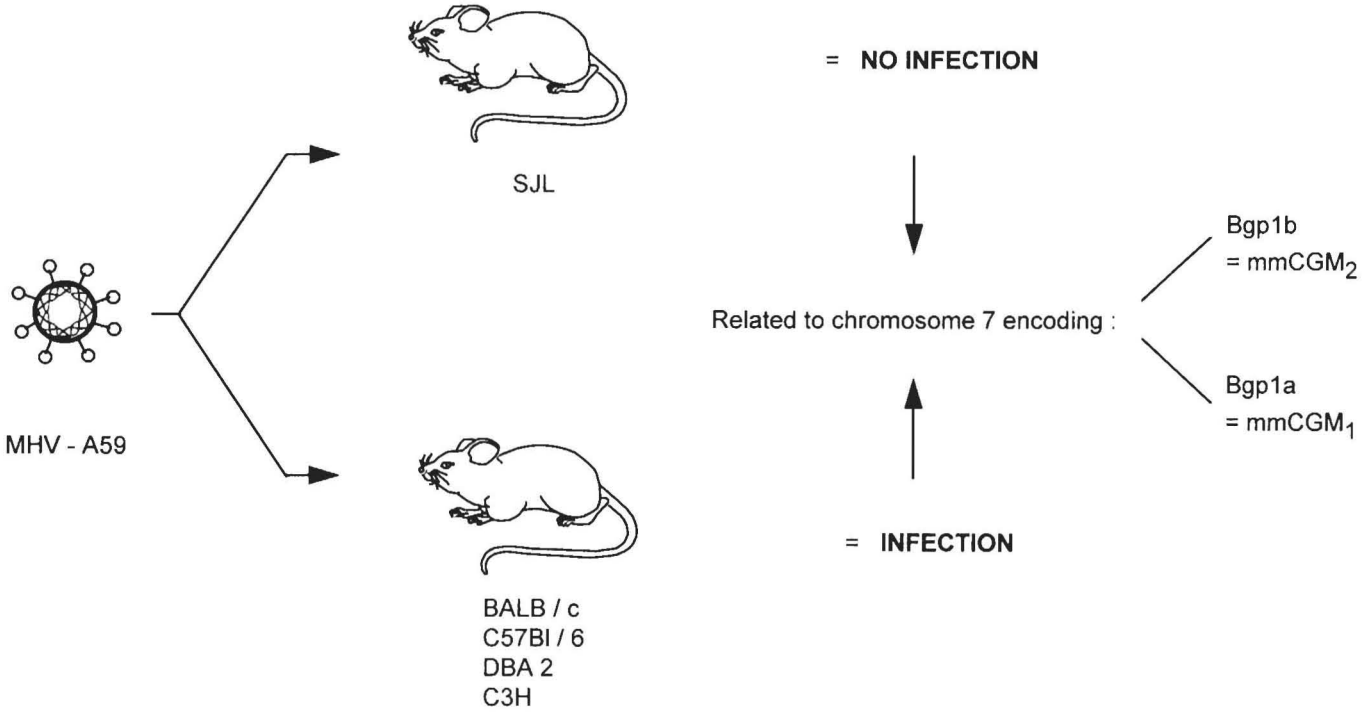

Fig 1. MHV-A59 infection in resistant and susceptible mice strains.

expressing MHV antigens (Mobley et al., 1992; Heemskerk et al., 1995; Wijburg et al., 1996). When stimulated by a specific MHV antigen, these anti-viral $CD4^+$ T cells also produce gamma-interferon, which is a major element in protection against MHV infection (Smith et al., 1991a, Schijns et al., 1996).

Mouse biliary glycoprotein 1, a receptor for mouse hepatitis viruses

Depending on their genetic background, mouse strains may be susceptible to infection with MHV, like BALB/c, C57Bl/6, DBA2 and C3H animals, or resistant to this infection, as observed for SJL/J mice (Knobler et al., 1981; Wege et al., 1982; Barthold and Smith, 1987; Fig. 1). *In vitro* infectivity of macrophages and hepatocytes has been shown to reflect the *in vivo* susceptibility of animals from which the cells were derived (Bang and Warwick, 1960; Arnheiter et al., 1982). The susceptibility of macrophages to MHV infection is controlled by a single autosomal dominant gene located on mouse chromosome 7 (Knobler et al., 1984a; Smith et al., 1984). These observations pointed to a cell-virus interaction as the key factor determining the ability of the host to resist MHV infection.

The role of virus-cell interactions in determining *in vivo* susceptibility to infection was suggested by studies showing that MHV-A59 virions bind to membranes from hepatocytes and intestinal epithelial cells of MHV-susceptible BALB/c, but not to membranes from MHV-resistant SJL/J mice (Boyle et al., 1987). This approach permitted the identification of a 110- to 120 KDa glycoprotein expressed on the hepatocyte plasma membranes and enterocyte brush border membranes, that serves as a receptor for MHV-A59 (Williams et al., 1990). Purification and sequencing of this MHV receptor indicated that it is a biliary glycoprotein, belonging to the carcinoembryonic antigen family, in the immunoglobulin superfamily (Williams et al., 1991). Accordingly, it has been designated MHVR or Bgp1a.

