Chapter 3
Measles Virus and CD46

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Contents

Abstract Measles virus (MV) was isolated in 1954 (Enders and Peeble 1954). It is among the most contagious of viruses and a leading cause of mortality in children in developing countries (Murray and Lopez 1997; Griffin 2001; Bryce et al. 2005). Despite intense research over decades on the biology and pathogenesis of the virus and the successful development in 1963 of an effective MV vaccine (Cutts and Markowitz 1994), cell entry receptor(s) for MV remained unidentified until 1993. Two independent studies showed that transfection of nonsusceptible rodent cells with human CD46 renders these cells permissive to infection with the Edmonston and Halle vaccine strains of measles virus (Dorig et al. 1993; Naniche et al. 1993). A key finding in these investigations was that MV binding and infection was inhibited by monoclonal and polyclonal antibodies to CD46. These reports established CD46 as a MV cell entry receptor. This chapter summarizes the role of CD46 in measles virus infection.

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CD46 Discovery and Characterization

CD46 was discovered 1985 as a protein expressed on human peripheral blood mononuclear cells that bound C3b, the major opsonic and activation fragment of the complement system (Cole et al. 1985). It was initially termed gp45-70 because of its unusually broad, doublet, mobility pattern on SDS-PAGE. Subsequent functional analysis showed that gp45-70 functions as a complement regulator by serving as a cofactor for the plasma serine protease factor-I to cleave C3b and C4b (Seya et al. 1986; Yu et al. 1986). The protein was therefore renamed membrane cofactor protein (MCP) with a cluster of differentiation designation CD46 (Hadam 1989).

The complement system is a major player in the innate immune response, where it functions as a first-line defense against invading pathogens (Whaley et al. 1993). The complement system is activated by lectins and natural antibodies upon ligand binding and also serves as an independent immune system with sensing and effector activities (the alternative pathway). Once activated, it mediates microbial destruction by opsonizing microbes for adherence and internalization via phagocytic cells and through lysis (Whaley et al. 1993). It promotes the inflammatory process by the release of proinflammatory mediators, especially the C3a and C5a anaphylatoxins, which activate a wide range of cells involved in the host's immune response (Kohl and Bitter-Suermann 1993; Hawlisch and Kohl 2006), including endothelial and epithelial cells (Whaley et al. 1993). The complement system is often called a double-edged sword. Thus, while instrumental in fighting infections and promoting the immune response, it can cause damage to host tissues at a site of infection, in the setting of autoantibodies and immune complexes, or in acute and chronic injury states (Whaley et al. 1993; Walport 2001a, 2001b). To avoid undesirable damage to self, tight control is critical (Richards et al. 2007). Such control is achieved in part by two fluid-phase (factor H and C4b-binding protein) (Morgan and Harris 1999) and two membrane-bound (decay accelerating factor, DAF/CD55 and membrane cofactor protein, MCP/CD46) regulators. These proteins interact with C3 and/or C4 activation fragments through shared structural features (Morgan and Harris 1999). Also, the gene locus for these complement regulators is in a cluster that occupies an approximately 800-kb segment at 1q32 (de Cordoba et al. 1984; Holers et al. 1985; Reid et al. 1986; Hourcade et al. 1989). CD46 is in this regulators-of-complement-activation protein/gene cluster (Fig. 1A) (Cui et al. 1993).

Structure and Isoforms

The CD46 gene consists of 14 exons and 13 introns (Hourcade et al. 1989), spanning about 45 kb within the RCA gene cluster (Fig. 1B). It encodes a type I transmembrane protein (Liszewski and Atkinson 1992). The analysis of distinct cDNAs derived from cDNA libraries revealed one of the intriguing features of CD46: multiple isoforms arising from a single gene by alternative splicing (Fig. 1C) (Hourcade et al. 1989; Liszewski and Atkinson 1993). CD46 consists of four short consensus

