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Minireview

Molecular mechanisms of HIV-1 mother-to-child transmission and infection in neonatal target cells

Nafees Ahmad *

Department of Immunobiology, College of Medicine, University of Arizona, Tucson, AZ, United States

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ABSTRACT

HIV-1 mother-to-child transmission (MTCT) occurs mainly at three stages, including prepartum, intrapartum and postpartum. Several maternal factors, including low CD4+ lymphocyte counts, high viral load, immune response, advanced disease status, smoking and abusing drugs have been implicated in an increased risk of HIV-1 MTCT. While use of antiretroviral therapy (ART) during pregnancy has significantly reduced the rate of MTCT, selective transmission of ART resistant mutants has been reported. Based on HIV-1 sequence comparison, the maternal HIV-1 minor genotypes with R5 phenotypes are predominantly transmitted to their infants and initially maintained in the infants with the same properties. Several HIV-1 structural, regulatory and accessory genes were highly conserved following MTCT. In addition, HIV-1 sequences from non-transmitting mothers are less heterogeneous compared with transmitting mothers, suggesting that a higher level of viral heterogeneity influences MTCT. Analysis of the immunologically relevant epitopes showed that variants evolved to escape the immune response that influenced HIV-1 MTCT. Several cytotoxic T-lymphocyte (CTL) epitopes were identified in various HIV-1 genes that were conserved in HIV-1 mother–infant sequences, suggesting a role in MTCT. We have shown that HIV-1 replicates more efficiently in neonatal T-lymphocytes and monocytes/macrophages compared with adult cells, and this differential replication is influenced at the level of HIV-1 gene expression, which was due to differential expression of host factors, including transcriptional activators, signal transducers and cytokines in neonatal than adult cells. In addition, HIV-1 integration occurs in more actively transcribed genes in neonatal compared with adult cells, which may influence HIV-1 gene expression. The increased HIV-1 gene expression and replication in neonatal target cells contribute to a higher viral load and more rapid disease progression in neonates/infants than adults. These findings may identify targets, viral and host, for developing strategies for HIV-1 prevention and treatment.

Contents

Introduction

Mother-to-child transmission (MTCT) of HIV-1 occurs at a rate of 30% without any antiretroviral treatment and accounts for 90% of all

* Mailing address: Department of Immunobiology, College of Medicine, University of Arizona, Tucson, AZ 85724, United States. Tel.: +1 520 626 7022; fax: +1 520 626 2100.
E-mail address: nafees@u.arizona.edu.

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HIV-1 infections in children (Ahmad, 2005, 2008a). While antiretroviral therapy in HIV-infected pregnant women has significantly reduced the rate of MTCT in developed countries, HIV-1 infection in children is still a major concern because approximately 500,000 new HIV-1 infected infants are born every year worldwide. In addition, more women in childbearing age group continue to be infected with HIV-1 worldwide increasing the risk of MTCT. More importantly, HIV-1 infected infants born to these infected mothers develop a higher viral load and progress to AIDS more rapidly than infected adults and their own infected mothers, including differences seen in clinical manifestations (Little et al., 2007). However, the molecular mechanisms of HIV-1 MTCT and differential infection in neonates/infants remain poorly understood. This article describes the characteristics of HIV-1 associated with and lack of MTCT and molecular mechanisms of differential HIV-1 infection in neonatal and adult target cells.

Overview of HIV-1 mother-to-child transmission

HIV-1 MTCT occurs mainly at three stages: prepartum (transplacental passage), intrapartum (exposure of infants skin and mucus membrane to maternal blood and vaginal secretions), and postpartum (breast milk) (Ahmad, 2005, 2008b). Several studies have demonstrated the infection of placentas or fetuses, including the capability of HIV-1 to pass through an intact placental barrier maintained *ex vivo* (Bawdon et al., 1994). The intrapartum transmission occurs in more than 50% of the cases due to the exposure of maternal blood to the child during labor and passage through birth canal (Kourtis et al., 2006). Postpartum HIV-1 MTCT mainly occurs through breastfeeding, with estimated rate of 14% to 29% and is a major route of MTCT in developing countries (Taha et al., 2009). While antibodies to HIV-1 in breast milk are not protective (Becquart et al., 2000), early development of T-helper cell responses to HIV-1 envelope proteins showed protection. Infants born to HIV-1 infected mothers are evaluated at regular follow-ups up to 3 years before they are declared uninfected based on Center for Disease Control (CDC) guidelines. Usually, a positive PCR on HIV-1 proviral DNA and virus culture in newborns is considered to be indicative of HIV-1 infection.

While MTCT rate is around 30% without any antiretroviral treatment, viral and/or host factors protect the majority of children against HIV-1 infection. Several maternal parameters, including advanced clinical stages of the mother, low CD4+ lymphocyte counts, maternal immune response to HIV-1, recent infection, high level of circulating HIV-1, and maternal disease progression have been implicated in an increased risk of MTCT of HIV-1 (Ahmad, 2005, 2008b; Petropoulou et al., 2006). Several studies indicate that elevated maternal viral load, plasma HIV-1 RNA levels, with different threshold may play an important role in MTCT (Garcia et al., 1999) However, the Ariel Project reported that the risk of transmission increased slightly with a higher viral load, but no threshold value of virus load was identified and that a high maternal viral load is insufficient to fully explain HIV-1 MTCT (Cao et al., 1997).