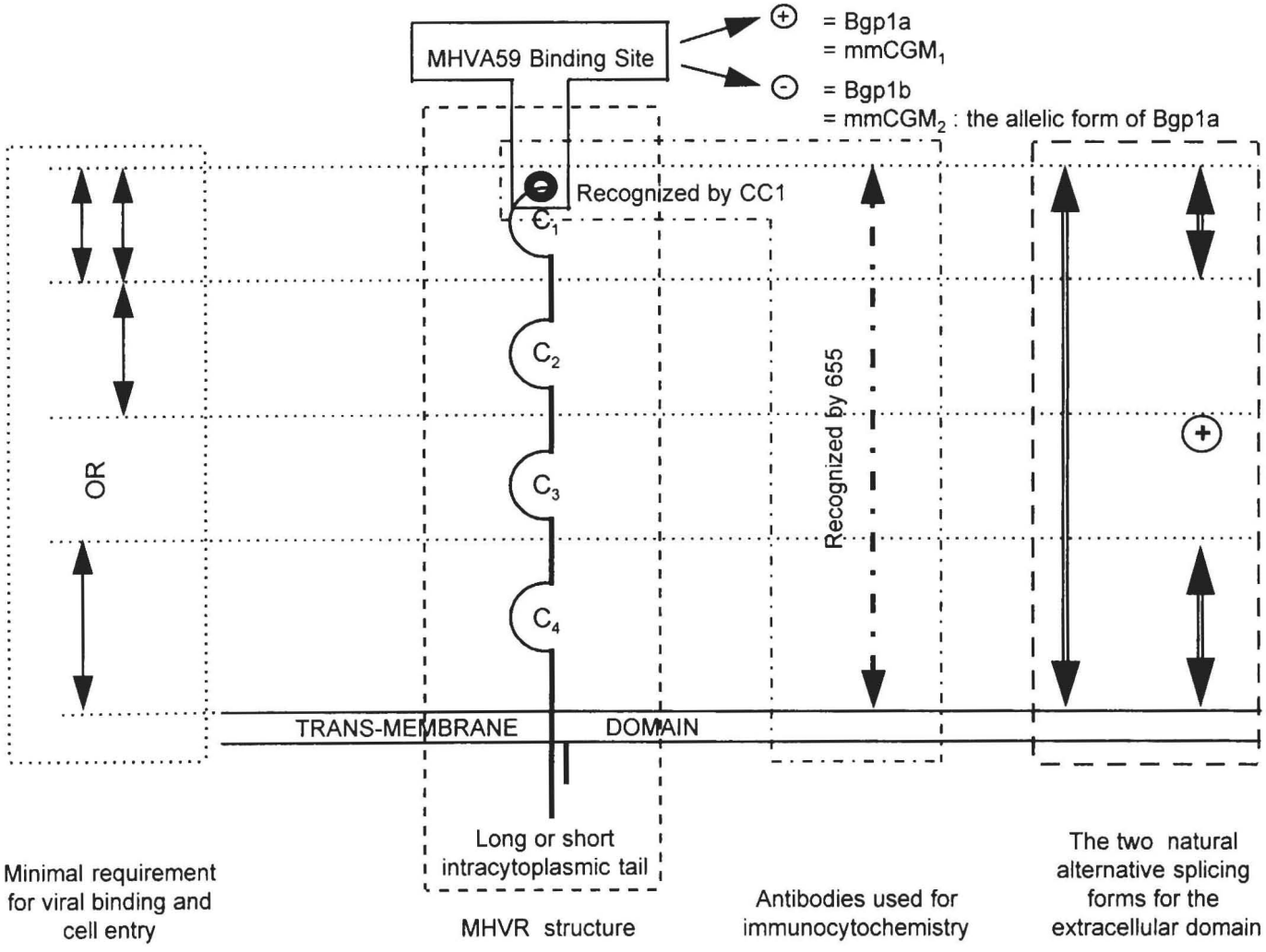

Fig 2. Molecular structure of Bgp1 isoforms.

Its function as a viral receptor was further demonstrated by its ability to confer susceptibility to MHV infection after transfection of the corresponding cDNA into human and hamster fibroblasts that were initially resistant to this virus (Dveksler et al., 1991).

The carcinoembryonic antigen family is divided into two major subgroups: the pregnancy-specific glycoproteins that are mainly expressed in the placenta and the foetus and the carcinoembryonic antigen subgroup that includes the normal cross-reacting antigen, CEA and the biliary glycoproteins (Khan et al., 1992). Expression of human biliary glycoprotein has been found in the

