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Virus entry: old viruses, new receptors

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The long-sought entry receptors for rubella, sindbis and respiratory syncytial viruses (RV, SV and RSV), together with the missing measles virus (MV) receptor for infection of epithelial cells, were identified in 2011. These have been major developments in the field of virus entry. In addition, 2011 was rich in new information about the interactions of MV, RSV and phleboviruses with DC-SIGN during infection of dendritic cells, a crucial step allowing the virus to breach the epithelial barrier and gain access to the lymph nodes. This facilitates dissemination to susceptible tissues where it can develop a vigorous and sustained replication, to eventually target specific organs from which it can propagate into the environment and efficiently infect new hosts, closing the merry-go-round of the virus cycle.

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Introduction

A key step in the virus cycle is the process of entry into a new cell, during which the viral genome is translocated across the membrane of the target cell. This process requires specific interactions with a cell surface receptor, or more often, several surface receptors. This can lead to mere ‘attachment’, resulting in accumulation of virus particles at the cell surface, and the cellular molecules involved are termed attachment factors. A different set of interactions at the cell surface results in an active entry process, either by inducing a conformational change in the virus particle that is necessary for entry, or by inducing uptake of the virion into an endosomal compartment. In this second case, the local environment of the endosome — its acidity, or the presence of cellular proteases, termed convertases — activates the virion to interact with the membrane in such a way that the viral genome is delivered across into the cytoplasm. The cell surface molecules involved in these active processes are called

entry receptors. Each virus has a different set of cellular surface molecules with which it interacts for entry, and the identification of these receptors is a major goal in contemporary virology. Understanding the nature of the receptors may have important implications for understanding tissue tropism and host range, and sometimes the pathogenicity of a virus.

Beyond the fundamental question of how a virus translocates its genome into the cytoplasm once it is in front of a target cell, an additional important question is how it reaches that particular cell, or the particular tissues in which it can sustain the infection to levels that are sufficient to ensure its propagation to other organisms. Such cells are not necessarily at the anatomical site of entry into a susceptible host. The cells with which a virus interacts early during infection of a new organism therefore may be different to those where it sustains the infection, which in turn may be different to the tissues used in the final stages, from which it can efficiently propagate to other hosts. In addition, the receptors involved in each case may also be different. Many viruses were found to target dendritic cells for dissemination within a new organism, because these cells are often among the first to be encountered. Some viruses, like measles virus, target the tracheobronchial airways at a late stage, such that aerosols can efficiently propagate them through the air. Other viruses, like the *arthropod-borne* viruses (arboviruses) induce high viremia to ensure infection of a biting insect or tick — the vectors that transmit and perpetuate the virus in nature. Once in the vector, the virus journey is such that at the late stages it targets the salivary glands to be efficiently transmitted upon a new bite to another vertebrate. In the past year, there have been considerable new findings about the nature of some of the receptors involved, and about the way viruses initially target dendritic cells in order to be transported across the epithelial barrier and for downregulating the immune response of the host.

Dendritic cells (DCs) are the sentinels of the immune system, activating the innate response and making the link between antigens and lymphocytes to trigger the adaptive immune response [1]. Immature DCs are present at peripheral tissues, deliberately exposed by the organism to invading pathogens. DCs also detect aberrant self-molecules circulating in the extracellular environment — for instance glycoproteins secreted from tumor cells with an aberrant glycosylation pattern. Antigen capture by DCs induces their maturation concomitant with migration to the lymph nodes, where the processed antigens are presented to T cells. Many viruses have

evolved to specifically rely on DCs for their own benefit, either by reprogramming DCs in order to interfere with an efficient immune response by the host organism, and/or by taking advantage of the induced migration of DCs across the epithelium to reach the lymph nodes, from which the newly synthesized virus can gain access to other susceptible tissues. There are several types of DCs in the body, organized into several phenotypic and functional subsets [2]. All of them express pattern-recognition receptors at their surface, and among these, toll-like receptors and specific lectins for detecting high-mannose glycans.

