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Review

Vaccine-induced enhancement of viral infections

W. Huisman [1], B.E.E. Martina, G.F. Rimmelzwaan, R.A. Gruters, A.D.M.E. Osterhaus *

Erasmus MC, Institute of Virology, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands

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ABSTRACT

Examples of vaccine-induced enhancement of susceptibility to virus infection or of aberrant viral pathogenesis have been documented for infections by members of different virus families. Several mechanisms, many of which still are poorly understood, are at the basis of this phenomenon. Vaccine development for lentivirus infections in general, and for HIV/AIDS in particular, has been little successful. Certain experimental lentiviral vaccines even proved to be counterproductive: they rendered vaccinated subjects more susceptible to infection rather than protecting them. For vaccine-induced enhanced susceptibility to infection with certain viruses like feline coronavirus, Dengue virus, and feline immunodeficiency virus, it has been shown that antibody-dependent enhancement (ADE) plays an important role. Other mechanisms may, either in the absence of or in combination with ADE, be involved. Consequently, vaccine-induced enhancement has been a major stumble block in the development of certain flavi-, corona-, paramyxo-, and lentivirus vaccines. Also recent failures in the development of a vaccine against HIV may at least in part be attributed to induction of enhanced susceptibility to infection. There may well be a delicate balance between the induction of protective immunity on the one hand and the induction of enhanced susceptibility on the other. The present paper reviews the currently known mechanisms of vaccine-induced enhancement of susceptibility to virus infection or of aberrant viral pathogenesis.

Contents

1. Introduction

Lentiviruses have infected several mammalian species including humans (human immunodeficiency virus-1 (HIV-1) and HIV-2), non-human primates (simian immunodeficiency viruses (SIV's)) and cats (feline immunodeficiency virus (FIV)), sometimes affecting a significant proportion of the host population (for reviews see [1,2]). Despite their relatively wide distribution, the transmission of lentiviruses is generally not very efficient. After inoculation, the virus enters host target cells via interaction with one or more cellular receptors. For HIV-1, HIV-2 and SIV, CD4 is used as the primary receptor while chemokine receptors like CCR-5 or alternatively CXCR-4 are required as secondary receptor. Similarly, FIV enters its target cell using CD134 as a primary and CXCR-4 as a

* Corresponding author. Tel.: +31 10 7044066; fax: +31 10 7044760.
E-mail address: a.osterhaus@erasmusmc.nl (A.D.M.E. Osterhaus).
[1] Present address: Nobilon International B.V., P.O. Box 320, 5830 AH Boxmeer, The Netherlands.

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co-receptor. Interference with viral entry by vaccine-induced antibodies or antiviral therapy has been one of the major goals in the development of lentiviral intervention strategies. In spite of huge investments, success in the field of lentivirus vaccine development has been limited and in some cases the use of experimental lentiviral vaccines proved to be counterproductive: it rendered vaccinated subjects more susceptible to infection. Here we review reported examples of vaccine-induced enhanced susceptibility to virus infection in general and lentivirus infection in particular, as well as currently known mechanisms that may underlie this phenomenon.