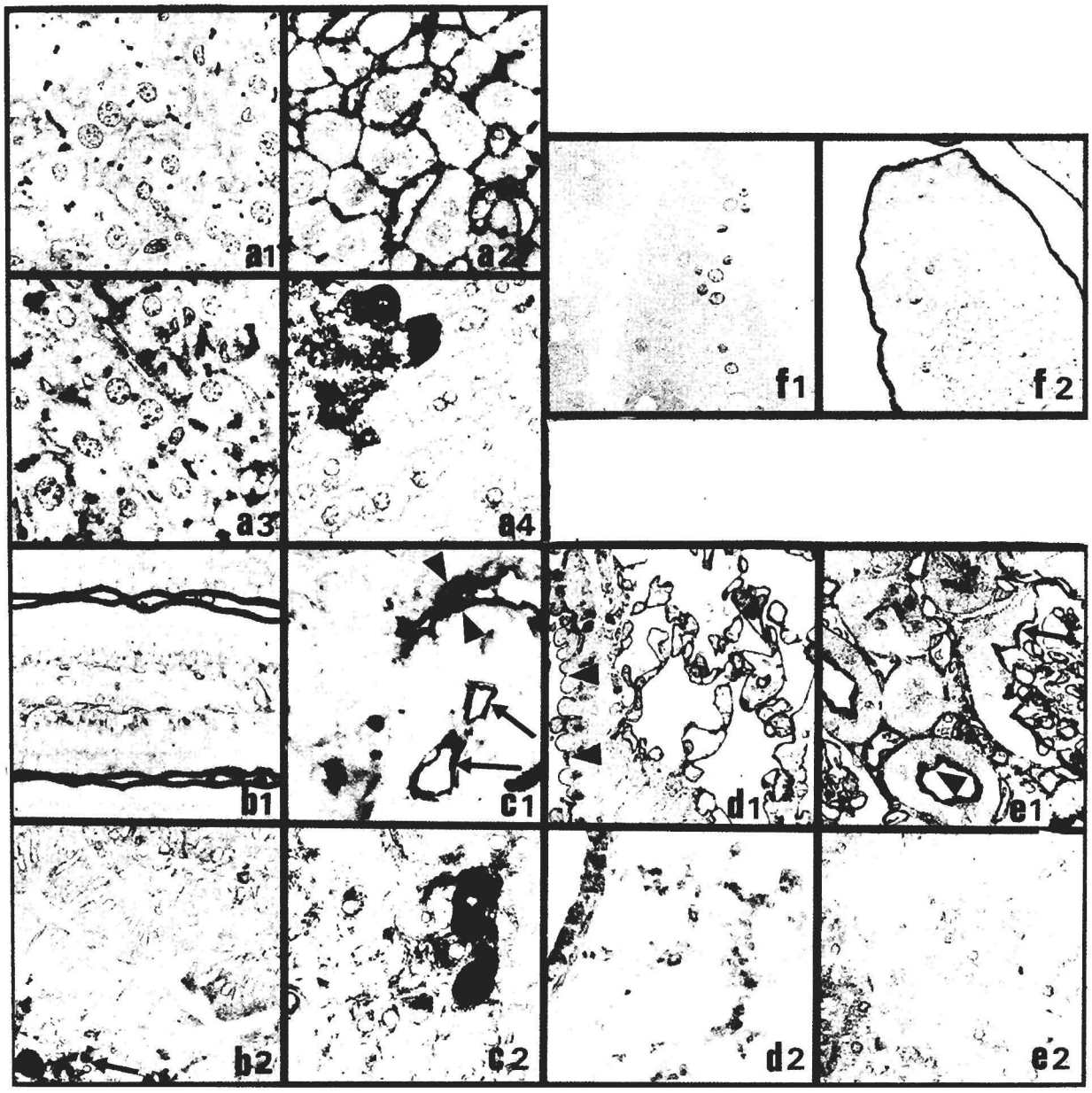

Fig 3. One-micron cryostat sections of Balb/c mouse tissues labelled with CC1 Ab **(a1; b1; c1; d1; e1)** or 655 Ab **(a2)** showed the presence of Bgp1a around the bile canaliculi and on the membranes facing the space of Disse in the liver (**a1**, magnification: x 400; **a3**, magnification: x 400), on brush border in the small intestine (**b1**, magnification: x 400), on the apical pole of exocrine pancreas excretory ducts (arrow head, **c1**, magnification: x 600), on the apical pole of ciliated and non-ciliated epithelial cells of lung airways (arrow head, **d1**, magnification: x 240), on the apical pole of proximal kidney tubule epithelial cells (arrow head, **e1**, magnification: x 240), on the endoluminal pole of endothelial cells (arrow, **c1**, magnification: x 600). Sections of SJL small intestine were not labelled with CC1 Ab (**f1**, magnification: x 400) while the brush border was labelled with 655 Ab (**f2**, magnification: x 400) indicating the presence of Bgp1b. Paraffin sections from MHV-A59-infected Balb/c mouse labelled with goat serum directed against S viral protein reveal the infection of hepatocytes (**a4**, magnification: x 250), immune cells (arrow head, **b2**, magnification: x 400), pancreatic exocrine cells (c2, magnification: x 400), while no infection is observed in the lung (**d2**, magnification: x 250) or in the kidney (**e2**, magnification: x 250).

normal colon as well as in the immune system, where it is designated CD66 (Hinoda et al., 1988; Watt et al., 1991, 1994; Stoffel et al., 1993). The rat homologous glycoprotein to human biliary glycoprotein is called C-CAM 105 (Ocklind and Öbrink, 1982; McEntire et al., 1989; Lin and Guidotti, 1989); mouse counterparts have also been identified and are designated mmCGM or Bgp (Beauchemin et al., 1989; Robbins et al., 1991; McCuaig et al., 1993; Nedellec et al., 1994). Interestingly, the mouse gene coding for biliary glycoprotein is located on chromosome 7 (Robbins et al., 1991). Several isoforms of Bgp glycoproteins are produced after alternative splicing of transcripts in rodents and humans (Barnett et al., 1989; McCuaig et al., 1992, 1993; Edlund et al., 1993; Nedellec et al., 1995). Allelic variation has also been reported for the genes coding for the mouse biliary glycoproteins (Dveksler et al., 1993a). The structure of the Bgp glycoproteins consists of two or four extracellular immunoglobulin-like domains, a transmembrane domain and an intracytoplasmic tail that can be either 9 to 10 or 70 to 71 amino acids long (Barnett et al., 1989; Dveksler et al., 1991; McCuaig et al., 1993).

Several reports have suggested that cell-cell adhesion is an important function of molecules in the carcinoembryonic family, including CEA and Bgps (Benchimol et al., 1989; McCuaig et al., 1992). This property, which is mediated by the N-domains of these glycoproteins, but not for CEA, has been observed with hepatocytes, colon epithelial cells and CHO cells transfected with cDNA encoding recombinant Bgp or CEA (Ocklind and Öbrink, 1982; Pignatelli et al., 1990; Oikawa et al., 1991, 1992). Both calcium-dependent and calcium-independent, homophilic and heterophilic cell adhesion activities have been reported for this molecule family (Tingström et al., 1990; Turbide et al., 1991; Oikawa et al., 1992; Zhou et al., 1993). Several other functions, including bile transport and ecto-ATPase activity have been ascribed to biliary glycoproteins (Lin and Guidotti, 1989; Sippel et al., 1993). Although expression of human carcinoembryonic antigen is increased in many types of tumor cells (Shuster et al., 1980; Beauchemin et al., 1987), mouse and human biliary glycoprotein isoforms are downregulated in malignant cells (Neumaier et al., 1993; Rosenberg et al., 1993), and may be involved in negative regulation of tumor growth (Kunath et al., 1995; Hauck et al., 1994).

The ability of murine biliary glycoproteins to serve as receptors for mouse hepatitis virus has been described for several isoforms of this molecule (Fig. 2; Yokomori and Lai, 1992a; Dveksler et al., 1993a). It has been shown using deletion mutants that the minimal requirement for virus binding and entry was the expression on the cell of a biliary glycoprotein with the entire N-terminal domain and either the second or fourth extracellular domain (Fig. 2, Dveksler et al., 1993b, 1996). A chimeric protein with the N-terminal domain of Bgp1a and two immunoglobulin-like domains, with the anchor, of the mouse poliovirus receptor homolog is also a functional receptor for MHV (Dveksler et al., 1995). Although complete deglycosylation of the MHVR protein was shown to abolish viral binding (Pensiero et al., 1992), the glycosylation of the N-terminal domain of the molecule is not required for this function (Dveksler et al., 1995).