In mammals, the glycoproteins found in the extracellular environment normally have glycan chains that are extensively modified by specific glycosyl-transferases that reside in the Golgi apparatus (see [3] for a recent review). During glycoprotein synthesis, an initial mannose-rich core glycan is attached to the protein cotranslationally, upon translocation of the nascent polypeptide chain across the ER membrane after interaction with the signal recognition particle. The mannose residues of this core glycan are then cleaved sequentially in the Golgi apparatus, and are replaced by N-acetylglucosamine, glucose and other sugar residues to form complex and/or hybrid glycans. The mature glycoproteins exiting the Golgi thus essentially have complex N-glycans, with only an internal core of 3 mannose residues left from the initial core glycan [4,5]. High mannose oligosaccharides are therefore rarely found circulating in the extracellular environment in mammals under normal conditions [6]. However, they can become abundant in the case of certain tumors [7], when the malignant transformation affects the glycosylation pattern. Similarly, viral proteins are often heavily glycosylated, and the glycosyl-transferase enzymes responsible for processing the high mannose sugars become saturated in the virus-infected cell. This results in high mannose glycans present at the surface of viral proteins, in spite of being synthesized in mammalian cells.

Several related, Ca^{2+} -dependent type C lectins specific for high-mannose glycans [8] are displayed at the surface of different types of DCs. The most studied is DC-SIGN (CD209) [9], which is expressed on myeloid-lineage DCs [10–14], in activated B cells [15,16] and in some macrophages [17,18]. The related L-SIGN (CD299) [19] is displayed on liver sinusoidal endothelial cells, in the lung and lymph nodes [20–22]. A similar lectin is langerin (CD207) [23,24], present at the surface of Langerhan cells, which constitute a distinct population of immature DCs derived from the bone marrow, located in the epidermis and in stratified mucosal epithelia [25–27]. All three lectins have been reported to be involved in interaction with viruses. These are just a few examples among many other lectins at the surface of the various types of DCs that have been described (for a review, see [28]).

DC-SIGN is a homo-tetrameric type II membrane protein and C-type lectin. Crosslinking of DC-SIGN at the cell

surface by multiple high-mannose sites on the virion triggers uptake of the bound particle, resulting in antigen capture (see [29] for a recent review). DC-SIGN is used by many viruses for attachment to DCs, including MV [30], HIV-1 (see the recent review in [31]), HCV [32–34], Influenza A viruses [35,36], the herpes simplex virus type 1 [37], the human cytomegalovirus [38], Ebola virus [39], the SARS coronavirus [40,41], the human T-cell leukemia virus type 1 [42,43], and arboviruses belonging to the flavivirus genus — dengue virus [44,45] and west Nile virus [46] — and to the alphavirus genus, like SV [47] and aura virus [48]. In this review, we focus on recent insights for understanding the mechanism by which DC-SIGN signaling induces the uptake of the virus particle by the cell, beyond the initial attachment step. We thus discuss the role of DC-SIGN in promoting infection of DCs by MV and RSV and the impact on the immune response of the host. Furthermore, we discuss the implications of the newly identified entry receptors for MV, RSV, RV and SV, which were major highlights of the year 2011.

DC-SIGN as a phlebovirus receptor

Bunyaviruses are negative-sense single-stranded RNA viruses with a segmented genome. Many of them cause severe illnesses in humans, such as encephalitis and hemorrhagic fever (reviewed in [49]). They are classified in five genera (*Hantavirus*, *Nairovirus*, *Orthobunyavirus*, *Phlebovirus* and *Tospovirus*), all being arboviruses except for hantaviruses, which are transmitted by rodents. Helenius and collaborators [50**] studied two members of the *Phlebovirus* genus as model systems to explore interactions with DC-SIGN: the non-pathogenic Uukuniemi virus (UUKV) transmitted by infected ticks, in parallel to the human pathogenic Rift Valley fever Virus (RVFV), which is transmitted by infected mosquitoes. They show that both viruses infect DCs in a DC-SIGN-dependent manner. Raji cells, normally poorly infectable by phleboviruses, become susceptible to infection upon transfection with DC-SIGN. DC-SIGN binds to both viruses directly via their high-mannose N-glycans. On the opposite side of the membrane, the cytosolic tail of DC-SIGN contains several sequence motifs involved in signaling, including the classical dileucine (LL) motif, which serves as signal for its endocytotic internalization. They show that UUKV entry into DC-SIGN expressing cells occurs via endocytosis, and DC-SIGN is internalized together with the virion. When the LL motif in DC-SIGN is mutated, the virus still binds to the cells, but is not internalized and there is no infection. This is in contrast to an earlier study that found that the endocytosis motifs of DC-SIGN had no effect on dengue virus uptake [51]. Using total internal reflection fluorescence (TIRF) microscopy, the authors were able to directly observe the clustering of DC-SIGN molecules — tagged with a monomeric version of the enhanced green fluorescence protein (mEGFP) — at the cell surface upon UUKV binding. This suggests that binding of virions can create