2. Antibody-dependent enhancement of viral entry

2.1. Lessons from non-lentivirus systems

Antibody-dependent enhancement (ADE) of virus infection by increasing viral entry is a mechanism that has been observed for viruses of several families and has also been shown to play an important role in the natural pathogenesis of some of these (for review see [3]). Probably the best-known example of ADE of infection is the *in vitro* enhancement of Dengue virus (DENV, a member of the Flaviviridae family) entry by virus specific antibodies. The genus Flavivirus, family Flaviviridae, consists of arthropod-borne viruses such as Murray Valley encephalitis virus (MVEV), West Nile virus (WNV), Japanese encephalitis virus (JEV), and DENV. Four serotypes of DENV have been described, with multiple serotypes co-circulating in endemic areas. Infection with any of the DENV serotypes may result in a spectrum of clinical signs and symptoms, ranging from a mild influenza-like illness, known as dengue fever (DF), to the most severe forms of the disease characterized by coagulopathy and increased vascular permeability: dengue hemorrhagic fever (DHF). This may progress to hypovolemic shock in certain patients causing dengue shock syndrome (DSS). ADE was first described in *in vitro* systems for MVEV and WNV in 1964 [4]. ADE was subsequently postulated by Halstead and colleagues based on the observation that DHF and DSS were predominantly seen in children experiencing a second infection with a heterologous DENV serotype [5,6]. They observed that the incidence of DHF and DSS peaked in two populations of young children [7]. One peak occurred in infants (aged 6–9 months) that were infected with a DENV serotype different from the serotype that had infected their mothers previously. The key observation was that severe disease occurred in infants whose maternal antibodies had declined to low, sub-neutralizing levels. The other peak was observed in young children who had experienced an earlier, usually mild or subclinical, infection and were later infected with a different DENV serotype. These observations led to the conclusion that pre-existing immunity against DENV could predispose individuals for a more serious infection with a heterologous serotype of DENV and did not afford protection against disease. Later, several epidemiological studies provided circumstantial evidence for the role of pre-existing humoral immunity in the pathogenesis of DHF [8–12]. *In vitro* experiments showed that DENV infection could be enhanced using polyclonal antisera raised against heterologous DENV serotypes [5,6]. Furthermore, it was shown that administration of DENV-specific maternal antibodies enhanced the severity of DENV infection of *Rhesus macaques* [13]: monkeys infected in presence of anti-DENV antibody developed higher levels of viremia and for a longer period than the control monkeys.

Although many of the details regarding Fc receptor γ (FcγR)-mediated entry of DENV are still unclear, FcγRIa and FcγRIIa were shown to play an important role [14–18]. FcγRIIa was more efficient than FcγRIa in enhancing DENV infection of FcγR-transfected cells *in vitro* [17]. The role of FcγRIII in ADE of DENV infection remains unknown, but is likely to be involved as well. The expected result of ADE for viral infection would be an increased viral load [19–21], most likely caused by infection of a higher number of susceptible cells. Alternatively, FcγR-mediated entry may modulate the antiviral immune response [22]. Recent studies with Ross River virus and DENV showed that entry via the FcγR pathway could suppress the expression of antiviral genes and enhance IL-10 production in mononuclear cells *in vitro*. In contrast, entry via the usual cellular receptor did not affect the induction of antiviral effector mechanisms [23,24]. Although the pathogenesis of DHF/DSS has not been elucidated, the ADE of infection hypothesis remains a significant concern in the development of safe and effective vaccines.

Feline Corona Virus (FCoV) infection of cats is usually mild but can also lead to the development of a chronic immune-mediated disease with a high fatality rate, called feline infectious peritonitis (FIP). FIP develops upon the occurrence of spontaneous mutations in certain regions of the FCoV genome that change the cell tropism of the virus, allowing it to replicate in macrophages. This is considered to be largely responsible for FCoV infection to develops from a relatively apathogenic into a chronic, immune-mediated disease. FIP disease manifests itself with a variety of clinical symptoms due to the infection of multiple organs, often including the central nervous system [25]. Early experiments had shown that transfer of plasma containing high-titred FCoV specific antibodies to naïve kittens rendered these animals susceptible to more rapidly developing FIP than kittens receiving FCoV negative serum [26]. ADE of infection was subsequently shown to be mediated by antibodies directed against the viral spike (S) protein. Immunization with recombinant vaccinia virus preparations expressing the FCoV-S protein resulted in the induction of S-specific antibody responses and low-level neutralizing antibody titers and lead to an enhanced susceptibility to challenge infection in young cats [27]. During FIP, FCoV primarily targets cells of the macrophage/monocyte lineage and ADE is thought to occur through binding of antibody-bound FCoV to the Fc receptor on the cell membrane [28–31]. Collectively, these data show that ADE mediated by S-specific antibody and increased viral entry into monocytes/macrophages are at the basis of the enhanced susceptibility of pre-immune cats to develop FIP.