The *in vivo* functional ability of Bgp1a to mediate MHV binding has been demonstrated by inhibition of viral replication in the mouse with a monoclonal antibody called Mab-CC1 that reacts with the N terminal domain of the biliary glycoprotein that serves as a virus receptor *in vitro* (Smith et al., 1991b; Dveksler et al., 1993b). The viral protein that binds Bgp1a is the spike glycoprotein S, as demonstrated by the ability of both anti-receptor MAb-CC1 and anti-S antibodies to prevent lysis of infected target cells mediated by recognition of the spike protein on these cells by normal B lymphocytes that express the biliary glycoprotein (Holmes et al., 1986; Coutelier et al., 1994). Moreover, infection of L-2 cells by pseudotype virions containing the RNA of lactate dehydrogenase-elevating virus and the MHV envelope is inhibited by antibodies directed against the MHV S glycoprotein (Even and Plagemann, 1995).

Natural MHV infection occurs only in mice and this species specificity can be related to species-dependent differences in the biliary glycoproteins (Compton et al., 1992). Similarly, mice that are resistant to MHV infection, like the SJL/J express a different allele of the Bgp gene, resulting in a decreased virus binding activity of the glycoprotein (Williams et al., 1990). However, transfection of the SJL/J Bgp, called Bgp1b, into Cos 7 cells resistant to MHV infection confers MHV susceptibility to these cells, suggesting that other factors may be involved in resistance to this virus (Yokomori and Lai, 1992b). Finally, a biliary glycoprotein closely related to Bgp1a and encoded by adjacent gene designated Bgp2 has also been shown to mediate MHV infection, but with a lower efficiency than Bgp1a (Nedellec et al., 1994). Similarly, a pregnancy-specific glycoprotein expressed in the central nervous system may also serve as a functional receptor for MHV (Chen et al., 1995).

Bgp1a expression in the mouse: correlation with MHV-induced pathogenicity

1. The digestive, respiratory, urinary and endocrine systems

Using both mouse monoclonal (CC1 Ab) and rabbit polyclonal antibodies (655) elicited against Bgp1a (Williams et al., 1990; Dveksler et al., 1991), we investigated the expression of the MHV receptor in various organs by immunocytochemistry (Fig. 3; Godfraind et al., 1995b). Both BALB/c and SJL/J mice biliary glycoproteins were found on the membranes of epithelial cells in many tissues. In the Balb/c small intestine, Bgp1a was located on the brush border membranes in the crypts and on the villus tips (Fig. 3b1). By electron microscopy it what shown that Bgp1a

expression was limited to the apical pole of these enterocytes. It was not found on tight junctions nor on the cellular basolateral membranes. The presence of Bgp1a was also shown on the epithelial cell brush border membranes in the colon, but not in the esophagus, nor in the stomach. Biliary glycoprotein was also detected on hepatocytes, with a preferential localization around the bile canaliculi and on the membranes facing the space of Disse. Bgp1a expression was similarly demonstrated on the apical pole of epithelial cells of the bile duct (Fig. 3a1, a2; Godfraind et al., 1995b).

In the respiratory tract, Bgp1a was observed on the apical membranes of ciliated and non-ciliated epithelial cells of the trachea and of smaller airways, but not on the basolateral surfaces of these cells (Fig. 3d1; Godfraind et al., 1995b). Similarly, epithelial cells of different endocrine organs, including cells of the thyroid follicles and the fascicular and reticular zones of the adrenal gland as well as acinar cells forming the excretory ducts of the exocrine pancreas, displayed this molecule (Fig. 3c1). Bgp1a expression was also observed on the brush border membranes of proximal kidney tubules, but not distal and collecting tubules. Epithelial cells of the parietal side of Bowman's capsule also expressed this molecule (Fig. 3e1).

In all the organs that were analyzed, Bgp1a was found on the arterial and venous endothelial cells, regardless of the size of the blood vessels (Godfraind et al., 1995b). In all these vessels, the glycoprotein was located mainly on the endoluminal surface of the endothelial cells (Fig. 3c1).

The tissue distribution of C-CAM, the rat homolog of mouse Bgp1a, has been analyzed by radioimmunoassay (Odin and Öbrink, 1987) and immunohistochemistry (Odin et al., 1988). In general, a good correlation exists between the expression of the rat and mouse molecule in various tissues. Indeed, rat C-CAM expression was detected on epithelial structures from many organs, including liver, gastrointestinal and respiratory tracts, kidney, glands and blood vessels (Odin and Öbrink, 1987; Odin et al., 1988). However, some differences were observed, since the rat but not the mouse Bgp was detected in the esophageal stratified epithelium, whereas mice but not rats expressed biliary glycoprotein on tracheal ciliated cells, parietal epithelial cells of Bowman's capsule, pancreatic acinar cells and thyroid follicular cells. Expression of CD66a, the human biliary glycoprotein is also similar to that of its mouse and rat counterparts (Prall et al., 1996). The human biliary glycoprotein has been found on epithelial cells,