a receptor-rich microdomain to induce its endocytosis. Indeed, DC-SIGN cross-linking with antibodies at the cell surface had been shown to induce efficient endocytosis of the lectin in DCs [52], so it is proposed that the UUKV-mediated clustering of DC-SIGN leads to activation of signaling pathways that trigger endocytic uptake of DC-SIGN and bound virus. These findings appear to establish DC-SIGN not just as an attachment factor, but also as a true receptor required for entry of phleboviruses and their uptake into an endosomal compartment. This is the first report describing a role for DC-SIGN in virus entry that goes beyond its involvement in virus attachment, as documented before for other viruses.

The above studies highlight an early interaction constituting the first stage of the infection of a new organism. Nothing is known about other potential receptors that are necessary to sustain phlebovirus infection in the host and allow its dissemination in nature. For instance, for the arbovirus SV, which was also shown to interact with DCs via DC-SIGN for reaching the lymph nodes [47], the studies discussed below have now identified an entry receptor — NRAMP — that is more likely to be used in these further stages of the infection, and perhaps at all stages, since it is very well conserved between humans and mosquitoes. Similarly, phleboviruses infect a wide spectrum of tissues, most of which do not express DC-SIGN, and so there must be other entry receptors for other tissues both in the mammalian and arthropod hosts. Nevertheless, DC-SIGN is clearly identified as a critical player in the initial transmission after bites by insects or ticks infected by phleboviruses.

DC-SIGN and measles virus

MV is the type species of the Morbillivirus genus in the *Paramyxovirinae* subfamily, which together with the *Pneumovirinae* subfamily makes up the *Paramyxoviridae* family of negative-sense, single-stranded RNA viruses. MV disease is characterized by fever, running nose, coughing, and a typical macular rash covering most of the body. Importantly, MV infection leads to a generalized immunosuppression that can cause serious complications. For a long time, laboratory-adapted strains of MV were known to use CD46 for entry [53], whereas wild type strains use the signaling lymphocyte activation molecule (SLAM, also termed CD150) [54], although it was suspected that additional receptors were involved. SLAM/CD150 functions as a lymphotropic receptor for both clinical and laboratory adapted isolates of MV [54]. CD46 is a complement regulatory protein, ubiquitously expressed with the exception of erythrocytes, while SLAM/CD150 is expressed on activated B and T cells, monocytes and DCs. CD150⁺ DCs, alveolar macrophages and lymphocytes are the first cells to be infected by MV, although CD150 appears not to be abundant at the surface of DCs. Epithelial cells become important for later stages of infection during

which the virus is spread via aerosol droplets. This year, in addition to the identification of nectin 4 as a new entry receptor for wild type MV for epithelial cells (reviewed below), new insight into the role of DC-SIGN to allow CD150-mediated entry of MV into DCs [55**] has been brought forth. Although it was known that MV interacts with DC-SIGN for entry into DCs, the mechanism was not clear, since ectopic expression of DC-SIGN in CHO cells was not sufficient to allow cell entry [30]. Schneider-Schaulies and colleagues [55**] now show that the interaction of MV with DC-SIGN at the cell surface signals via the mitogen-activated protein (MAP) kinases ERK1 and 2, resulting in the activation of cellular sphingomyelinase (SMase) activities. The corresponding cellular enzymes process sphingomyelin lipids present in the membrane to yield phosphocholine and ceramides, and the latter accumulate to form clusters in the plasma membrane. Both neutral and acid SMase (NSM and ASM), become activated as a consequence of DC-SIGN signaling induced by interactions with MV particles. NSM is anchored at the cytoplasmic leaflet of the plasma membrane, whereas ASM is soluble, and is stored in intracellular compartments (reviewed in [56]). The authors find that this internal compartment, which is apparently induced to fuse with the plasma membrane, also contains CD150/SLAM anchored in the membrane. This fusion event results in exposure of CD150 to the extracellular environment, together with the activated ASM that degrades sphingolipids. The presence of activated NSM and ASM at either side of the plasma membrane leads to the formation of ceramide-rich platforms that concentrate the receptor and allow virus entry.

