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Immune pathogenesis of pediatric HIV-1 infection

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Abstract

Vertical exposure to HIV occurs at a time when functional capacity of the infant's immune system is attenuated through immaturity. Immune response capability is rooted in host genetic makeup, and the broad and fine specificity of innate and adaptive immune responses, respectively, shape the outcomes of HIV encounter in some instances and imprint viral changes through selective immune pressure in others. Findings from recent studies have profound implications for understanding immune pathogenesis of pediatric HIV infection, and in particular highlight the importance of host genetics of both mother and child in determining whether an exposed child acquires HIV infection or not, and if infected, the rate of disease progression. This review focuses on the key host molecules, the CC chemokine CCL3 and HLA, which have taken center stage in these new developments.

Introduction

Newly acquired pediatric HIV infections have virtually been eliminated in the developed world, with mother-to-child transmission (MTCT) rates reduced to approximately 1–2% since the advent of highly active antiretroviral (HAART) therapy. Pediatric HIV infection remains a significant public health problem in resource-poor countries, particularly in sub-Saharan Africa, where the HIV-seroprevalence among pregnant women is exceedingly high. More affordable, short-course regimens of anti-retroviral drugs have been tested and found to reduce HIV transmission [1]. However, the efficacy of these short regimens is less than longer, more potent regimens, and is further reduced by postnatal transmission of HIV through breastfeeding [1]. Although improving access to HAART remains a priority, better understanding of the immune pathogenesis of pediatric HIV infection may provide insights into new approaches to prevention and treatment.

Even in the absence of anti-retroviral drugs, most infants (65–85%) born to HIV-infected mothers do not acquire HIV infection themselves. Thus, vertical exposure to HIV offers a unique window of opportunity to investigate immune mechanisms associated with protection against HIV. Viral and host characteristics of both transmitter (mother) and recipient (child) can be measured, the timing of transmission ascertained with reasonable precision, and distinctions made between infants who escape vs. those who succumb to infection. However, understanding of the complexities of immune responses to HIV is further compounded in this route of transmission by several factors. These include exposure to the virus at a time of early immune development when fetal and neonatal immaturity needs to be complemented by maternal immune responses (which may in turn already be compromised by HIV), factors related to the immune circumstances of pregnancy in which the fetal allograft is tolerated by the genetically-distinct mother, and by genetic similarity between a mother and her infant.

We review here new studies that advance our understanding of immune processes that can predict the likelihood of infection and rate of disease progression among children, and focus in particular on major findings pertaining to the HIV coreceptor CCR5 and its ligands (CC chemokines) in the context of early human development and perinatal HIV exposure, and those of viral evolution in the context of HLA-mediated pressures.

Innate and adaptive immunity in pediatric HIV infection – dependent rather than independent components

The immune system of the infant in early life is immature as there is little or no recall (specific or adaptive immunity mediated by T-cells and B-cells) of prior exposure to antigens, and this capability develops with time as a result of increasing exposure to various antigens. The innate immune system, on the other hand, is designed to mount an immediate, antigen-non-specific response after exposure to a microorganism, and is orchestrated by dendritic cells (DC), natural killer (NK) cells, phagocytic cells (neutrophils and monocytes/macrophages), mast cells, and humoral proteins such as complement, acute phase proteins, cytokines, chemokines and antimicrobial proteins.

Given the altered immune environment during early life (favoring innate vs acquired and a possible Th2 type immune bias), cell types that link innate and acquired immunity are emerging as important in the pathogenesis of pediatric HIV infection. A recent study has shown that percentage and function of NK cells and plasmacytoid (the major IFN- α producing cell population) and myeloid DCs are impaired in viremic HIV-infected children, irrespective of viral load, particularly in those children with a clinical history of decreasing percentages of CD4⁺ T cells [2]. Their findings further suggested that differences may exist between adults and children in innate immune reconstitution following HAART. It may be important that NK cells, aside from their cytolytic function have immunoregulatory activity, and have been demonstrated to provide a novel DC-mediated helper function for Th1 and CTL responses [3]. Other cells emerging as critical cells in bridging the gap between innate and adaptive immunity are invariant natural killer T cells (NKT) that express a restricted T-cell receptor (TCR) Valpha24Vbeta11 repertoire, recognize glycolipid antigen in the context of the CD1d antigen-presenting molecule, and share both phenotypic and functional similarities between NK and T-cells. NKT cells have been found to be targets for productive HIV infection [4,5] and are selectively depleted during HIV infection in adults [6] and in children [7]. Collectively, these findings suggest that impairments in innate immune functions are likely to influence the development of HIV-specific immunity.