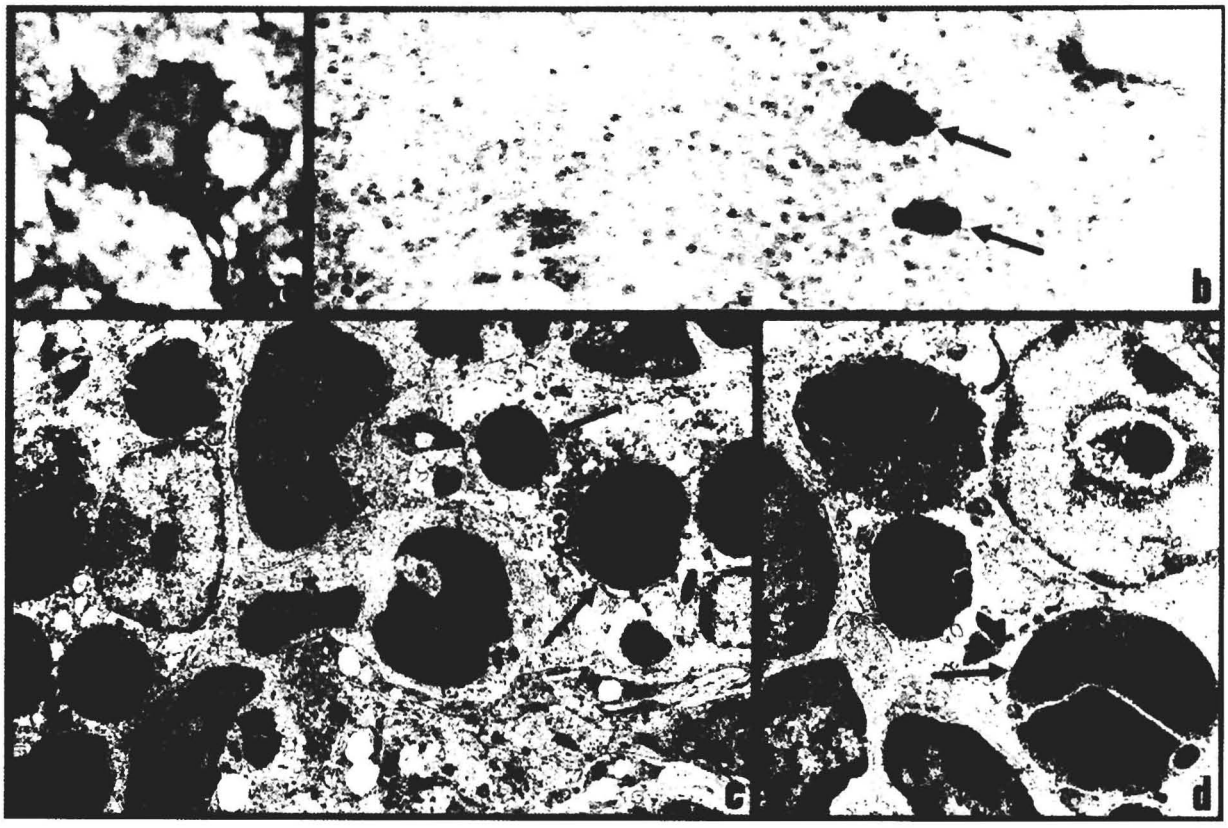

Fig 4 . One-micron section of a thymus from a Balb/c mouse infected for 5 days with MHV-A59 labelled with 655 Ab reveal the presence of Bgp1a on the membrane of thymic epithelial cell (**a**, magnification: x 2,100. Godfraind et al., 1995a). By in situ hybridisation, the viral genome is observed in epithelial thymic cells (arrow, **b**, magnification: x 400). Electron microscopy of one of these infected thymuses shows the classical features of apoptosis: nuclear condensation (arrow, **c**, magnification: x 4,600), and nuclear fragmentation (arrow, **d**, magnification: x 9,200).

including hepatocytes, enterocytes, cells of the bile and pancreatic ducts, and cells of the proximal kidney tubes, as well as on endothelial cells. In many of these cells, it has an apical membranous localization, as was reported for the mouse Bgp1a.

Bgp1a localization during mouse embryogenesis differs significantly from that reported in adult animals. In embryos, Bgp1a expression has been reported in mesenchymal cells, in the muscles, meninges, bone, cartilage, dermis and blood vessel walls (Huang et al., 1990). Therefore, it may be postulated that the localization of biliary glycoprotein expression depends on the stage of development. Quite possibly, Bgp expression on various cell types both in embryos and adult mice may reflect its putative physiological functions as an adhesion molecule in the structural organization of the corresponding tissues.

To determine whether Bgp1a expressed in tissues *in vivo* could serve as a functional receptor for MHV-A59, a direct virus binding assay on thin frozen sections was developed (Godfraind et al., 1995b). Using this test, it was possible to show that MHV-A59 indeed binds to BALB/c hepatocyte membranes, mainly near the bile canaliculi, and the brush border membranes of intestinal epithelial cells (Fig. 3a1). Since this binding could be blocked with an anti-Bgp1a MAb (CC1 Ab), these results indicate that Bgp1a expression permits recognition of potential target cells by the virus. No virus binding was detected in corresponding tissues from SJL/J mice.

The correlation between Bgp1a expression and viral tropism for different tissues was analyzed after MHV-A59 inoculation to BALB/c mice by the detection of viral antigens in different tissues by immunocytochemistry with a goat serum recognizing the S viral protein (Godfraind et al., 1995b). In the liver, foci of infected hepatocytes were detected beginning on day 3 after virus inoculation (Fig. 3a4). Although induction of monocyte procoagulant activity may also play an important role in the development of liver necrosis (Li et al., 1992; Fingerote et al., 1996), focal hepatitis lesions are usually associated with the presence of MHV antigens in hepatocytes (Barthold and Smith, 1987; Godfraind et al., 1995b). MHV-A59 infection of acinar cells of the exocrine pancreas (Fig. 3c2) that bear Bgp1a on their surface was also detected after intra-peritoneal inoculation of the virus (Godfraind et al., 1995b). In contrast, with this route of inoculation no MHV replication was observed in enterocytes and respiratory epithelial cells (Fig. 3b2, d2), which may reflect a difficulty for the virions to reach the biliary glycoproteins expressed on these cells from the general circulation. Other studies have indicated that these cells can become infected when different routes of viral administration are used (Barthold and Smith, 1984, 1987). Although it has been postulated that transmission of MHV can occur through the urine, it has not been possible so far to demonstrate infection of tubular kidney cells (Fig. 3e2) which nevertheless express Bgp1a. Similarly, no viral replication was found in thyroid cells (Godfraind et al., 1995b).

Together, these results show that Bgp1a can function *in vivo* as a natural receptor for MHV-A59, leading to infection of cells expressing this molecule and to pathological lesions in these tissues. However, some cells that bear the MHV receptor either cannot be reached by the virus or have a block in some later step of virus entry or replication. Similar findings have been reported, with poliovirus, since some cells expressing the appropriate receptor for recognition by this infectious agent cannot sustain virus replication (Freistadt et al., 1990; Ren and Racaniello, 1992).