Nectin 4 is a measles virus receptor

Human airway epithelial cells are CD150 negative, yet wild-type MV can efficiently infect them. This feature propelled the search for an MV receptor in epithelial cells. In 2011, the Richardson [57**] and Cattaneo [58**] laboratories independently identified adherens junction molecule nectin 4 — also called ‘poliovirus receptor-like 4’, or PVRL4 — as MV receptor for epithelial cells. Both groups used comparative microarray analysis of susceptible versus non-susceptible tumor cell lines to identify the receptor.

Nectin 4 is expressed during phases of rapid cellular growth, and it is highly abundant in placenta during embryogenesis, as well as in cancer cells. This is in line with the observation that MV efficiently infects adenocarcinoma cells derived from breast, lung and colon cancers, and with reports that lytic MV infection causes regression of certain tumors [59]. In addition, human smooth-airway epithelial cells, normally expressing low levels of nectin 4, could be infected by MV independently of CD46 and SLAM only when grown in serum-containing medium,

which increases nectin 4 expression. Antibodies specific for human nectin 4 and transient knockdown of nectin 4 using siRNA abolished MV infection of these cells.

Nectin 4 is a member of the Nectin family of Ca^{2+} -independent immunoglobulin-like cell adhesion molecules. They are composed of an extracellular ectodomain, containing three sequential Ig-like domains, a single TM domain and a C-terminal cytoplasmic tail (reviewed in [60]). The ectodomain is organized such that the N-terminal domain, which is furthest from the membrane, is a variable-type Ig domain, whereas the other two are of the constant C2-type Ig domains, resulting in a 'V-C-C' organization, where V and C are the variable and constant domains, respectively. Antibodies directed against the V domain block infection, whereas antibodies directed against the other two domains do not, or block to a much lower extent [58**]. Using a fusion protein with a C-terminal Fc, the authors tested inhibition with V-Fc and VCC-Fc, and found that both efficiently inhibited infection. Affinity measurements by surface-plasmon resonance indicated that the affinity of the two forms is very similar, measuring a dissociation constant of 20 nM, which is an affinity about 5-fold higher than that of a similar soluble construct of CD150/SLAM. Nectins are localized, together with cadherins, at the adherens junction between cells, forming homotypic or heterotypic interactions *in trans* to establish and maintain cell-cell connections. Members of the Nectin family function as receptors for poliovirus (PVR or CD155) and herpes simplex viruses (Nectins 1 and 2) [61–63]. The new reports now clearly establish the involvement of nectin 4 in entry of MV into airway epithelial cells.

RSV and DCs

RSV is a common cause of respiratory infections, in particular bronchiolitis, which can be fatal in infants and in the elderly. In contrast to MV and RV, there is no effective vaccine for RSV, and the use of passive immunoprophylaxis with anti-RSV-specific antibodies is expensive and limited to high-risk patients (reviewed in [64]). RSV is the type species of the pneumovirus genus in the *Pneumovirinae* subfamily of the *Paramyxoviridae*. Like MV, the RSV virion contains two major envelope glycoproteins, called F and G. In addition, it contains a small hydrophobic (SH) protein, which is thought to play the role of ion channel and not to be involved in entry. The F proteins are homologous in all members of the *Paramyxoviridae* family, and are responsible for the membrane fusion reaction. Contrary to MV, for which receptor binding by H triggers the fusogenic conformational change in F [65,66], RSV F does not require G to induce membrane fusion [67]. G appears to mainly play a role in attachment, and both G and F were shown to interact with GAGs [68,69]. In addition, F binds to ICAM-1 [70] and G to annexin II [71] although these interactions are not essential for entry. While the

primary tissues targeted in the lungs are the airway epithelial cells, many reports describe RSV infection of DCs [72–79]. In the past year Johnson and colleagues showed that the G glycoprotein interacts both with DC-SIGN and L-SIGN, although antibodies directed against the lectins do not block infection of DCs [80*]. They show that the interactions of G with the lectin signals via ERK1 and 2 phosphorylation to produce an immunomodulatory effect, and that inhibition of these interactions leads to significantly higher levels of IFN- α , MIP-1 α , and MIP-1 β secretion during the maturation process induced by RSV infection of immature DCs [80*].