Studies on HIV-specific immunity have shown that only a fraction of HIV-specific CD8 T-cells (determined by tetramer staining and flow cytometry) have the capacity to produce cytokines and chemokines important in their antiviral functions [8]. CD4 T-cells play an important role in providing help for both the production of antibodies and CTL responses. Maintaining the integrity of these cells is therefore crucial to controlling HIV disease progression, and this has been highlighted by recent findings that show that HIV-specific CD4⁺ Th responses are readily detected in long-term surviving non-progressor children [9].

It remains important to direct efforts at defining markers of protection and susceptibility, markers that define varying rates of disease progression in HIV infected children and subsequent immune reconstitution in the presence of antiretroviral therapy. Furthermore, unravelling how innate immunity supports adaptive immunity in pediatric HIV infection will provide important opportunities for intervention. Figure 1 depicts the complexities introduced by host genetic content, maturational immune development, and HIV exposure/infection on innate and adaptive immune response capacity in pediatric HIV infection.

CC chemokines as antiviral molecules

The CC chemokines CCL3, CCL4 and CCL5 are the natural ligands for CCR5 [10], a chemokine receptor utilized by R5 HIV in addition to CD4 for entry into leukocytes [11,12]. By virtue of binding to CCR5 these chemokines have the ability to block replication of macrophage-tropic (R5) viruses *in vitro* [10]. It was this finding that raised the possibility that these molecules may contribute to protective immunity against HIV *in vivo*. This hypothesis was supported by prototype HIV vaccine studies in rhesus macaques, showing production of CC chemokines by CD8 T-cells to be associated with protective immunity [13,14]. Elevated production of these chemokines has also been observed in persons who remain uninfected despite multiple high-risk sexual exposures [15,16]. Also vigorous HIV-specific CD4 T-cell responses associated with the control of viremia in HIV-infected long-term non-progressing patients, are coupled to the enhanced production of CC chemokines [17]. Naturally-occurring host genetic variants of chemokine and chemokine receptor genes have further shown the important role of these molecules in altering the host immune response to HIV (Reviewed in [18]). Collectively, these findings have raised the possibility that these molecules may contribute to protective immunity against HIV *in vivo* and to attenuation of disease progression once infection is established.

CC chemokines, HIV and the developing immune system

It stands to reason that components of innate immunity that require no prior priming would be critical in protection against HIV infection among infants. Yet the role of innate immunity in this context has not been well studied. Given the many positive effects of elevated levels of the CC chemokines reported in adult and animal studies, and the fact that R5 HIV strains that utilize CCR5 as the primary coreceptor for cell entry are the strains most often transmitted from mother-to-child [19,20], it is important to understand how infant production capacity might differ from that of adults.

Neonatal NK and CD8 T-cells have been shown to be comparable in their ability to suppress HIV replication of an R5 virus in autologous CD4 T-cells through production of CC chemokines, and this suppression was greater than that found for adult NK cells [21]. Newborns (uninfected and HIV-exposed-uninfected) have significantly higher levels of the CC chemokines CCL3, CCL4 and CCL5 than their mothers, in both plasma and mitogen-induced cultures of mononuclear cells. CCR5 expression on immune cells is very low at birth and proportions of CCR5-expressing cells rise with increasing age [22]. Accordingly, one might expect that levels of CC chemokines would decrease over time to adult levels. Better understanding of these relationships and how they alter with immune maturation and in interaction with HIV exposure and infection may provide novel opportunities for intervention.