Enhanced respiratory syncytial virus (RSV) disease and atypical measles were observed in children who had been vaccinated with formaldehyde inactivated and alum adjuvanted candidate vaccines in the sixties upon exposure to wild type RSV or measles virus, respectively, later in life [31]. It has long been speculated that an aberrant antibody response against the viral glycoproteins was at the basis of this phenomenon. Although indeed the neutralizing serum antibody responses induced by these vaccine candidates were relatively weak, short-lived and resulted in a rapid renewed susceptibility to infection after vaccination, other mechanisms than ADE could have been at the basis of the observed immunopathology [32,33]. Besides anomalous antibody responses, there are several differences between the immunological response that is induced by either formaldehyde inactivated vaccines or natural infection that could explain the observed enhancement phenomenon: absence of specific cytotoxic T-cell responses, immune complex deposition in infected tissues, increased specific proliferative $CD4^+$ T lymphocyte responses, and a bias of the specific immune response towards a Th2 phenotype [34,35]. This was largely concluded on the basis of immunization and infection data generated in preclinical studies using mouse and macaque infection models for these viruses. Alternatively, the generation of carbonyl groups through the formaldehyde treatment of the vaccines could have contributed to the increased sensitivity to infection [36].

Recently, it was shown in a macaque model that formalin-inactivated human metapneumovirus (HMPV, also a member of the

Paramyxoviridae family) vaccines have the same propensity to predispose for immune-mediated disease as inactivated RSV and MV vaccines: FI-HMPV-primed monkeys developed eosinophilic bronchitis and bronchiolitis upon challenge, which like in the RSV and MV models is indicative of a hypersensitivity response [37]. Collectively, these data provide us with animal models for enhanced paramyxovirus disease, which are useful to screen new generation candidate vaccines at an early stage for the potential induction of enhanced sensitivity to infection.

2.2. Antibody-dependent enhancement of lentivirus entry

Also after vaccination of cats with candidate FIV vaccines enhanced susceptibility rather than protection against infection was observed [38–40]. In one study, passive transfer experiments were carried out which demonstrated that antibodies were probably responsible for the observed enhancement of infection [40]. Similarly, vaccination of horses against EIAV with a recombinant S protein-induced enhancement of subsequent infection, although the results of *in vitro* ADE assays did not correlate with the observed enhancement of infection [41–45].

Already in the early days of HIV research Robinson and Montefiori described that *in vitro* infectivity of the virus could be enhanced by virus specific antibodies [46]. Multiple mechanisms have been described that may cause or contribute to ADE in HIV infection. Virus that is complexed with antibodies may be captured and internalized by FcR [47,48] or complement receptor (CR) [49,50]. This process may or may not bypass the natural route via CD4 and a chemokine receptor depending on the experimental conditions [3,47–49,51–53]. In addition, the receptors may provide an activation signal to the cell after binding the virus–antibody complex, which could support virus endocytosis and increase virus production [54].

Enhancement independent of FcR and CR may also occur. Neutralizing antibodies, but also soluble CD4, can enhance NSI/R5 virus infectivity [55,56] by inducing conformational changes in the viral envelope [57,58] and bringing the envelope in proximity of the CCR-5 co-receptor.

In general, prolonged contact of the virus and the target cell will increase the chance that receptor binding and subsequent fusion will occur. This may also be accomplished through the deposition of antibody–complement complexes on the cell, independent of CR capture, via the formation of fibrils [59,60].

Also for SIV infection of macaques ADE of infection has been described. In sera from monkeys infected with SIVmac251, ADE could be demonstrated, while this was not observed in macaques that were vaccinated with HIV-2 envelope preparations [61]. Furthermore, it has been reported that plasma obtained from SIVmac251 infected animals enhanced SIVmac infection of a human $CD4^+$ cell line, which was dependent on the presence of complement [62], in a manner similar to the complement-mediated ADE activity observed with HIV-positive human sera in *in vitro* experiments described above [46,63,64].

3. Enhancement of HIV replication after activation of cell-mediated immunity

Lentiviruses replicate best in activated cells of the immune system and systemic activation of the immune system generally results in enhanced virus replication, e.g. during opportunistic infections [65–68]. The higher number of activated target cells, i.e. $CD4^+$ T-cells and $CD4^+$ cells of the myeloid lineage, most likely accounted for the viral bursts that had been observed. For example, bacterial products may activate $CD4^+$ T-cells via toll-like receptor (TLR) 2 and possibly also TLR-4, 5 and 7 [69]. Direct intracellular interaction of replication enhancing molecules from other viruses (e.g. herpesviruses) and HIV has been shown in *in vitro* studies [70]. Given the relatively low chance that two different viruses would replicate in the same cell *in vivo*, the contribution of this mechanism will not be of great importance to the overall virus production [71].