Nucleolin is an entry receptor for RSV

In the past year, the first clear identification of a molecule with all the characteristics of an entry receptor for RSV was reported [81**]. Indeed, Hegele and colleagues performed a virus overlay protein binding assay [82] that led to the identification of cell surface nucleolin as an RSV entry receptor. Nucleolin and RSV F were coprecipitated, demonstrating a direct interaction. RSV infection was decreased in neutralization experiments using anti-nucleolin antibodies, in competition experiments in which the virus was preincubated with nucleolin before addition to the cell cultures, and upon RNA interference to silence the expression of cellular nucleolin. Nonpermissive Sf9 insect cells became susceptible to RSV infection upon expression of human nucleolin, and RNA-mediated knockdown of lung nucleolin in mice was associated with a significant reduction in RSV infection, demonstrating nucleolin involvement in the RSV cycle *in vivo*. Nucleolin also plays a role in entry of another paramyxovirus, the human parainfluenza virus 3 (hPIV-3) [83].

Nucleolin has a dual localization, and is found both at the cell surface and in the nucleus. It is an RNA and protein-binding multi-functional molecule (reviewed in [84]) involved in diverse processes such as ribosome biogenesis, chromatin decondensation and transport of nucleolar proteins between nucleus and cytoplasm [85]. Intracytoplasmic vesicles shuttle nucleolin between the cell surface and the nucleolar pool [86–88]. The cell-surface bound nucleolin has not been well characterized so far. It has been shown to associate with intracellular actin filaments, but because the nucleolin sequence does not contain any potential membrane-anchoring domains, it was proposed to connect to actin via intermediary transmembrane proteins [88]. Nucleolin is expressed on many tissues and its use as RSV entry receptor does not explain the restricted tropism of RSV, which may be rather specified by other yet unknown co-receptors or intracellular cofactors.

MOG as a Rubella virus receptor

RV, together with the alphaviruses, belongs to the *Togaviridae* family of positive-stranded RNA viruses, and encodes two envelope glycoproteins, E1 and E2. RV

E1 is responsible both for receptor binding and for inducing membrane fusion. RV is the etiological agent of rubella disease, and also of the congenital rubella syndrome (CRS), which is associated with intra-uterine infection of the fetus during early pregnancy. Rubella disease is also called 'german measles', because its symptoms are similar to the ones caused by MV. Similar to MV, RV propagates efficiently by aerosols, but the specific receptors that are targeted by RV are not known. It is possible that DCs play a role in dissemination of RV, although this has not been investigated.

RV enters cells by receptor-mediated endocytosis [89,90]. As with its alphavirus cousins, exposure of the virion to low pH in the endosome leads to a fusogenic conformational change in the membrane fusion protein E1 [91]. RV infects a wide range of human derived cell lines, indicating that the receptor is likely to be a ubiquitous molecule, or that the virus can interact with different receptors depending on the cell type. In contrast to protease treatment, which had no effect, phospholipase or glycosidase treatment of susceptible cells was reported to decrease RV infection, suggesting that the receptor may not be a protein [92]. However, Tien and colleagues have recently identified 'Myelin Oligodendrocyte Glycoprotein' (MOG) as a putative Rubella receptor by pull-down experiments of host cell proteins that bind to recombinant RV E1 [93**]. MOG is a highly conserved type I transmembrane protein and a minor component of myelin (0.05%). It is present at the surface of mature oligodendrocytes in the central nervous system (CNS), and is suspected to function in maintenance of myelin sheaths (reviewed in [94]).

Tien and colleagues demonstrated that the soluble MOG ectodomain binds RV particles and blocks binding of the virus to cells [93**]. Expression of MOG in 293T cells, which are normally refractory to RV infections, were shown to render them permissive for RV entry and replication. Finally, they showed that antibodies directed against MOG block RV infection.

Most research interest on MOG has been driven by its role as an autoantigen in demyelinating diseases such as multiple sclerosis (MS). The MOG immunodominant epitope that maps to residues 33–55 [95,96] is responsible for binding to both T cells and demyelinating antibodies. The crystal structure of the MOG ectodomain revealed a classical Ig-variable domain fold [97], which is found in other adhesion molecules. MOG is found as a dimer when purified from CNS tissue [98], and the crystal packing of the ectodomain indicates contacts that are compatible with MOG dimerization *in trans* to glue the myelin sheaths together [97].