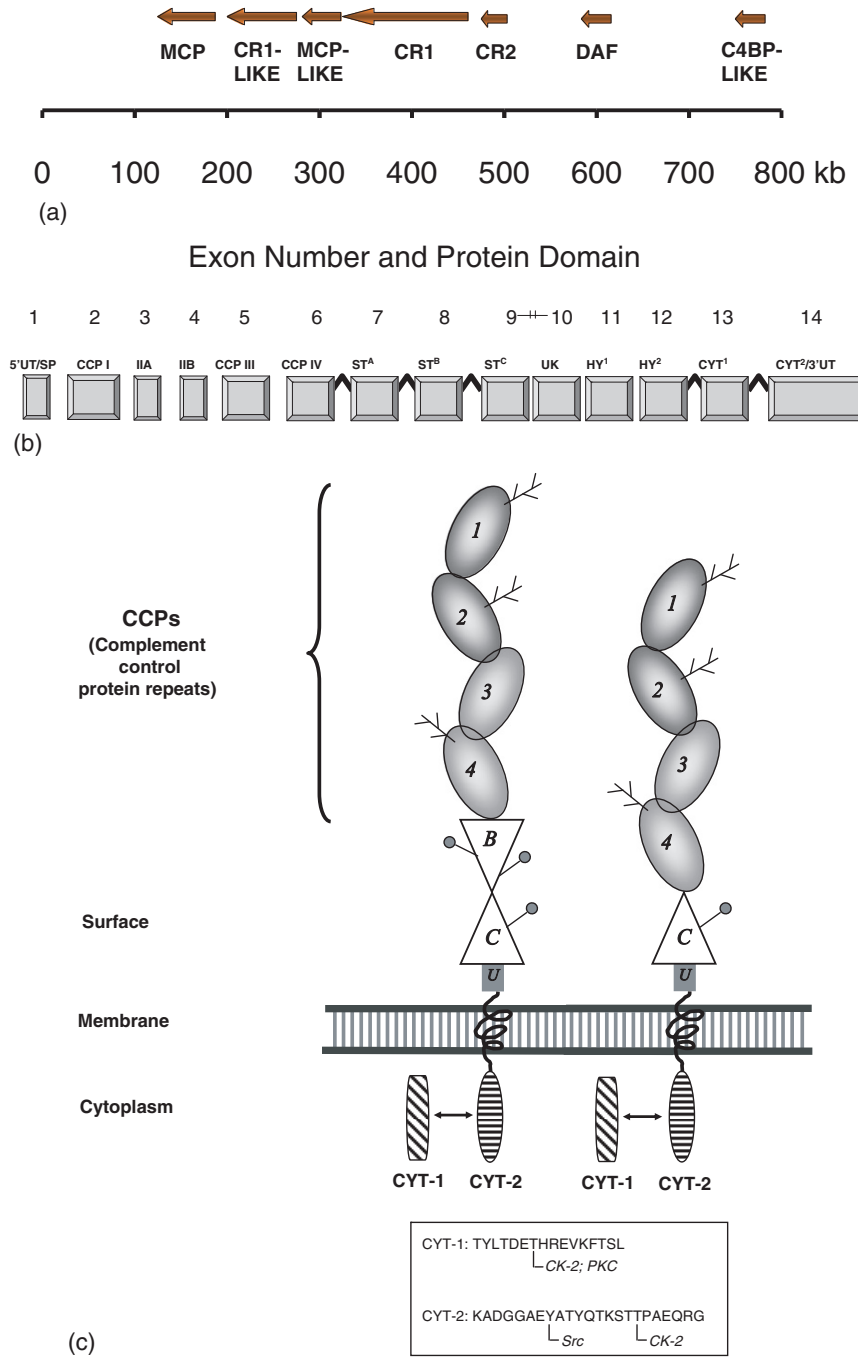

Fig. 1 (a) The gene sizes and intergenic distances are approximately drawn to scale. **(b)** Exon number and protein domain. The intergenic distances are not drawn to scale. The gene comprises approximately 46 kb. This is approximately 15 kb of DNA between exon 9 and 10. **(c)** Diagram of

repeats (SCRs) at its amino-terminus. These SCRs are also called complement control protein repeats (CCPs) or sushi domains and are independently folding protein modules of approximately 60 amino acids in length (Barlow et al. 1991). RCA members contain 4–30 CCPs and their C3 and C4 fragment binding sites reside within these structural units, usually requiring three CCPs to form a binding site. CCPs 1, 2, and 4 of CD46 are *N*-glycosylated. Glycosylation of CCP2 is essential for CD46 to function as MV receptor (Maisner and Herrler 1995; Maisner et al. 1994, 1996). The four CCPs are followed by a serine/threonine/proline (STP)-rich region. The STP region is encoded by three differentially spliced exons (giving rise to STP regions A, B, and C of 14–15 amino acids each). The STP regions are sites of *O*-glycosylation and the number and composition of amino acids of the STP region determines the quantity of *O*-glycosylation (Liszewski and Atkinson 1992). The STP region is followed by a short, juxtamembraneous 12 amino acid-long domain (separate exon) of yet unknown function, a transmembrane domain, an anchor, and one of two cytoplasmic tails, termed CYT-1 and CYT-2 (Liszewski and Atkinson 1992).

Thus, based on the observed STP splicing pattern and the distinct cytoplasmic tails, multiple CD46 isoforms can be generated (Fig. 1C). However, Northern and Western blotting and RT-PCR analyses of multiple cell lines, peripheral blood cells, and tissue samples demonstrate that CD46 is regularly expressed as variable amounts of four predominant isoforms, BC1, BC2, C1, and C2. Due to their difference in *O*-glycosylation, the BC1/2 isoforms show an M_r of 62,000–67,000, and the C1/2 forms have an M_r of 54,000–60,000 (Liszewski et al. 1991). The expression ratio of the four main isoforms is inherited in an autosomal codominant fashion, with three phenotypes in the population: the majority (65%) expresses predominantly the highly *O*-glycosylated BC1/2 forms, 6% express predominantly the less glycosylated C1/2 forms, and 29% of the population express both forms in roughly equal amounts (Liszewski et al. 1991; Wilton et al. 1992; Seya et al. 1999). All four isoforms serve as a MV receptor and binding of MV to CD46 is independent of the quantity of *O*-glycosylation (Maisner and Herrler 1995; Varior-Krishnan et al. 1994; Iwata et al. 1994). Soluble forms of CD46, possibly shed from the cell surface via metalloproteinases (Hakulinen and Keski-Oja 2006), are present in low concentrations in plasma, seminal fluid, and tears (Hara et al. 1992; Simpson and Holmes 1994). Their biological significance is unknown. Similarly, a role for the low frequency CD46 mRNAs encoding other isoforms, identified primarily in

Fig. 1 (Continued) CD46 structure. CD46 is a type I transmembrane glycoprotein that is expressed on most tissues as four major isoforms derived by alternative splicing of a single gene. The N-terminus of eachisoform consists of four complement control protein repeats CCPs, and CCPs 1, 2, and 4 each bear one *N*-linked complex sugar. The CCPs are followed by a serine, threonine, and proline-rich (STP) region that is *O*-glycosylated. The STP region, a site of alternative splicing, arises from three separate exons, designated A, B, and C. The four major isoforms of CD46 utilize the C region, whereas the B region is alternatively spliced, giving rise to either a BC or C STP region. Isoforms containing the A exon of the STP region have been reported, but are rarely observed in normal human tissue. The carboxyl terminus of CD46 is also differentially spliced, giving rise to two distinct cytoplasmic tails, designated CYT-1 (16 amino acids) and CYT-2 (23 amino acids)

EBV-transformed lymphocytes and leukemic cell lines (ABC1/2) and in the placenta (B1/2) (Hara et al. 1995; Matsumoto et al. 1992; Russell et al. 1992; Purcell et al. 1991; Johnstone et al. 1993), has not been identified.