Vaccination of HIV-1 infected individuals against other pathogens may [72–74] or may not [75,76] result in increased HIV-1 replication. Repeated T-cell activation in SIV-infected monkeys also shortened the survival of the animals [77]. Activation of the immune system can increase the number of activated $CD4^+$ T-cells, which are more susceptible to infection than resting T-cells. In addition, augmented TNFα production may be implicated in increased viral loads [74]. Infection of leukocyte adhesion molecule leukocyte function-associated antigen (LFA)-1 expressing cells may be further increased by incorporation of intercellular adhesion molecule (ICAM)-1 into the virus particles that bud from activated T-cells [78–80].

In addition to activated $CD4^+$ T-cells there may also be a role for activated macrophages. It has recently been reported that herpes virus infection of mice can protect against Listeria monocytogenes and *Yersinia pestis* pathogenesis via activated macrophages [81]. In contrast, CMV infection of humans may lead to an increased susceptibility to infection with HIV-1 [82,83].

Dendritic cells are key players in generating immune responses. Many DC express DC-SIGN, a C-type lectin that can capture HIV through its Env protein [84]. HIV bound to DC-SIGN may follow different pathways leading to virus destruction (and MHC-restricted antigen presentation) or to infection. Infection of mature DC in *cis* results in low level virus production [85]. More interestingly, infection may also occur in *trans*, when the DC delivers the infectious particle to T-cells that interact with the DC [84,86]. In this regard, mature DC has been shown to increase transmission of both R5 and X4 viruses to T-cells [87–90]. The precise involvement of DC-SIGN in this process is still unclear [91]. Regardless of the molecules involved, HIV infection of T-cells is greatly enhanced when mature DC delivers the virus. DC may act as a vehicle that, like a "Trojan horse", delivers the virus to an environment of activated T-cells. The immunological synapse that forms between DC and T-cells may further facilitate infection of those T-cells. In addition, virions are less susceptible to inactivation when associated with DC [85].

4. Lentivirus candidate vaccines that have predisposed for enhanced susceptibility to infection

4.1. FIV vaccine candidates

Since its discovery in 1986 [92], numerous attempts to develop an effective and safe vaccine against FIV have been made [93–95]. Recently, a whole inactivated cell vaccine containing two FIV subtypes has been licensed in the US [93,96]. The effectiveness and breadth of this FIV vaccine are still subject to debate [97]. Passive and adoptive transfer studies suggested that both virus neutralizing and cellular immune responses are at the basis of the reported efficacy [96]. Nevertheless, virtually all FIV vaccines that have been evaluated so far failed to induce protective immunity and several induced increased susceptibility to infection.

The first report on enhancement of infection after vaccination against FIV dates from 1992 [38]. Cats vaccinated with ISCOM preparations containing either purified FIV particles or recombinant FIV Gag protein, as well as cats vaccinated with formaldehyde fixed infected cells became viremic 2–3 weeks earlier than control cats. Furthermore, all FIV vaccinated cats became viremic upon challenge, which was not the case for the control cats in this

experiment. All the vaccines used were shown to be immunogenic, although Env-specific, virus neutralizing antibody responses were only detectable on the day of challenge in the cats vaccinated with the infected cell vaccine. In another study, vaccination with a synthetic peptide representing a linear epitope in the V3 loop of the FIV envelope protein, with Freund's adjuvant, induced virus neutralizing antibodies and predisposed cats for accelerated virus replication upon challenge infection [39].

In another study with ISCOM-based vaccines containing several FIV envelope glycoprotein preparations, all the cats that received eukaryotically expressed Env glycoprotein developed Env-specific, virus neutralizing antibodies. These cats became viremic at least 2 weeks earlier than control cats [40]. The increased susceptibility to infection was also seen in naïve cats after transfer of plasma obtained from vaccinated cats. Collectively, these results suggested that FIV envelope specific antibodies were involved in this vaccine-induced enhancement of infection. In particular antibodies to the V3–V6 regions of the envelope protein were associated with the observed enhancement of infection. In a follow-up study, recombinant envelope protein was prepared from which the part encompassing the region between V3 and V6 was deleted [98]. Vaccination with this engineered protein still predisposed for increased susceptibility to infection and it was concluded that also antibodies directed to epitopes outside the V3–V6 region were able to cause enhancement of infection.