Molecular mimicry between RV protein E2 and MOG had been reported as a cause of the autoimmune response resulting in demyelination, characteristic of MS [99].

Residues 1–10 of MOG, which map to the signal sequence, had been found to exhibit close similarity to RV E2 residues 50–62 [99]. However, this particular E2 sequence is only found in one partial sequence of the structural region of the M33 RV strain [100] (accession code AAA47423.1). Numerous sequences corresponding to RV are available in the databank and none of them contains the mentioned E2 peptide. Furthermore, closer inspection reveals that the mimicry E2 peptide sequence is not present in the complete sequence of the structural polyprotein gene of the same RV M33 strain, deposited later [101] (accession code P08563). These observations strongly suggest that the reported mimicry was due to a sequencing artifact in the initial submission of the M33 polyprotein sequence.

Demyelination appears to be at least one of the underlying pathologies of CRS, and RV replication in the brain has been demonstrated in CRS [102]. It is likely that RV infection via MOG expressed by oligodendrocytes directly contributes to this process, rather than an autoimmune effect triggered by molecular mimicry as postulated earlier. However, RV has a wide cell tropism, and after initially infecting the nasopharyngeal lymphoid tissues, the virus is transmitted to other hosts through airborne droplets and aerosols. Expression levels of MOG reported in lymphoid tissue are very low [103], but as suggested by Cong *et al.* may be sufficient for infection to occur. More likely, additional receptors in tissues where MOG is not expressed exist (which would explain the wide tropism of the virus), and remain to be identified.

NRAMP is an SV entry receptor

SV is, together with Semliki Forest virus, one of the best-studied alphaviruses, a group of arboviruses that includes serious human pathogens such as Chikungunya virus, Ross River virus or Venezuelan Equine Encephalitis virus (reviewed in [104,105]). They form a genus within the *Togaviridae* family of positive-strand RNA viruses, which also includes the rubivirus genus with RV as only member. Alphavirus particles have two envelope glycoproteins, E2 and E1, with E2/E1 heterodimers forming a surface icosahedral glycoprotein shell that encases the viral membrane. Alphaviruses enter cells by endocytosis. E2 is responsible for receptor binding, inducing receptor-mediated endocytosis, while E1 drives membrane fusion in response to the low pH of the endosome (reviewed in [106]). Fusion of alphavirus virions with artificial liposomes can be induced *in vitro* by exposing purified virions to low pH [107], indicating that the fusion trigger is low pH and not an interaction with the receptor.

Alphaviruses are transmitted by mosquitoes and infect a wide range of insect and mammalian cells. As discussed above, SV interacts with DC-SIGN for infection of DCs [47], which are used for translocation of the epithelial barrier and subsequent dissemination within the organism.

The high-affinity laminin receptor [108] and heparan sulfate [109] have been reported to enhance, but not to be essential for alphavirus infection into certain cell types. In the past year, Cherry and collaborators identified the 'Natural Resistance-Associated Macrophage Protein' (NRAMP) as an SV entry receptor [110**]. They performed a genome-wide RNAi screen in *Drosophila melanogaster* cells, which are not a natural host for SV. They found that dNRAMP, the *Drosophila* ortholog of NRAMP, is required for virus infection. Flies mutant for dNRAMP were protected from the virus. dNRAMP was shown to physically bind to virus particles, and this interaction was necessary for entry.

NRAMPs constitute a family of highly conserved proteins, found in bacteria as well as in insects and mammals. They function as proton gradient driven transporters of divalent metal ions such as Fe^{2+} . They are integral membrane proteins, spanning the membrane 12 times (reviewed in [111]). There are two NRAMP genes in mammals, NRAMP1 and NRAMP2. Only NRAMP2 is localized at the plasma membrane of cells of peripheral tissues [111]. High Fe^{2+} concentrations downregulate NRAMP2 expression (reviewed in [112]), and as anticipated, iron treatment attenuated SV infection both in mosquito and mammalian cells. This indicated that NRAMP is also a receptor in the relevant vector host, the mosquito. Direct binding of SV to the receptor was demonstrated by coprecipitation of NRAMP2 with SV particles. This interaction was lost at high iron concentrations due to decreased presence of NRAMP2 in the membrane.