Several studies have demonstrated a direct association (Devash et al., 1990) or lack of correlation (Parekh et al., 1991) between the presence of maternal antibody against the V3 domain of the envelope protein and a lower rate of HIV-1 MTCT. More importantly, vertically transmitted HIV-1 variants were found to be neutralization resistant to their maternal plasma (Wu et al., 2006). Several other factors such as acute infection during pregnancy, the presence of other sexually transmitted diseases or other chronic infections, disruption of placental integrity secondary to chorioamnionitis, and smoking have been shown to be associated with MTCT of HIV-1(Report, 1992).

The AIDS Clinical Trials Group recommended that women treated with zidovudine (ZDV) during pregnancy significantly reduces the risk of HIV-1 MTCT, including oral ZDV to the newborn for six weeks (Cooper et al., 1996). A short course of ZDV from 36 weeks gestation and every 3-hour from onset of labor till delivery reduced MTCT in Thailand (Shaffer et al., 1999). The HIVNET study proved that oral administration of one dose of nevirapine to the mother and neonate could significantly reduce MTCT (Guay et al., 1999). Recently, highly active antiretroviral therapy (HAART) that includes at least three agents in combination of different classes of reverse transcriptase inhibitors and/or protease inhibitor has been found to reduce the MTCT rate to less than 2% (Taha et al., 2009). While use of antiretroviral therapy ART/HAART significantly reduces the risk of MTCT, MTCT of ART and multidrug-resistant HIV-1 has been reported (Johnson et al., 2001).

Characteristics of HIV-1 associated with and lack of mother-to-child transmission

Characterization of the molecular and biological properties of HIV-1 variants that are associated with and lack of MTCT has been performed by our and several other groups, with the idea that the strategies for prevention and treatment should be targeted at the properties of transmitted viruses. We and others have shown that a minor genotype, subtype or variant of maternal virus from a genetically heterogeneous virus population was transmitted to the infant based on HIV-1 envelope gp120 sequences analysis (Ahmad et al., 1995; Contag et al., 1997; Dickover et al., 2001; Mulder-Kampinga et al., 1995; Scarlatti et al., 1993; Wolinsky et al., 1992). The minor HIV-1 genotype predominates initially as a homogeneous population in the infant and then becomes diverse, as the infant grows older. However, transmission of a major or multiple (Dickover et al., 2001; Lamers et al., 1994) HIV-1 genotypes from mother-to-child has also been reported. In addition, selective transmission of minor SIV genotypes from mother-to-child was demonstrated in five macaque mother–child pairs following transplacental transmission (Amedee et al., 1995). Similar observations of selective transmission of minor HIV-1 genotypes have also been found in transmitter-recipient partners involving sexual transmission, including a homogeneous sequence population present initially in the recipients (Zhu et al., 1993).

Several studies have characterized the biological properties of HIV-1 associated with horizontal and vertical transmission and shown that macrophage-tropic and non-syncytium-inducing or R5 HIV-1 are transmitted during sexual (Zhu et al., 1993) or vertical transmission (Matala et al., 2001. These maternal R5 viruses that are transmitted to infants utilize CCR5 chemokine receptor (Matala et al., 2001). In addition, the viral phenotype of SIV involved in MTCT was found to be R5 (Amedee et al., 1995). Furthermore, the role of CCR5 in HIV-1 MTCT was investigated and found that infants with two copies of 32 bp deletions in CCR5 were prone to infection by X4 viruses following vertical transmission. However, in a study of 552 mother–child pairs, no babies were found to be infected who were homozygous for 32 bp deletion for CCR5 (Philpott et al., 1999).

We have also analyzed the characteristics of HIV-1 from non-transmitting mothers (who failed to transmit HIV-1 in the absence of antiretroviral therapy) in the region of *env* V3 region, *gag* p17, *vif* and *vpr* and compared with transmitting mothers' isolates. We found that the coding potential of the envelope ORF, including several patient-specific amino acid motifs and earlier described molecular features across the V3 region were highly conserved in non-transmitting mothers (Matala et al., 2000). However, there was a low degree of viral heterogeneity within each non-transmitting mother's sequence as compared to transmitting mothers' sequences. In addition, the estimates of genetic diversity of non-transmitting mothers' sequences were significantly lower compared to transmitting mothers' sequences (Matala et al., 2000). The *gag* p17 matrix sequences of HIV-1 were analyzed from three non-transmitting mothers, including multiple deliveries in case of one mother. There was a low degree of heterogeneity of gag p17 matrix sequences in non-transmitting mothers (Hahn and Ahmad, 2001) compared to our previously