To attempt immunizing cats with an antigen preparation that mimics the natural conformation more closely, the use of formaldehyde fixed FIV infected autologous PBMC was evaluated [99]. Despite the induction of Gag and envelope specific antibodies, vaccinated cats were not protected from infection and again were more susceptible to infection than control cats immunized with fixed uninfected PBMC. In another study using formaldehyde inactivated FIV vaccines which induced no or poorly virus neutralizing antibody responses, enhancement of infection after a low-dose challenge infection was observed [100].

In a study by Richardson et al., general immune activation was suggested as an alternative mechanism for the induction of vaccine-mediated increased susceptibility to FIV infections [101]. Vaccination with DNA from which the FIV *env* gene was expressed induced no or weak Env-specific antibody responses and predisposed for enhancement of infection [101]. It was speculated that the immunization increased the target cell population for FIV infection, through a mechanism similar to that described after heterologous vaccination of HIV-1 infected subjects, as described above. The enhancement of FIV infection was associated with increased susceptibility of lymphocytes obtained after vaccination to *ex vivo* FIV infection and the induction of Env specific T-helper cell responses [102]. Collectively, these results suggest that after FIV vaccination in addition to ADE also other mechanisms may contribute to increased susceptibility to FIV infection. Schwartz suggested that the induction and expansion of HIV-1 specific $CD4^+$ cells through vaccination might constitute a serious confounding factor in HIV vaccine development [103]. Indeed, it has since been shown that HIV-1 preferentially targets HIV-1 specific $CD4^+$ cells in infected individuals [104].

Likewise, enhancement of FIV infection by immune activation may result from the activation and expansion of $CD134^+$ cells [105]. CD134 – the primary receptor for FIV – is a T-cell activation marker and a co-stimulatory molecule and its expression is strictly confined to $CD4^+$ T-cells [106]. With $CD4^+$ T-cells constituting the major target for FIV early in infection [107,108], expansion of this subpopulation (through, e.g. vaccination) would provide the virus with an ideal opportunity for its replication [109]. Furthermore, the FIV co-receptor CXCR4 molecule is expressed on activated T-, B-cells and monocytes [110]. It was demonstrated that increased expression of CXCR4 in cell lines resulted in enhanced FIV replication *in vitro* [111]. Recently, using flow cytometric analysis of cell populations *ex vivo*, a clear positive association between CXCR4 expression and FIV infection was demonstrated, although results also suggested the existence of an CXCR4-independent mechanism of infection [112].

In summary, selective expression of CD134 induced by vaccination against FIV or other pathogens may support FIV replication during the early stages of infection in lymphocytes that are essential for sustaining memory immune responses. This parallels the targeting of R5 strains of HIV to memory $CD45RO^+$ T-cells that exclusively express CCR5 early after infection [113]. Activation and subsequent signalling via upregulated CXCR4 expression may induce cellular changes favouring further viral integration and replication in the lymphatic system, thus facilitating dissemination of FIV infection.

Recent studies suggest that feline dendritic cells (feDC) play a role in the transmission of FIV comparable to that of human DC and HIV infection. It was shown *in vitro* that feDC can increase FIV infection of resting cells, but in particular of activated $CD4^+$ T-cells [114,115], which is reminiscent of *in vivo* results obtained for HIV and SIV [89,116,117]. Early studies showed that FIV can interact with C-type lectin receptors, like human DC-SIGN, and that this interaction facilitated FIV infection in *trans* [118], similar to the mechanism described for HIV-1 (see above). Furthermore, it was shown that feDC expressed the primary CD134 receptor and, to a lesser extent, the CXCR4 co-receptor. Although less efficient than lymphocytes, feDC support productive FIV replication [119]. feDC may contribute to the infection of (activated) $CD4^+$ T-cells by immediate transfer involving exosomes, endolysosomal pathways or transfer of *de novo* generated FIV particles during productive infection of DC [114]. Collectively, these data suggest an additional role for feDC in vaccine-induced enhancement of infection in that they might facilitate the infection of (vaccine-induced) activated $CD4^+$ T-cells.