Tissue Distribution

CD46 is expressed by nearly all nucleated cells (Seya et al. 1988). Human erythrocytes, in contrast to other primates, including the chimpanzee, do not express CD46 (Cole et al. 1985). The inherited specific CD46 expression pattern is generally identical on most all cell types in an individual (Liszewski et al. 1991). There are, however, notable exceptions. For example, in the fetal heart, CD46 is only found in the C1/2 isoforms (Gorelick et al. 1995), while the salivary gland and kidney express the -BC forms (Johnstone et al. 1993). Interestingly, sperm, kidney, salivary gland, and brain only express CYT-2 (Johnstone et al. 1993; Buchholz et al. 1996; Riley-Vargas and Atkinson 2003). Given that both tails of CD46 transduce intracellular signals upon CD46 crosslinking (see p. 42), tissue-specific expression of certain CD46 isoforms may play an important role during MV infection. Direct proof of this idea is lacking and is hampered by the fact that a suitable mouse model accurately recapitulating human MV infection is not available (see p. 46). A connection between specific CD46 isoform expression patterns and MV infection pathogenesis has not been observed. Although CD46 gene polymorphisms have been identified (Wilton et al. 1992), an analysis of a role for CD46 polymorphisms in the susceptibility to subacute sclerosing panencephalitis (SSPE) after MV infection has not shown an association (Kusuhara et al. 2000).

Functions

Complement Regulation

CD46 is an inhibitor of complement activation. It protects host cells from complement deposition by functioning as a cofactor for the factor I-mediated proteolytic inactivation of C3b and C4b (Morgan and Harris 1999; Liszewski et al. 1991) (Fig. 2). The binding sites for C3b and C4b and cofactor activity have been mapped to CCPs 2–4 (Adams et al. 1991; Iwata et al. 1995). The importance of CD46 in this process is demonstrated by the observation that individuals with CD46 haploinsufficiency secondary to mutations compromising its expression or regulatory function are predisposed to atypical or familial hemolytic uremic syndrome (HUS) (Richards et al. 2003, 2008; Kavanagh et al. 2008; Zheng and Sadler 2008). Atypical HUS is characterized by a triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure (Richards et al. 2008; Caprioli et al.

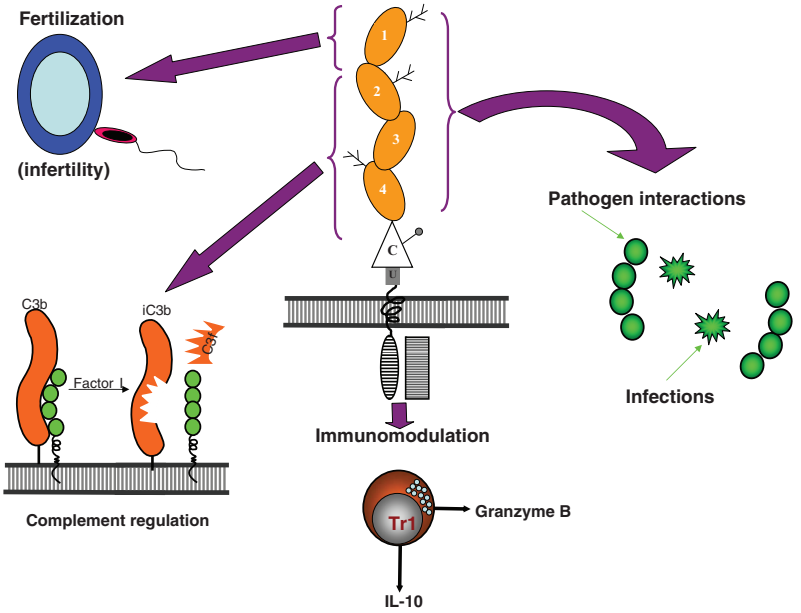

Fig. 2 Functions of CD46. CD46 was originally identified as a C3b-binding protein and then shown to have cofactor activity (promotion of the degradation of C3b and C4b by factor I) (*bottom left*). The complement regulatory activity of CD46 resides within CCPs 2–4. CD46 also plays a role in fertilization at the time sperm/egg union (*top left*). Human pathogens utilize CD46 as a cell entry receptor (*right*) (see Table 1). Concurrent activation of the T cell receptor and CD46 on primary human $CD4^+$ T cells in the presence of IL-2 leads to the induction of IL-10 and granzyme B-producing regulatory T cells (*bottom*)

2005). A partial deficiency of CD46 is thought to lead to excessive complement activation at the site of endothelial cell injury (Caprioli et al. 2006). The resulting overexuberant innate immune and inflammatory response to injury produces a thrombomicroangiopathy of glomerular vessels.

Fertilization

CD46 serves additional functions besides complement regulation (Riley-Vargas et al. 2004). A role in male fertility was initially suggested by its expression on the inner acrosomal membrane of spermatozoa. Variations in CD46 expression levels have been associated with male infertility (Kitamura et al. 1997). CD46 is important during fertilization by presumably promoting the sperm/egg interaction (Riley-Vargas and Atkinson 2003; Riley-Vargas et al. 2004, 2005; Harris et al. 2006). Although the exact role of CD46 during fertilization is unclear (Riley-Vargas et al. 2004), another

indication of its importance here is the CD46 expression pattern in rodents. In mice, rats, and guinea pigs, CD46 expression is restricted to spermatozoa (Morgan and Harris 1999; Riley-Vargas and Atkinson 2003; Tsujimura et al. 1998), while another, mouse-specific, complement regulator, Crry, takes over CD46's regulatory function on somatic tissue (Kim et al. 1995; Xu et al. 2000). The disruption of mouse CD46 causes an accelerated spontaneous acrosome reaction in sperm, suggesting that CD46 participates in this important process (Inoue et al. 2003) (Fig. 2).