There are interesting relationships among HIV uninfected adults between HIV coreceptors CCR5 and CXCR4, and their ligands CCL4 and CXCL12, respectively. Specifically, reduced surface expression (molecules per cell) of CCR5 (as found in CCR5 Δ 32 heterozygotes) on CD3 T-cells is associated with a compensatory increase in the expression of CXCR4 and decreased levels of CXCL12 in plasma [23]. We have subsequently shown that these parameters are also associated with increased CCL4 levels in plasma. The sequence of events that allows for the maintenance of these reciprocal relationships among uninfected individuals is not known, nor is it known how age or exposure to HIV might alter these. It is further thought-provoking that these same molecules in cord blood (uninfected infants) present a relative profile similar to CCR5 Δ 32 heterozygote adults when compared to healthy adults. One can therefore speculate that the milieu present in infants at birth is one more conducive to providing protection from HIV, and may help explain why the majority of infants born to HIV-infected mothers escape infection even in the absence of drug intervention. In support of this, one small

study has shown that HIV envelope-specific T-helper cell responses detected in uninfected infants born to HIV-seropositive mothers were associated with the enhanced expression of CC chemokines. The authors postulated that these factors could mediate non-cytolytic inhibition of infection during vertical transmission of HIV [24].

CC chemokine ligand 3-like 1 (CCL3-L1) is one of two active genes (CCL3/LD78 $\forall$ and CCL3-L1/LD78 $\exists$) that code for CCL3 and occurs in variable copy number in different individuals [25]. In new striking results, quantification of CCL3-L1 found that increased copy numbers of this gene were associated with protection against maternal-infant HIV transmission [26**]. In the context of a large study of adults, Gonazalez *et al.* [26] very convincingly demonstrated the importance of copy numbers of this gene on host risk of acquiring HIV infection and on disease progression once infected. Within this same study, Argentinean children with CCL3-L1 copy numbers less than their population median were found to have a higher risk of acquiring HIV vertically whereas those with copy numbers greater than the median had lower risk [26]. In the HIV-infected children, in contrast to the adults, copy number did not associate with disease progression [26].

A major question raised by these findings is whether the actual protein encoded by the gene is involved. Does susceptibility to HIV-1 lie at the level of induction of gene expression of CCL3/CCL3-L1, resulting in quantitative differences in protein production? Because increased CCL3-L1 gene copy number has been correlated with increased CCL3 production in lipopolysaccharide-stimulated monocytes from uninfected adults [27], it is very likely that copy number of this particular gene influences levels of CCL3 production *in vivo*. It is envisaged that at first encounter with HIV the amount of CCL3 produced in response is critical in determining outcome of HIV infection. What is also important is that the other CC chemokines do not compensate for the loss of CCL3 function, indicating that there are functions unique to this molecule that are important in protective immunity. Aside from non-cytolytic inhibition of R5 HIV-1 infection by blocking virus entry, CC chemokines play an important role in chemotaxis and are involved in the regulation of cell-mediated immunity [28]. Reduced levels of CCL3 at the site of HIV encounter, could affect one or all of these processes resulting in an ineffective immune response and the inability to clear HIV infection.

It should be kept in mind that with increasing age of the child the ability to produce CCL3 will decrease to adult levels, with the result that production at a particular copy number of CCL3-L1 will alter as a result of maturity, possibly through differences in cell distribution with age, the activity of transcription factors in specific cells, and altered responsiveness to various stimuli. The presence of HIV infection, aside from enhancing the production of CC chemokines, is also likely to interfere with immune cell maturation processes, and these factors together may mask the relationship between copy number and CCL3 production with disease progression. As HIV-infected children have more rapid HIV disease progression, higher absolute CD4 lymphocytes, and maintain much higher HIV RNA loads than HIV-infected adults, much higher levels of CCL3 in particular may be required to maintain effective virus control.

HLA “footprints” on HIV

In addition to the immunogenetics of chemokine receptor and ligand systems, a major focus of research attention on the immune pathogenesis of HIV infection has been on the human leukocyte antigen (HLA) complex. Numerous studies, including a few among children, have identified associations between HLA alleles (mostly class I) and rapid or non-progression of HIV infection, although relatively few of these associations have been consistently observed across studies and populations (see review [29]).