2. The central nervous system

So far, Bgp1 expression has not been detected *in vivo* on neurons or glial cells of the central nervous system (Williams et al., 1991; Godfraind et al., 1995b). Similarly, absence of biliary glycoprotein expression on neural cells has been reported in rats (Odin and Öbrink, 1987; Odin et al., 1988). However, intracerebral inoculation of MHV-A59 in C57Bl/6 and BALB/c mice is followed by the development of a transient demyelinating disease that is characterized by infection of glial cells of the spinal cord gray and white matters. This is the reason why this virally-induced neurological disease has been considered as a model for at least some aspects of human multiple sclerosis (Lavi et al., 1984a,b; Jordan et al., 1989; Godfraind et al., 1989). In addition, *in vitro* infection of cultured glial cells was prevented with an anti-Bgp1a antibody (CC1; Godfraind et al., 1995b). This result indicates that biliary glycoprotein is expressed on glial cells, at least *in vitro*, and that it is the only receptor capable of mediating cell infection under these conditions. Therefore, failure to detect the receptor *in vivo* might be due to a low density of this molecule on glial cells, below the threshold of detection of the assays, or to relative inaccessibility of the antibodies to Bgp1a expressed on glial cells, or to differences between *in vivo* and *in vitro* expression of this receptor glycoprotein. In the latter case, infection of glial cells could involve binding of MHV-A59 virions to these cells via another receptor. It has been suggested that such a role of MHV-A59 receptor on glial cells may be played by an isoform of Bgp1a (Yokomori and Lai, 1992a,b). The relative efficiency of various MHV strains to recognize this alternative receptor might then explain the diverse neurovirulence of these viruses. On the other hand, either Bgp2 or a pregnancy-specific glycoprotein that are both expressed in the brain and that could both serve as functional receptors for MHV-A59 might also mediate *in vivo* infection of glial cells by this virus (Nedellec et al., 1994; Chen et al., 1995).

Although MHV-A59 can induce neurological infection and disease after intracerebral inoculation, this virus is not able to cross the blood-brain barrier after peripheral inoculation (Robb et al., 1979; Godfraind, manuscript in preparation). In some other models of

viral CNS infection, viruses able to pass through the blood-brain barrier can also infect endothelial cells forming this barrier (Krakowka et al., 1987; Zurbriggen and Fujinami, 1988; Soilu-Hänninen et al., 1994; Cosby and Brankin, 1995). After intraperitoneal inoculation of MHV-A59, no *in vivo* infection of endothelial cells was detected in the central nervous system, in contrast to virus replication observed in endothelial cells from other organs, such as the liver (Godfraind, manuscript in preparation). However, immunocytochemical analysis of brain and spinal cord tissue sections indicated that expression of Bgp1a on the endoluminal pole of endothelial cells was comparable in the central nervous system and in other organs. In addition, a direct virus binding assay, on thin sections, demonstrated that the receptor expressed on endothelial cells of CNS binds MHV-A59 virions (Godfraind, manuscript in preparation). These results suggest that endothelial cells forming the blood-brain barrier may have evolved particular mechanisms that enable them to prevent passage of viruses like MHV-A59 from the general circulation into the central nervous system.

Therefore, the MHV-A59 model illustrates the fact that the encounter by a virion of a cell bearing an appropriate receptor may result either in viral entry and replication or in absence of cell infection, depending on the cell type. A similar observation has been reported with other viruses, including poliovirus which may replicate in some, but not in all cell types expressing the PVR molecule (Shepley and Racaniello, 1994; Shepley, 1994). Whether this difference of cell susceptibility to infection is related to a differential expression of some coreceptor required for efficient virus entry remains to be determined.

3. The immune system

Multiple immune alterations have been reported after experimental infection of mice with diverse MHV strains. Experimental inoculation of BALB/c mice with MHV-JHM impairs antigen presentation by splenic and peritoneal adherent cells, probably macrophages (de Souza and Smith, 1991). These infected animals also show a transient immunosuppression characterized by a depressed proliferative response of splenic T cells to concanavalin A, correlated with a decreased production of interleukin-2, interleukin-4 and gamma-interferon, that is independent of the antigen-presenting cells (Smith et al., 1987, 1991c; de Souza and Smith, 1991; de Souza et al., 1991). BALB/c mice infected with MHV-3 also show altered T cell proliferation and interleukin-2 production in response to challenge with this virus (Dindzans et al., 1987). Similarly, MHV-A59 infection induces a decreased response of T lymphocyte to T cell stimuli like concanavalin A and anti-CD3 antibody and an impaired ability of these cells to secrete gamma-interferon (Cray et al., 1993; Even et al., 1995).

MHV-induced effects on B lymphocyte functions are quite varied. MHV-3 infection of C57BL/6 B lymphocytes at different stages of differentiation leads to atrophy of the spleen (Lamontagne et al., 1989b; Jolicoeur and Lamontagne, 1990, 1994). Mice chronically infected with MHV-3 display depressed Ig levels as well as decreased antibody responses following simultaneous immunization with SRBC (Virelizier et al., 1976; Leray et al., 1982). In contrast, enhancement of antibody production which could be related to variations of gamma-interferon levels has been reported in BALB/c and C57BL mice acutely infected with the MHV-JHM and MHV-3, respectively (Virelizier et al., 1976; Smith et al., 1991a). Similarly, MHV-A59 infection of CBA/Rij mice causes an IgG2a-restricted hypergammaglobulinemia (Coutelier et al., 1988). This polyclonal B lymphocyte activation, is partly dependent on T helper lymphocytes leading to enlargement of the spleen without structural alterations (Lardans et al., 1996). This modulation of B cell responses by MHV-A59 may follow a cascade of events, including expression of interleukin-12 by macrophages (Coutelier et al., 1995) and production of gamma-interferon by T helper lymphocytes (Coutelier, unpublished results). Moreover, MHV-A59 infection of 129/Sv mice at the time of immunization with a soluble protein antigen results in an immunostimulation with complete modification of the isotypic distribution of the anti-protein antibodies towards the IgG2a subclass (Coutelier et al., 1988, 1991). Similar mechanisms induced by MHV may also trigger enhancement of autoimmune responses concomitant to infection (Lardans et al., 1996).