T Cell Regulation

CD46 is a costimulatory molecule during T cell receptor (TCR)-mediated activation of human $CD4^+$ T lymphocytes (Astier et al. 2000; Zaffran et al. 2001). Specifically, concurrent crosslinking of CD46 with monoclonal antibodies, C3b dimers or a pathogenic ligand of CD46, along with CD3 on naïve human $CD4^+$ T cells induces a population of cells that is characterized by high IL-10 secretion (Kemper et al. 2003) and granzyme B/perforin production (Grossmann et al. 2004a, 2004b; Kemper and Atkinson 2007). CD3/CD46-activated T cells suppress the activation of bystander effector T cells through the immunosuppressive action of IL-10 and via direct killing featuring granzyme B. These characteristics place CD3/CD46-activated T cells in a regulatory T cell subpopulation. Similar to other IL-10-secreting regulatory T cells, the induction of this phenotype (including cell proliferation) (Meiffren et al. 2006) is highly dependent on the presence of exogenous IL-2 (Kemper and Atkinson 2007; Bluestone and Abbas 2003; Groux et al. 1997; Groux 2001; Roncarolo et al. 2001). Thus, the activation of T cells in the presence of complement components drives a functional phenotype distinct from that of classically CD3/CD28-activated T cells (Fig. 2).

Pathogen Receptor

CD46 is used as a receptor and port of entry by multiple human pathogens. Beside measles virus, herpes virus 6 and several adenovirus of the species B serotype utilize CD46 as cell entry receptor (Santoro et al. 1999; Cattaneo 2004; Gagar et al. 2003; Mori et al. 2002) (Fig. 2). A number of pathogenic bacteria, including *Streptococci pyogenes* as well as *Neisseria meningitides* and *N. gonorrhoeae*, bind to CD46 (Cattaneo 2004). The reason for CD46 being so attractive (pathogen magnet) for microbes is not clear yet. Obvious possibilities are that (a) CD46 could protect the invading organism from complement attack or (b) the induction of a T cell immunomodulatory phenotype. Also, in a strategy that is probably more commonly employed than currently recognized, *Escherichia coli* permit sufficient C3b deposition so as to be able to engage CD46 on epithelial cells in the urogenital system (Li et al. 2006) (Table 1).

Table 1 Pathogen/CD46 interactions and their major cellular/biological consequences

Pathogen	Ligand	Binding domain(s) within CD46	Ref	Major cellular consequences	Ref
Measles virus	Hemagglutinin (MVH)	CCPs 1–2	Manchester et al. 2000	Downregulation of IL-12 production by monocytes/macrophages	Karp et al. 1996
				Alterations in internalization pathways	Crimeen-Irwin et al. 2003
				Modulation of Th1/Th2 responses	Marie et al. 2002
				Induction of IFNα/β	Katayama et al. 2000; Kurita-Taniguchi et al. 2000
Neisseria (*gonorrhoeae* and *meningitides*)	Type IV pilus	CCPs 3–4	Kallstrom et al. 2001	CD46 cluster formation below bacteria attachment site	Gill et al. 2003
				Ca^{2+} flux	Kallstrom et al. 1998
				Phosphorylation of CYT-2 CD46 downregulation	Gill et al. 2003; Kallstrom et al. 1998; Lee et al. 2002
Herpesvirus 6 (human)	Complex of glycoproteins H, L and Q	CCPs 2–3	Santoro et al. 2003; Mori et al. 2003; Greenstone et al. 2002	Suppression of IL-12	Smith et al. 2003
				CD46 downregulation	Santoro et al. 1999
Streptococcus pyogenes	M protein	CCPs 3–4	Giannakis et al. 2002	Bacteria binding to human T cells in the presence of TCR stimulation in-duces IL-10 and granzyme B production (regulatory T cell development)	Price et al. 2005

Adenovirus (groups B and D)	Fiberknob Ad35	CCPs 1–2	Gaggar et al. 2003; Segerman et al. 2003; Fleischli et al. 2005	Decreased pro-inflammatory cytokine production by PBMCs	Iacobelli-Martinez et al. 2005
Escherichia coli	C3b deposited on pathogenic *E. coli*	CCPs 2–4	Li et al. 2006	Unknown	
Bovine viral diarrhea virus	Unknown	CCP 1	Maurer et al. 2004; Krey et al. 2006	Virus entry	Maurer et al. 2004; Krey et al. 2006

CD46 and Measles Virus Interaction

MV Hemagglutinin Binding Site Within CD46

The MV outer envelope consists of two glycoproteins, the fusion (F) and hemagglutinin (H) protein (Griffen 2001). Both are essential for host cell entry and viral pathogenesis (Griffen 2001). While the MVF protein plays a role in cell membrane penetration and syncytium formation (Wild et al. 1994), MVH is responsible for binding of the vaccine strains Edmonston and Halle to CD46 (Maisner et al. 1994; Maisner and Herrler 1995; Devaux et al. 1996) (for a detailed description of MVF and MVH proteins see chapter 4 by C. Navaratnarajah and R. Cattaneo, this volume). MVH also binds to signaling lymphocyte-activation molecule (SOLAM, CD150), which has been identified as a second MV receptor (Tatsuo et al. 2000; Khiman et al. 2004; Erlenhofer et al. 2002) (see the chapter by Y. Yanagi et al.) (for more information on MV receptor usage see chapter 2 by Yanagi and Hashiguchi, this volume).