Cytotoxic T-lymphocytes (CTL) responses play an important role in control of HIV infection and mutation at critical amino acids in the viral epitopes recognized in the context of HLA class I molecules on infected cells by CTL may allow the virus to evade detection [30], ultimately resulting in failure of the immune response to contain viral replication. Important new work taking an evolutionary perspective on the interplay between HLA-mediated immunity and HIV has thrown new light on these dynamics [31]. In a large population study, HLA genotype, polymorphisms in reverse transcriptase viral genes and markers of disease progression were ascertained in the same HIV-infected individuals to demonstrate that an individual's HIV heterogeneity had been shaped by their HLA and this, in turn, had clinical consequences [31]. As the editorial accompanying the article so evocatively put it: "HLA leaves its footprints on HIV" [32]. This study showed that HLA-influenced viral polymorphisms were correlated with higher viral load and escape mutants were observed to be associated with the most prevalent class I allele, HLA*A02 [31]. Thus it seemed that HLA immune pressure may have already influenced the evolution of circulating viral variants in the population to avoid detection by the most common HLA alleles, contributing to failure of the immune system to control viral replication [33]. Selective advantage for those individuals who express rare HLA alleles was also subsequently demonstrated in a different population of HIV-infected adults [34]. These findings have profound implications for pediatric HIV infection.

Children acquire virus with a history

For children with vertically-acquired infection, the period of acute infection is the neonatal period, a time characterized by exceedingly high viral levels that decline more slowly than in adults over the next two or more years to reach set-point. Viral set-points are higher in children than in adults, consistent with more rapid disease progression [35]. In the absence of effective therapy, about a quarter of HIV-infected children progress to AIDS and 10–15% die within the first year of life [36,37].

Heterogeneity is known to be a defining characteristic of HIV, and this diversity, fueled by high rates of error-prone viral replication, may be a cornerstone of host immunity failure [38]. Host genetic diversity, including the extreme polymorphism of HLA, in turn, is one of the means to combat the spread of pathogens through populations. Even given the adaptability of HIV to evolve to escape immune control, adaptation to one individual's immune response does not necessarily provide a particularly strong advantage (from the virus' point of view) when infection is passed to the next host since the chances are low that two unrelated individuals share key genetic parameters [39]. However, with children this situation is quite different [40].

By definition, mother-to-child transmission involves transmission of virus between genetically similar individuals. At the least, a child will share 3 of the 6 HLA-A, HLA-B and HLA-C class I molecules with his or her mother. Similarity between mother and child may be greater for more common alleles on stochastic grounds alone where there is a greater probability that the mother is homozygous for the allele and/or that the child may inherit the allele of the father. To the extent that the maternal immune response shapes the evolution of autologous virus and the mother and child are genetically similar, the child acquires virus that has already "learned" how to evade his or her immune responses. Therefore the child acquires virus with a history of encounter with maternal immune responses. Interestingly, children who acquired HIV through blood transfusions, even during the neonatal period, tend to have a better prognosis than children who acquire infection from their mothers [41]. Mother-child genetic similarity may play a role in explaining the differences in the natural history of HIV infection between children and adults.

Two studies have demonstrated the relevance of maternal HLA-mediated selection pressure on virus transmitted from mother to child. A detailed study of four HIV-infected mother-child pairs observed mutations in viral epitopes and defective CTL responses among three children sharing the usually protective B*27 allele with their mother. In contrast, the one child who inherited B*27 from the father had robust CTL responses and was a long-term, non-progressor [42]. In another study, the child's HLA class I alleles were grouped into those usually associated with rapid disease progression (risky alleles) or long-term non-progression (protective alleles) based on adult studies [43–45] and alleles distinguished as being inherited either from the mother or the father. It was observed that children who inherited protective alleles from their father had a good prognosis but that maternally-inherited protective alleles did not appear to convey any benefits for slowing disease progression. Furthermore, children with greater similarity to their mothers with respect to their HLA genes had faster disease progression [46*]. These observations are consistent with the thesis that virus transmitted to the child has evolved to evade maternal HLA-mediated responses. To the extent that the child relies on these same HLA-mediated responses to contain viral replication, the child's immune response is set up to fail.