Bgp1a expression in the mouse immune system has been analyzed by immunocytochemistry and flow cytometry (Coutelier et al., 1994). In the spleen, the Bgp1a glycoprotein was found in clusters of lymphoid cells that were identified as B lymphocytes. Cells of the B-1a lineage that are known to produce autoantibodies (Hardy, 1992) also bear this MHV receptor. Bgp1a was also expressed on splenic macrophages, but not on T lymphocytes, irrespective of their characterization in the CD4 or CD8 subpopulation. These results were confirmed by RNA PCR analysis of the message corresponding to diverse isoforms of Bgp1a, which was not found in T lymphocytes, although it was detected in B cells and macrophages. Similarly, B cell and macrophage cell lines expressed the Bgp1a protein, but a T cell line did not express Bgp1a (Coutelier et al., 1994). In the thymus, immunolabelling with anti-Bgp1 antibody revealed a reticular pattern in the cortical region that corresponded to expression of this glycoprotein on epithelial cells (Godfraind et al., 1995a). Bgp1a was also detected on murine granulocytes, mast cells and bone marrow stem cells (unpublished results). Both rat C-CAM and human CD66a are expressed on cells of the myeloid lineage such as granulocytes (Odin et al., 1988; Watt et al., 1991, 1994; Skubitz et al., 1992; Stoffel et al., 1993; Prall et al., 1996). In addition, expression of some alternatively spliced forms of human biliary glycoprotein has been observed on B cell lymphomas and Epstein-Barr virus-transformed B lymphocyte lines

(Khan et al., 1993). CD66a has also been detected after *in vitro* stimulation on human T lymphocytes and on a subpopulation of natural killer cells, although its expression is low when those cells are resting (Moller et al., 1996).

As mouse Bgp1a expression was observed on B lymphocytes, macrophages, endothelial cells and thymic epithelial cells (Coutelier et al., 1994; Godfraind et al., 1995a), which all require close contact with T lymphocytes to exert some of their physiological functions, we hypothesize that Bgp1a plays a role of adhesion molecule in recognition and binding of T cells. Thus, Bgp1a could be involved in such immune interactions as antigen presentation, lymphocyte margination and T cell differentiation. Possibly an as yet unknown ligand for Bgp1a should be found on T lymphocytes.

Susceptibility of mouse macrophages expressing Bgp1a to MHV infection has been recognized for a long time (Bang and Warwick, 1960; Lamontagne et al., 1989a), and could account for impairment of macrophage functions observed after natural or experimental inoculation of this virus (Boorman et al., 1982; Dempsey et al., 1986; de Souza and Smith, 1991). Whereas cells of the B lymphocyte lineage can be readily infected *in vitro* through binding of the virus on Bgp1a (Coutelier et al., 1994), no significant MHV-A59 replication has so far been detected *in vivo* in B cells of BALB/c mice (unpublished results). This is in contrast with *in vivo* infection of B lymphocytes from susceptible mouse strains, which has been reported with pathogenic MHV-3 (Lamontagne et al., 1989b; Jolicoeur and Lamontagne, 1990). Replication of the latter virus in pre-B cells and B cells of the bone marrow leads to a chronic immunodeficiency (Jolicoeur and Lamontagne, 1994).

In several mouse strains, like 129/Sv and CBA/Ht, MHV-A59 induces a polyclonal activation of B lymphocytes leading to hypergammaglobulinemia mostly restricted to the IgG2a isotype (Coutelier et al., 1988; Lardans et al., 1996). When MHV infection occurs concomitantly with an independent stimulus of the immune system, this B cell activation results in immunostimulation of antibody responses directed against non-viral antigens, including autoantibody production (Virelizier et al., 1976; Coutelier et al., 1991; Lardans et al., 1996). The IgG2a preponderance of these T-dependent antibodies, as well as an increased message for gamma-interferon (unpublished results) suggest that the virus induces a shift in the T helper lymphocyte differentiation, in favor of the Th1 subpopulation. This modulation of the immune responses may involve several mechanisms, possibly including direct interaction of MHV particles with B cells through Bgp1a expressed on these cells (Coutelier et al., 1994) and a cascade of cytokine secretion starting with the production of interleukin-12 by macrophages (Coutelier et al., 1995). Thus, alteration by the virus of the function of several cell types bearing the Bgp1a receptor, like macrophages and B lymphocytes, may result in the development of immunopathology. Similar observations have been reported with lactate dehydrogenase-elevating virus, murine adenovirus and lymphocytic choriomeningitis virus (Coutelier and Van Snick, 1985; Coutelier et al., 1988, unpublished results).

A marked thymus involution has been observed after infection of several mouse strains with MHV-JHM, MHV-3 or MHV-A59 (Knobler and Oldstone, 1987;