The MVH binding site of CD46 resides within CCPs 1 and 2 (Maisner et al. 1994; Maisner and Herrler 1995; Iwata et al. 1995; Devaux et al. 1996; Manchester et al. 1997). Although dispensable for the MV/CD46 interaction, CCP4 enhances binding of MVH to CCPs 1 and 2 (Christiansen et al. 2000). CCPs 1 and 2 each contain a single site for *N*-glycosylation. The complex sugar linked to asparagine in CCP2 is critical for MVH binding, while the carbohydrate residue in CCP1 does not influence virus–receptor interaction. Epitope mapping employing monoclonal antibodies and peptides that inhibit the MVH/CD46 interaction and functional analysis of single amino acid substitution exchanges within CCPs 1 and 2 showed that amino acids 36–59 (CCP1) and 103–118 (CCP2) of CD46 are vital in interaction of CD46 with MVH (Hsu et al. 1998; Buchholz et al. 1997). That single amino acid changes not completely abolish the CD46/MVH interaction but rather led to varying degrees of reduced binding suggests that several distinct regions in CCPs 1 and 2 cooperate in binding MVH (Casasnovas et al. 1999; Hsu et al. 1997; Lecoutrier et al. 1996; Mumenthaler et al. 1997). This notion is supported by the crystal structure and molecular modeling studies of CCPs 1 and 2 (Casasnovas et al. 1999; Mumenthaler et al. 1997).

The location of the MV-binding and the C3b-binding sites within CD46 suggest that the MV interaction may not interfere with CD46's regulation of the alternative complement pathway (Christiansen et al. 2000a, 2000b). Although the MVH recognition site partially overlaps with the C4b-binding domain of CD46 (Iwata et al. 1995), in vivo interference of MV with classical complement pathway activation has not been reported.

One specific amino acid residue of CCP1 seems to be of exceptional importance among those constituting the MVH binding site as mutation of the arginine in position 59 decreases binding of MVH to CD46 by approximately 80%. This is particularly interesting because the major families of New World monkeys lack CCP1 on somatic cells (Hsu et al. 1997). This splicing out of CCP1 may account for the low susceptibility of these species to MV infection (Hsu et al. 1997, 1998). The

complement regulatory activity of monkey CD46 is not compromised as the domains for this activity reside within CCPs 2–4. In addition, the expression of CCP1 is retained in CD46 expressed on the sperm of New World monkeys (Riley et al. 2002). This manipulation of the CD46 structure by New World monkeys may represent deletion of CCP1 on peripheral blood cells to protect against infection by a major pathogen but yet conserve the vital functions of CD46 in complement regulation (CCPs 2–4) and fertilization (CCP1 in sperm). CCP1 of CD46 also harbors the binding sites for herpes virus 6 and for all CD46-binding adenoviruses. This raises the interesting question of why humans did not adapt/continue the monkey strategy and only retain CCP1 expression on sperm but delete it on somatic cells and suggests a potential yet unidentified role for CCP1 in CD46 biology besides that in sperm–egg interactions.

CD46 Binding Site Within MV Hemagglutinin

CD46 functions as a receptor for the MV vaccine strains Edmonston and Halle (Dorig et al. 1993; Naniche et al. 1993) but wild-type MV strains isolated from blood or throat swabs of patients generally do not bind to CD46 (Dhiman et al. 2004; Buckland and Wild 1997). In contrast, all known MV strains interact with SLAM (Dhiman et al. 2004; Yanagi et al. 2006; Kerdiles et al. 2006; Masse et al. 2004). Wild-type MV strains propagated in the marmoset lymphoblastic cell line B95 or Epstein-Barr virus-immortalized human B cell lines continue to only interact with SLAM (Lecouturier et al. 1996; Shibahara et al. 1994). However, wild-type strains passaged through Vero cells (Schneider-Schaulies et al. 1994) bind both receptors, CD46 and SLAM (for detailed information on MV tropisms on pathogenesis in relation to receptors, see chapter 2 by Yanagi and Hashiguchi, this volume).

Analyses of the regions within MVH responsible for this difference in receptor usage showed that only two amino acid changes at positions 546 and/or 481 determine the ability of MVH to bind to CD46 and/or SLAM. MVH (Erlenhofer et al. 2002; Hsu et al. 1998; Seki et al. 2006; Bartz et al. 1996, 1998; Rima et al. 1997; Takeuchi et al. 2002; Vongpunsawad et al. 2004; Li and Qi 2002) proteins that have a serine to glycine substitution at position 546 or a tyrosine at position 481 interact with both CD46 and SLAM. MVH containing an asparagine at the 481 position only binds SLAM. All strains analyzed after prolonged passage in Vero cells have a tyrosine at the 481 position (Yanagi et al. 2005). Because Vero cells express CD46 but not SLAM (Takeuchi et al. 2002; Johnston et al. 1999), MV is forced to adapt in Vero cell culture with the appropriate amino acid change to CD46 usage. It is, however, unclear how the wild-type virus with initial low binding and cell-entry capability overcomes this crucial entry step to propagate strongly in Vero cells.

CD46 is ubiquitously expressed in humans, suggesting that the factors that drive wild-type MV strains to favor SLAM as a receptor in vivo are likely not based on the differences in the receptor expression profiles alone. Several studies analyzing the residues within MVH relevant for the binding to CD46 identified 12 amino

acids (A428, F431, V451, Y452, L464, Y481, P486, I487, A527, S546, S548, and F549) (Masse et al. 2002, 2004; Vongpunsawad et al. 2004; Santiago et al. 2002). Mapping of these amino acid residues onto the MVH crystal structure (Colf et al. 2007) (see p. 23) demonstrated that the CD46 binding site is on the rim of the so-called dead neuraminidase fold. The authors of this study also determined that the binding site for SLAM within MVH is approximately 35 Å removed from the C3b CD46 binding domain. Because of this distance, sites of these binding domains within MVH likely do not overlap (Colf et al. 2007) (for further reading on the CD46/MVH interaction, see chapter 2 by Yanagi and Hashigachi, this volume).