4.2. EIAV vaccine candidates

Vaccination of ponies against EIAV with inactivated whole virus or envelope subunit vaccine preparations completely protected the animals from homologous challenge infection but failed to induce protective immunity against infection with a heterologous virus strain. However, in the animals vaccinated with inactivated whole virus, levels of viral replication after challenge with a heterologous EIAV strain were merely suppressed. Moreover, 40% of ponies vaccinated with the envelope subunit vaccine exhibited signs of enhanced disease upon heterologous challenge infection [42]. The use of recombinant envelope protein failed to afford protection against infection with a homologous virus and predisposed for enhanced virus replication and disease in animals after heterologous challenge infection [45]. The vaccine-induced Env-specific antibody titers did not correlate with the outcome of challenge infection and the mechanism underlying the observed enhancement of EIAV infection remains to be elucidated [41,43,44].

4.3. SIV vaccine candidates

Vaccination of *Rhesus macaques* with attenuated varicella–zoster virus vaccine expressing SIV Env elicited non-neutralizing Env-binding antibodies and little if any Env-specific cytotoxic T lymphocyte responses. Upon challenge infection with a heterologous SIV strain increased levels of SIV replication, more rapid $CD4^+$ lymphocyte depletion, and accelerated progression towards AIDS was observed in these animals compared to control animals. This correlated with increased $CD4^+$ T-cell proliferation immediately after SIV challenge, which most likely was the result of an anamnestic response to SIV antigens. This indicates that activation

of the virus-specific CD4+ T-cells in the absence of an adequate CD8+ T-cell response may enhance virus replication and disease [120]. These findings were corroborated by the increased viral set point and accelerated disease progression in macaques treated with IL-15, which activates CD4+ T-cells [121]. The concomitant enhanced CD8+ T-cell responses against SIV were not capable of containing the virus replication.

Similarly accelerated disease progression was observed in macaques vaccinated with defective provirus or recombinant Sendai expressing Gag. Although the latter approach reduced viral loads during acute infection, some of the vaccinated animals developed increased viral loads during chronic infection and progressed more rapidly towards AIDS [122,123]. The increased viremia was independent of an observed SIV-specific CD8+ T-cell response, but correlated with the decline of SIV-specific CD4+ T-cells [123].

4.4. HIV vaccine candidates

Clinical trials in humans involving virtually all the approaches that are currently available for viral vaccine development have been carried out in the past decade. However, most of these were phase I or phase II trials in which due to the design of the trial enhancement phenomena would not be encountered. More recently a number of phase III trials have been conducted in seronegative volunteers at high risk for HIV infection, using monomeric gp120 preparations. The outcome of these trials was far from encouraging, with very limited induction of HIV neutralizing antibodies and no evidence for protection [124,125]. However in these trials so far no indication for ADE or other forms of enhanced susceptibility were found.

More recently, a phase IIb efficacy trial was conducted in a similar high-risk population, with attenuated recombinant adenovirus-5 (Ad5) candidate vaccines expressing HIV gag, pol and nef genes. Also in this trial no protective efficacy was observed. In contrast, a significant trend towards an increased HIV-1 infection rate was observed in volunteers that had high pre-existing antibody titers against Ad5 (>200), compared to individuals with low pre-existing Ad5-specific titers (<200) [126]. Due to the setup of this trial and the complexity of the required statistical analyses, a thorough assessment of possible confounding factors is pending (http://www.hvtn.org/science/1107.html, presentation: "STEP Trial: Efficacy Analyses"). Although the two categories of vaccinees were defined on the basis of their antibody titers against Ad5, it is unclear how Ad5 specific antibodies could enhance susceptibility to HIV infection. It has been proposed that the Ad5 antibodies would re-direct the vaccine to other cell types and that this could result in a different type of immunity [127]. How this would result in enhanced transmission of HIV in these vaccinees remains to be elucidated. Another hypothesis would be that the antibody levels in the persons naturally infected with Ad5 reflect the overall immunity against this virus. This would imply the presence of increased numbers of Ad5 specific memory CD4+ T-cells. These cells would be readily re-activated after vaccination with the recombinant Ad5-vaccine and thus create "an abundant pool of susceptible cells" as targets for incoming HIV in the Ad5 seropositive persons.