However, the situation may be more complex as some CTL epitopes appear to have fitness costs that then minimize their persistence in secondary hosts [47,48]. In addition, children not only appear to have the capacity to mount effective CTL responses, despite known deficits in T-cell function, that can drive CTL-escape but also appear to have greater plasticity than adults to mount new responses to the evolving virus [49].

HLA-mediated effects on HIV transmission

It might be expected that the dynamics of viral escape from infant CTL responses may account for HIV transmission but this has not been demonstrated. There is a large body of evidence accumulating that documents apparently HIV-specific anamnestic cellular immune responses (HIV-specific T-helper and CTL responses) among individuals exposed to HIV but who remain uninfected, including infants born to HIV-infected mothers (reviewed in [50,51]). However, it is difficult to know whether these responses are truly protective or whether they are simply epiphenomena of HIV exposure. In addition, these responses are very weak and often difficult to detect; made more difficult given small volumes of blood that can be drawn from newborns. In our own work, we noted the absence of HIV-specific responses among HIV-exposed infants who later succumbed to infection via breast-feeding and their presence in several different cohorts of HIV-exposed infants who remained free of infection suggesting the importance of these responses in protection [52,53]. However, it is likely that multifactorial processes in fetal and newborn life are necessary to prime and support effective anti-HIV immunity.

Associations between transmission and HLA class I and II alleles have not been as clear-cut or as consistent as for associations between HLA and disease progression once the host is already infected [29]. Greater than average similarity between mothers and their infants in their HLA class I alleles has been identified as a risk factor for perinatal HIV transmission [54] but mechanisms accounting for this association are unclear. We might expect that maternal HLA alleles associated with more rapid disease progression might be associated with transmission simply because these women have higher viral load. Markers of more advanced HIV disease, including maternal viral load and CD4 count, are strongly predictive of transmission to an infant [1] presumably due to greater viral inoculum. Since infants of mothers with rapid disease alleles are more likely than the background population to have inherited these alleles, it is perhaps not surprising that they were observed to be over-represented among infected children [55]. Thus the genetic background of the next generation of infected children may indeed be different, possibly independent of any role of child HLA alleles on HIV transmission per se. It is intriguing to note that in a new well-conducted study from Kenya [56], the child HLA

class I alleles found to be associated with less transmission, including HLA B*18, were those associated with faster (not slower) disease progression, suggesting a different HLA-mediated process for transmission and for disease progression.

Consistent with the notion that HLA-mediated effects on transmission may indeed be different from their role in disease progression, a large recent study observed strong associations between maternal HLA-B alleles and mother-to-child HIV transmission with little contribution of infant alleles [57**]. The alleles implicated in transmission in this study were not those generally associated with HIV-related disease progression, rather the alleles that predicted transmission were those involved with recognition of certain NK-cell receptors [57]. This is important because this system is central in mediating the inhibitory responses at the placenta that create the conditions for normal human pregnancy that requires maternal tolerance of the foreign fetal allograft [57]. NK cells and CD8+ T-cells with NK receptors accumulate at the placenta and may inhibit HIV transmission through production of CC chemokines or other mechanisms since HLA-B and NK receptors interactions have been identified as playing a role in controlling HIV disease progression [58]. These observations also suggest that some mechanisms of vertical HIV transmission may be unique to this route and also highlight the importance of the complex interplay between the innate and acquired immune systems and that a delicate balance may be at play in determining who becomes infected and who manages to escape from the encounter without infection.

Conclusion

The host immune response to HIV in early life is complex, and understanding the relationships between acquired immune responses to HIV, innate immune responses that include chemokines and their receptors, and host genetic influences that affect these immune processes in HIV-exposed infants will help us identify critical components of protective immunity, and help in the identification of infants at risk of acquiring HIV-1 infection and at risk of more rapid disease progression. As outlined, recent developments in these areas have vastly improved our knowledge of HIV-host interactions and further elucidation of these processes will contribute to the rational design of vaccines and the development of novel preventative and therapeutic anti-HIV strategies for children exposed to HIV.

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Figure 1.
Factors influencing the outcome of innate and adaptive immune responses to HIV in children.