Interaction of MVH with a receptor induces conformational changes. These changes in MVH affect the structure of the adjacent MVF protein and trigger a series of events leading to the fusion of the viral envelope with the host cell membrane (Wild et al. 1991). Similarly, the interaction of CD46 with a pathogenic ligand also affects its structure and cell surface distribution. For example, binding of the adenovirus type 11 knob protein profoundly alters the conformation of CD46: ligand-free CD46 shows a pronounced 60-degree bend between CCPs 1 and 2. Upon binding to the adenovirus knob protein, these CCPs realign and assume a rod-like shape (Persson et al. 2007). Also, the binding of pathogenic Neisseria to CD46 on human epithelial cells induces the formation of CD46 clusters below the bacteria attachment site and CD46-dependent changes in intracellular actin distribution (Gill and Atkinson 2004). Thus, the MV–CD46 interaction triggers a complex cascade of events on both the virus and the host cell side (for a detailed description of this event see the chapter by D. Gerlier and H. Valentin, this volume). Delineating these pathways and their intricate interplay most likely holds the key to understanding the MV pathogenesis and ultimately the improvement of MV vaccines.

CD46-Mediated Mechanisms of Immunosuppression in MV Infection

The mechanisms underlying the lymphopenia and immunosuppression that accompany MV infections are not well understood (Gerlier et al. 2006; Marie et al. 2004). All MV receptors so far identified produce intracellular signals upon their engagement (Dhiman et al. 2004; Yanagi et al. 2006; Kerdiles et al. 2006; Gerlier et al. 2006). Many of these signals initiate cellular events that modulate the immune response, seemingly in favor of the pathogen (Gerlier et al. 2006; de Witte et al. 2006). A first indication that CD46 activation could be beneficial for viral dissemination was the observation that human primary monocytes downregulate IL-12p70 and p40 upon CD46 crosslinking with MVH, anti-CD46 monoclonal Abs, or C3b dimers (natural ligand) (Karp et al. 1996; Karp 1999). Since IL-12 is essential for the generation of successful effector T cell responses, MV-induced IL-12 downregulation provides an attractive mechanism for virus-mediated immunosuppression. Suppression of IL-12 synthesis has indeed been observed in MV-infected patients (Atabani et al. 2001). Early CD46-mediated signaling events in human macrophages induce recruitment of the protein-tyrosine

phosphatase SHP-1 to CD46's cytoplasmic domain and then the subsequent synthesis of nitric oxide (NO) and IL-12p40 (Kurita-Taniguchi et al. 2000). The reasons for these apparently contradictory findings are unclear. One possibility is that the developmental stage of the MV-targeted cell (monocyte vs dendritic cell) elicits differential responses upon CD46 activation. Also, in one study MV was utilized as CD46 ligand while CD46 crosslinking antibodies were used in the other. Thus, signals induced upon CD46 engagement might also differ depending on the nature of the CD46-activating ligand.

MV binding to CD46 also modulates the production of another central cytokine, IFNα/β (Kurita-Taniguchi et al. 2000; Marie et al. 2001; Naniche et al. 2000). MV-exposed macrophages from huCD46-transgenic mice (see p. 46) resist infection but produce high amounts of IFNα/β (Katayama et al. 2000). The in-duction of IFNα/β is dependent on CD46-mediated signaling because macrophages expressing tail-less forms of CD46 do not produce IFNα/β and become susceptible to MV infection (Hirano et al. 2002). Little is known about the effect of the MV/CD46 interaction on B lymphocytes, but MV binding to CD46 expressed on B cells results in more efficient processing of MV antigens as well as enhanced MHC class II-restricted presentation to T cells (Gerlier et al. 1994a; Rivailler et al. 1998).

Altering the function of antigen-presenting cells such as macrophages and dendritic cells is a common strategy of many pathogens (de Witte et al. 2006). There is accumulating evidence that the MV–CD46 interaction also impacts effector T cell responses directly. The concurrent activation of CD3 and CD46 with mAbs on peripheral blood human $CD4^+$ T lymphocytes induces the production of high amounts of IL-10 and granzyme B. CD3/CD46-activated T cells acquire a phenotype reminiscent of Tr1 regulatory T cells and suppress the activation of bystander effector T cells via IL-10 and/or granzyme B (Kemper et al. 2003; Grossman et al. 2004b). T cells with these properties are predicted to aid in the contraction of an effector T cell response and in the prevention of autoimmunity (Kemper and Atkinson 2007; Bluestone and Abbas 2003; Sakaguchi 2000).

Although the in vivo role of such CD46-induced regulatory T cells is not clear, MV strains that bind CD46 may take advantage of CD46's T cell function modulatory property to perturb the protective T cell immune response and gain a foothold in the host. In accordance with this hypothesis is the observation that *Streptococci pyogenes* or the purified CD46-binding M protein of these bacteria indeed induce this suppressive Tr1 phenotype in primary human $CD4^+$ T cells (Price et al. 2005).

The notion of direct modulation of T cell responses by the MV–CD46 interaction is also supported by recent studies conducted in huCD46-transgenic mice expressing either a CYT-1 or CYT-2-bearing human CD46 isoform (see p. 46). When these animals are injected with inactivated vesicular stomatitis virus (VSV) expressing MVH, purified $CD4^+$ T cells from CYT-1-expressing animals proliferate strongly, produce IL-10 and inhibit the contact hypersensitivity reaction after concurrent TCR and CD46 activation. By contrast, CD3/CD46-activated T cells from CYT-2-expressing animals show weak proliferation, low IL-10 production, and an increased contact hypersensitivity reaction (Marie et al. 2002). The apparent

difference in the signaling events induced by the two intracellular domains of CD46 suggests first that the distinct CD46 isoform pattern observed in certain tissues (see p. 32 and 35) may be of importance in MV cell entry and virus spread and second that the inherited isoform expression pattern might be associated with differences in susceptibility of a given individual to MV infection or CD46-binding pathogens in general.