Yet another hypothesis would be that the groups with the highest Ad5 titers contain a larger percentage of people that have recently been in contact with Ad5, either as a first infection or as a re-infection. This would lead to the presence of activated memory T-cells, including CD4+ cells, which may contribute to increased susceptibility towards HIV infection. If any of these two last hypotheses would be valid this would prohibit the use of many viral and other vectors as carriers for lentiviral antigens in vaccines since many of the attenuated vectors that are being exploited to date are based on, or closely related to viruses that commonly circulate in the human population. Cross-reactive immune responses will be frequently present and the resulting activated immune system may lead to enhanced HIV replication rather than provide protection. This could also pose problems in Ad5 naïve persons since infection with the wild type Ad5 virus upon vaccination with the Ad5 vector virus, will result in enhanced immunity to the Ad5 virus and an enlarged pool of activated CD4+ T-cells. This pool might increase the susceptibility for HIV if co-infections occur in areas where both HIV and Ad5 are endemic [128].

Collectively, the data obtained in HIV-1 candidate-vaccine clinical trials have been disappointing so far. None of the candidate vaccines tested did afford protection and even worse, some even enhanced susceptibility to HIV infection. A better understanding of the mechanisms underlying vaccine-induced protection or enhancement, or in other words correlates of protection or immune pathogenesis, is urgently needed to further advance the field of HIV vaccine development.

5. Conclusion

Vaccine-induced enhancement of susceptibility to virus infection or aberrant pathogenesis of virus infections have been documented for infections by members of several virus families and is therefore not unique to lentiviruses.

Although identifying a single responsible mechanism for each virus/host relationship is difficult, in this review an attempt was made to identify and define the potential mechanisms involved in these phenomena (see Table 1). Firstly, ADE plays an important role in the vaccine-induced enhancement of FIV and FCoV and possibly Dengue virus infections. Secondly, a mechanism involving immune activation, mainly via activated CD4 memory T-cells (not necessarily virus specific), is seen in some lentiviral systems. Activated DC may play an additional role in this mechanism in the case of HIV and possibly also FIV. Thirdly, TH2 biased and/or aberrant T-cell responses often involving eosinophilia may be involved in the observed vaccine-induced enhanced disease in paramyxovirus infections such as RSV and (atypical) MV.

Vaccine-induced enhancement of infection or disease pathogenesis has been a major stumble block in the development of certain flavi-, corona- and paramyxovirus vaccines and also the

Table 1
Mechanisms of enhancement of susceptibility to virus infection or of aberrant viral pathogenesis mediated by pre-existing immunity.

Mechanisms	Virus families			
	Flaviviridae	Coronaviridae	Paramyxoviridae	Lentiviridae
Humoral				
ADE	DENV	FCoV	MV (?)	HIV*
	WNV		RSV (?)	SIV
	MVEV[a]		HMPV (?)	FIV
				EIAV
Cellular				
CD4 activation				HIV
				SIV
				FIV
DC/*trans*				HIV
				SIV
				FIV*
Aberrant			MV (?)	
T-cell response			RSV (?)	
			HMPV (?)	

(?) = mechanism unknown/ambiguous. Abbreviations—ADE: antibody-dependent enhancement; DENV: Dengue virus; WNV: West Nile virus; MVEV: Murray Valley encephalitis virus; FCoV: Feline Corona virus; MV: measles virus; RSV: respiratory syncytial virus; HMPV: human metapneumovirus; HIV: human immunodeficiency virus; SIV: simian immunodeficiency virus; FIV: feline immunodeficiency virus; EIAV: equine infectious anaemia virus; DC: dendritic cells.

[a] *in vitro*.

recent failures in the development of a safe and effective vaccine against HIV can at least in part be attributed to the induction of enhancement rather than the induction of protection towards virus replication by the current vaccine candidates. There may well be a delicate balance between these two outcomes and the final result of vaccination is most likely determined by the sum of these parameters. Other confounding factors that may be involved include type of candidate vaccine used, viral and/or host factors, co-infections and time after vaccination. Research specifically aimed at the identification of the mechanisms that lead to either protection or enhancement would greatly stimulate our ability to design safe and effective vaccines against lentivirus infections, and more specifically an HIV vaccine.

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