Although the authors discuss that the conservation of E2 among different alphaviruses is important (~50%), this conservation across alphaviruses concerns the residues that either form the hydrophobic core or are otherwise not exposed on the virion [113]. The surface exposed residues available for interactions with receptor show, on the contrary, a high degree of variation, in line with the observation that NRAMP is specific for SV and does not interact with other alphaviruses.

Conclusions

The identification of nectin 4 as a receptor for MV closes an important chapter in understanding the biology of this virus. Additional recent data have shown that as it enters a new host, it initially infects alveolar macrophages and DCs present in the airways, using CD150 [114*,115*,116*]. However, the fact that CD150 is not readily available at the surface of these cells was a puzzle, and understanding the role of DC-SIGN in making CD150 available for infection is now an important step forward. Infection of DCs thus has a dual effect: down-tuning the immune response of the host, while at the same time providing a means for transport across the epithelial barrier. DC infection allows the virus to reach the lymphatic organs, where it replicates vigorously and

subsequently propagates into lymphoid and myeloid cells of the trachea, located right under the epithelial cell layer. Infection of the latter cells through the basolateral side would then result in virus release into the lumen of the tracheobronchial airways, allowing propagation in the environment via aerosols. The MV studies lead the way: RSV has the same primary tropism as MV, targeting DCs to interfere with the immune defense of the host and to breach the epithelial barrier. However, the difference in the case of RSV is that it does not seem to actively involve DC-SIGN for entry, but rather the interactions with the G glycoprotein induce the necessary signaling to dampen the immune response so that the infection can proceed. The tissue distribution of nucleolin being very broad, it is not understood what restricts the RSV tissue tropism. A scenario similar to that of MV remains possible, although this needs to be investigated further. Similarly, RV is very efficiently propagated in aerosols, so that it must reach the airways at late stages of the infection. However, little is known about the overall journey of this virus within the host organism before propagation to other hosts, and receptors other than MOG are very likely important. In addition, no experiments have been reported to understand whether RV also targets DCs. The identified MOG receptor does, however, shed light on some of the complications of CRS, during which the virus disseminates into the CNS and causes demyelination.

In the case of SV, it was known that many different cell types were susceptible to the infection, from insect to humans, and the fact that the NRAMP family is so conserved is compatible with this feature. However, many other arboviruses have a very broad tropism as well, and the fact that the use of NRAMP is restricted to SV among all the alphaviruses was surprising. It is possible that there are other conserved surface molecules that are as conserved as NRAMP and could be exploited by other arboviruses for entry; this remains therefore an important area of study. The connection between SV infection and iron metabolism is interesting, and brings out another parallel: the relation between the pathogenicity of new-world arenaviruses targeting the transferrin receptor as entry receptor, and iron metabolism in the host [117].

Another important feature for SV and other arboviruses is the use of DC-SIGN to efficiently infect DCs. The new finding of the past year was that, in the case of the phleboviruses, DC-SIGN appears to act as a bona-fide entry receptor, and not just as an attachment factors as reported for all the other viruses that target DCs. However, the data discussed above about the interactions between MV and DC-SIGN suggest a possible re-interpretation: it cannot be ruled out that the interaction of phleboviruses with DC-SIGN does not trigger the same type of signaling, bringing out an as-yet unidentified entry receptor from an internal compartment into ceramide-enriched clusters at the plasma membrane. This

would be compatible with the DC-SIGN clustering observed in that study, leading to uptake of the virion.

Taken together, the various virus/host systems analyzed in parallel in this review suggest interesting approaches to spark additional research in each of them, with the MV system as paradigm. In particular, these data highlight the role of DCs in spreading and aggravating the infection — acting as a ‘trojan horse’ as described in the case of HIV. Indeed, DCs appear to be the Achilles heel of the host organism, being deliberately exposed to anything that is foreign. The fact that vertebrates have evolved to take this risk witnesses about its importance: the organism is ready to pay the price, because in the absence of DCs the toll would be much higher. The viruses that are being studied today are essentially those that cause disease, which in turn are those that appear to have managed to cope with DCs for their own benefit. Fortunately, the great majority of viruses to which an organism is exposed go unnoticed because of the efficient detection by the strategic DC network distributed throughout the body.

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