A puzzling observation is that wild-type MV strains favor SLAM over CD46 as their receptor despite the ubiquitous expression profile and immunomodulatory properties of CD46 (Dhiman et al. 2004; Yanagi et al. 2006). A possible explanation is that $CD4^+$ T cells not only produce IL-10 but also the proinflammatory cytokine IFN-γ upon CD3 and CD46 engagement (Kemper et al. 2003; Sanchez et al. 2004). In addition, it is not known if CD46-induced regulatory T cells suppress both Th1 and Th2 responses. Thus, an unfavorable skewing of the effector T cell response by CD46-activated T cells might have driven MV receptor usage in vivo toward SLAM. In addition, CD46 activation by multiple ligands, including MV and MVH, on several cell types analyzed so far induces CD46 downregulation (Dhiman et al. 2004; Yanagi et al. 2006; Bartz et al. 1996; Schnoor et al. 1995; Galbraith et al. 1998). In fact, CD46 downregulation is used as a common marker for a successful or infection-propagating interaction between CD46 and MV or MVH (Schnoor et al. 1995). This is commonly viewed as a protective measure by the host, as CD46 downregulation renders MV-infected cells more vulnerable to complement-mediated lysis (Schnoor et al. 1995). Furthermore, Gasque et al. proposed that CD46 expression provides a don't-eat-me signal, much like MHC class-I (Elward et al. 2005). Loss of CD46 expression, either via CD46-activation or after induction of apoptosis, flags the cells with an eat-me signal for uptake by phagocytes (Elward et al. 2005) (for further reading on the impact of MV on host immunity, see the chapter by Gerlier and Valentin, this issue).

CD46 activation on T cells and epithelial cells induces actin skeleton rearrangements (Zaffran et al. 2001; Gill et al. 2003) and CD46 activation on T cells has been implicated in uropod formation (Oliaro et al. 2006). In addition, CYT-1 of CD46 interacts with DLG-4, a protein that provides a scaffold for signaling complexes in epithelial cells (Ludford-Menting et al. 2002). The CD46/DLG-4 interaction results in the basolateral targeting of CD46 in several different epithelial cell lines. DLG4 is also implicated in tight junction formation and membrane fusion (Ludford-Menting et al. 2002). Thus, MV binding to CD46 possibly induces changes in the actin skeleton, thereby affecting the overall cellular shape or structure of the infected cell. Since a hallmark of MV infection is the induction of cell–cell fusion with the formation of multinucleated giant cells or syncytia, it would be interesting to address if CD46 is possibly involved in this process.

The existence of an unidentified additional MV receptors has been proposed since several groups observed MV attachment and entry to cells in a SLAM and CD46-independent fashion (Hashimoto et al. 2002; Andres et al. 2003; Hall et al. 1971). The identification of this putative receptor may help to explain the characteristics of MV infection that are not well accounted for by CD46's or SLAM's expression profile and function (Table 2).

Table 2 Measles virus/CD46 interactions and cellular signaling events

Cell type	Stimulation	Major observation	Ref
Human primary peripheral blood monocytes	MV hemagglutinin, mono clonal antibodies to CD46 and C3b dimers	Downregulation of IL-12 (p70 and p40)	Karp et al. 1996
Macrophages from hCD46-transgenic mice	MV	Increase in IFN-α/β production	Kurita-Taniguchi et al. 2000; Atabani et al. 2001; Naniche et al. 2000
$CD4^+$ T cells from hCD46-transgenic mice	MV hemagglutinin	CYT-1 dependent induction of IL-10 leading to inhibition of the contact hypersensitivity reaction	Marie et al. 2002
		CYT-2 dependent increased contact hypersensitivity reaction	
B cells from hCD46-transgenic mice	MV	Increase in MV antigen processing Enhancement of MHC class II-restricted antigen presentation	Rivailler et al. 1998; Gerlier et al. 1994

hCD46 human CD46; *CYT-1* or *-2* cytoplasmic tail of CD46

CD46-Transgenic Mouse Models

Nonhuman primates can be infected with MV experimentally and provide the animal model that most closely mimics the disease in humans (Hall et al. 1971; van Binnendijk et al. 1995). MV-infected rhesus macaques and African green monkeys show evidence of systemic viral replication, MV-induced immunosuppression, and clinical signs of disease, including maculopapular rash and conjunctivitis (Hall et al. 1971; van Binnendijk et al. 1995). On the other hand, nonhuman primate models are expensive and logistically challenging. In addition, they lack many of the advantages of small animal models, including the easy and basically unlimited access to tissue samples and the ability to study MV pathogenesis in gene knock out models. Unfortunately, the development of a successful small animal model has been hampered by the restricted function and/or expression of the two known MV receptors in rodents: mouse SLAM displays 60% structural and functional identity to human SLAM, but does not bind MV (Yanagi et al. 2006; Ono et al. 2001) and mouse CD46 is only expressed on spermatozoa (Riley-Vargas et al. 2004; Harris et al. 2006; Tsujimura et al. 1998). Similarly, rats including the cotton strain that was used in one study to analyze the function of the MV envelope outer glycoproteins in MV-induced immunosuppression (Niewiesk 1999) and guinea pigs do not express CD46 on somatic cells (Harris et al. 2006; Hosokawa et al. 1996). In addition, the intracellular domain of mouse and rat CD46 has no sequence or structure homology to either of the cytoplasmic domains of human CD46 (Hosokawa et al. 1996).