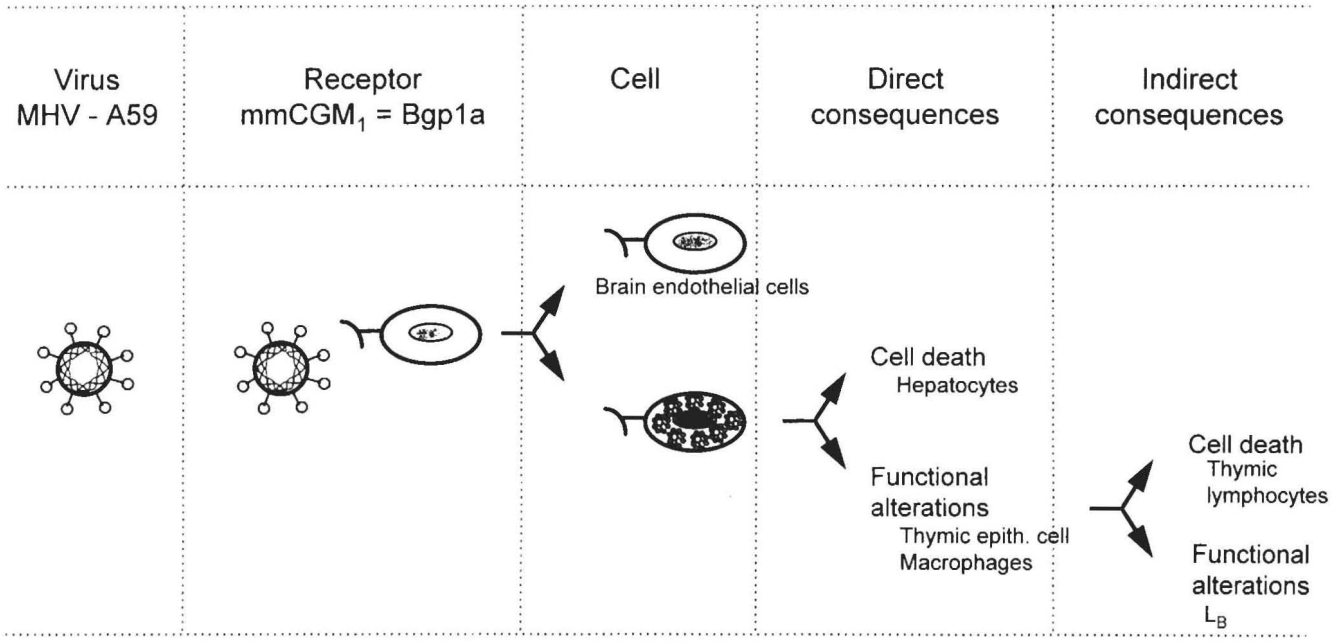

Fig 5. Outcome of interaction between MHV-A59 and different Bgp1a-bearing cell types.

Lamontagne et al., 1989b; Cray et al., 1993). Although thymic lymphocyte infection has been reported with MHV-3 (Lamontagne and Jolicoeur, 1991), no significant presence of MHV-A59 was detected in thymic lymphocytes of BALB/c mice which, like other T lymphocytes, do not express Bgp1a (Godfraind et al., 1995a,b). In the latter model, the decrease of thymic T cells resulted mainly from a dramatic drop of immature double positive $CD4^+$-$CD8^+$ cells. Electron microscopic analysis and *in situ* end labelling of DNA in thymus sections showed that apoptosis was responsible for this transient loss of T cells (Fig. 4). Since viral replication was observed in some thymic epithelial cells, it may be proposed that apoptosis of T lymphocytes may result either from an inappropriate secretion by these infected cells of a soluble factor able to trigger cell suicide, or to the suppression by the virus of some epithelial cell function required for the maturation and survival of T cells. Nevertheless, it appears that death of T lymphocytes is not the consequence of a direct infection of these cells, but rather results from an indirect mechanism following infection of thymic epithelial cells. Interestingly, similar indirect loss of thymic T lymphocytes concomitant with viral replication in epithelial cells has been reported after infection with murine cytomegalovirus and measles virus (Koga et al., 1994; Auwaerter et al., 1996).

Conclusions and perspectives

Although, as a general rule the development of pathology following infection with MHV-A59 requires the expression on some cells of a specific Bgp receptor recognized by the virus, when the relationship between this receptor expression and the pathogenicity of the infection is analyzed in greater detail, at least four different situations may be distinguished (Fig 5):

1. Some cells that express Bgp1a, like hepatocytes, are readily infected and rapidly destroyed by the virus, which results in pathology in the corresponding organ, in this case hepatitis.
2. In contrast, expression of the same Bgp1a glycoprotein on other cells, such as the cerebral endothelial cells does not result in viral replication in these cells after intra-peritoneal injection of MHV-A59. To explain the resistance of brain endothelial cells to MHV infection, we postulate the absence of some required cofactor, like a coreceptor that would allow virus entry. The consequence of the resistance to infection is the absence of any pathology in the CNS after intraperitoneal inoculation, as would be due for example to passage of the virus through the blood-brain barrier. Future investigations will focus upon identification of the cellular cofactor needed in addition to Bgp1a expression to allow MHV replication in these cells. Since human coronaviruses may possibly be involved in the pathogenesis of multiple sclerosis (Murray et al., 1992; Stewart et al., 1992), it might be of particular interest to further investigate the relationship between this family of viruses and the endothelial cells that take part in the formation of the blood-brain barrier. Along with those questions, it will be of great interest to define which the molecule acting as MHV-A59 receptor in the CNS is. Therefore, we will first try to localize in this tissue, the different molecules which might be involved.
3. Other cells, including the thymic epithelial cells, that also bear MHV receptor, become infected with MVH-A59. This results in an alteration of those cells which induce cell death of $CD4^+CD8^+$ lymphocytes leading to an important decrease in mature T lymphocytes. The nature of the altered relationship between epithelial cells and thymocytes remains to be determined.
4. Finally, some MHV-induced pathology, like immunostimulation with enhancement of autoimmune responses, may develop when the functions of two different cell types, the B lymphocytes and the macrophages that both express Bgp1a, are concomitantly affected, without death of these cells. A cascade of events may be triggered that involves additional cells, such as NK cells or T helper lymphocytes and that leads to pathogenesis. Again, the ultimate mechanisms by which MHV modulates B cell and macrophage functions are still unknown.

In addition to its role in MHV pathogenesis, Bgp1a may be an important cell adhesion molecule that could be involved in several immune functions. Being expressed on endothelial cells, Bgp1a might also play a role in the formation and maintenance of important physiological structures like the blood-brain-barrier. The availability of monoclonal and polyclonal anti-Bgp1 antibodies specific for the virus receptor glycoprotein may contribute to future studies on the function of Bgp1a as an adhesion molecule in embryos and adult mice that can be best analyzed by morphological techniques such as those illustrated in this paper. Solving this question will simultaneously throw some light on the timing of the Bgp1a switch off in the mesenchymal tissue and the Bgp1a switch on in the epithelial tissue. This in turn may help to study the gene involved in those events.

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