To study pathogen infections and immune reactions, several groups generated mouse strains transgenic for human CD46 (Marie et al. 2002; Mrkic et al. 1998; Rall et al. 1997; Horvat et al. 1996; Oldstone et al. 1999; Kemper et al. 2005). Some mouse strains express only one specific human CD46 isoform (Marie et al. 2002) and should be useful in analyzing functional differences between the distinct isoforms. A mouse line generated utilizing a yeast artificial chromosome that contains the complete CD46 gene, including the regulatory regions, mimics the CD46 expression pattern found in humans, including several tissue-specific distribution patterns of the four isoforms (Hourcade et al. 1990, 1992; Kemper et al. 2001). These mice have the obvious advantage that possible cooperative signaling events induced by both intracellular domains of CD46 can still occur, but it is unclear if the signaling platform and proper intermediates are present in rodents.

Intracerebral MV inoculation of mice expressing human CD46 isoforms under the control of a neuron-specific promotor induced disease and mortality, while nontransgenic control animal did not show signs of infection (Rall et al. 1997). In addition, injection of MV into the brain of these animals induced MV-associated cellular immune responses, including migration and infiltration of $CD4^+$ and $CD8^+$ T lymphocytes (Dorig et al. 1993; Rall et al. 1997; Manchester et al. 2000a). However, huCD46-transgenic mice are not susceptible to MV infection when the virus is administered via another route (for example, the natural respiratory route) than cerebral injection (Manchester and Rall 2001) because MV replication is limited (Oldstone et al. 1999; Horvat et al. 1996; Niewiesk et al. 1997; Thorley et al.

Table 3 Current hCD46-transgenic mouse strains

CD46 isoforms	Mouse model	Reference
C1	MV	Horvat et al. 1996
BC1	MV	Rall et al. 1997; Oldstone et al. 1999
C1	MV	Evlashev et al. 2000, 2001
C1 strain and a C2 strain	CD4 T cell activation/regulation	Marie et al. 2002
C1, C2, BC1, BC2 (YAC)	Xenotransplantation; MV	Oldstone et al. 1999; Yannoutsos et al. 1996
Minigene, isoforms*	Xenotransplantation; MV	Thorley et al. 1997
C1, C2, BC1, BC2 (YAC)	MV; *Neisseria meningitidis*	Mrkic et al. 1998; Johansson et al. 2003
80 kb Genomic fragment, isoforms*	MV	Blixenkrone-Moeller et al. 1998
C1, C2, BC1, BC2 (YAC)	Expression study; xenotransplantation; MV	Mrkic et al. 1998; Kemper et al. 2001; Yannoutsos et al. 1996
C1 or C2 (crossed with CD $150^{-/-}$ and $IFNAR1^{-/-}$)	Measles virus infection	Shingai et al. 2005

*Isoform expression pattern not depicted in study. YAC, yeast artificial chromosome.

1997) by the host's antiviral response. Crossing huCD46-trangenice mice with mice deficient in the type I IFN receptor (IFNAR1) (Mrkic et al. 1998) or the transcription factor STAT1 (Shingai et al. 2005) improved this model because respiratory inoculation of the virus resulted in enhanced virus spread and lung tissue inflammation (Oldstone et al. 1999). However, even in these animals, late-stage virus replication is inefficient and virus spread and MV pathogenesis only partially mimics the human disease (Peng et al. 2003).

The more limited expression of the protein in mice transgenic for human SLAM is thought to be one reason for the failure to obtain systemic MV infection in huSLAM-transgenic animals (Hahm et al. 2003, 2004). huSLAM/huCD46 double-transgenic mice, either with or without IFNAR1 expression, have been generated recently (Shingai et al. 2005). MV infection of huSLAM/huCD46 double-transgenic mice with a functional IFNAR did not induce systemic infection or disease. However, systemic infection occurred in huSLAM/huCD46/IFNAR1$^{-/-}$ animals or in huSLAM/huCD46/IFNAR1$^{+/+}$ mice injected with MV-infected DCs (Shingai et al. 2005). Thus, this study establishes that DCs and likely IFN production by these cells play a critical role in MV infection in mouse models. This is in agreement with the previous finding that MV-induced activation of CD46 expressed on human macrophages alters their cytokine profile (Karp et al. 1996) (see p. 42). It will be interesting to now delineate the roles of CD46 and SLAM in this process, specifically in the interplay between T lymphocytes and DCs.

In 2002, a study suggested an interaction between human toll-like receptor (TLR)2 and MV (Bieback et al. 2002). Wild-type MVH activates TLR2 on macrophages and monocytic cells, resulting in the production of IL-6 (Bieback et al. 2002). Given the essential role of TLRs in the recognition of pathogens (Medzhitov et al. 1997), MV infection likely triggers danger signals within this protein family. Thus, TLR knock-out mice should be considered in the generation of animal models studying MV pathogenesis.

Taken together, a number of mouse models are available to study certain aspects of MV pathogenesis. A model faithfully recapitulating the human disease does not exist. We anticipate the discovery of at least one additional human MV receptor. It does seem though that the mouse went through much effort to rid itself of MV cell entry receptors on somatic tissue. Thus, other murine factors important for viral RNA synthesis and virus assembly may also not support MV infection (Table 3).

Future Outlook

Successful immune defense is increasingly visualized as a process in which the innate part plays vital roles in instructing and guiding the adaptive system. That so many important human pathogens utilize CD46 as receptor attests to its central role at this important interface and communication between innate and adaptive immunity. Although we have learned much about CD46's functions as a measles virus

receptor, its role during MV infections remains largely enigmatic. Thus, delineating the cellular mechanisms that drive the diverse CD46–pathogen interactions in the context of the immune response model systems will be key to improving our understanding of MV pathogenesis.

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