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Molecular Epidemiology of HIV-1 Infection in the Amazon Region

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1. Introduction

No other group of infectious agents has received increased attention from scientists in recent years than that of retroviruses. This reflects not only their importance as pathogens of humans and animals, but also its great value in studying the interactions between pathogens and host.

The family *Retroviridae* comprises a large number of viruses that have the ability to insert its genome into the host cell and infect primarily vertebrates, despite having been described infections in other animals such as snails and insects.

Viruses pathogenic to humans which cause infections worldwide can be divided into two main groups: the transformants and the cytopathic. The first, induce changes in the control of cell division and can lead to tumors, such as Human T-lymphotropic virus (HTLV), belonging to the genus *Deltaretrovirus* and is linked to neurological and hematological. Cytopathic retroviruses are members of the *Lentivirus* genus, such as the Human immunodeficiency virus (HIV), and are related to severe immunodeficiency condictions.

The ubiquotous conditions, now known by the name of acquired immunodeficiency syndrome (AIDS) is caused by HIV and was first recognized in the summer of 1981. The spread of an emerging virus in all regions of the world, caused great losses both in terms of human lives as well as in the economic point of view.

HIV infection results in a profound disorder in the host immune system, which is characterized by a decrease in the number of lymphocytes with the CD4 glycoprotein on their surface, especially helper T lymphocytes (ATL), with subsequent reversal of the ratio of CD4+ or CD8+ T lymphocytes.

In Brazil, the HIV-1 dissemination reflects the grandeur and diversity sociogeographic of the country and its regional heterogeneity. The first cases of HIV/AIDS in Brazil, dates from 1982 and were originated the Southeast individual, which today still has the highest number of reported cases of the disease. Subtypes B, F, C and D, in addition to samples of virus recombinants and dual infections in different geographical areas. In the present chapter, we describe the molecular epidemiology of HIV-1 infection in the Brazilian Amazon region, emphasizing its impact in the city of Belem, Capital of the Para State, which is the main port of entry into the Amazon, highlighting the occurrence of the circulating subtypes and the genetic profile of the host which is associated with the infection.

Currently HIV-1 genetic heterogeneity is classified into four phylogenetic groups: M, N, O and P, which may reflect four interspecific transmission events from chimpanzees (Plantier et al., 2009). Group M (major) is the most frequently involves with human infectious worldwide and is composed of nine genetically distinct subtypes, named A, B, C, D, F, G, H, J and K, whose gene sequences differ approximately 20% (Taylor et al., 2008).

In Brazil, HIV-1 is characterized by the occurrence of several subtypes of the M group, and includes subtype B, the most prevalent in the majority of the regions, followed by subtypes F, C, and D, (Monteiro et al., 2009) although some cities present a distinct pattern of distribution of these subtypes (Vicente et al., 2000; Soares et al., 2003). This diversity of subtypes could represent more than one port of entry of HIV-1 in the country, with the emergence of the epidemic occurring, probably in the late 1970's or early 1980's (Morgado et al., 1998).

The circulating recombinant forms of HIV (CRFs) have an important role in regional and global epidemics of the virus, particularly in regions where multiple subtypes circulate simultaneously. Currently over 40 CRFs are recognized worldwide (http://www.hiv.lanl.gov), and five have been described in Brazil, designated as CRF28_BF, CRF29_BF, CRF39_BF, CRF40_BF e CRF31_BC (Sanabani et al., 2006; De Sá Filho et al., 2006, http://www.hiv.lanl.gov/content/sequence/HIV/CRFs/CRFs.html), where CRF_BC represents 11% of the HIV-1 viruses circulating in the Southern region of the country (Santos et al., 2006).

In addition to the CRF, a large number of unique recombinant forms (URFs) have been characterized worldwide (McCutchan, 2006). Notoriously, a recombination is a potentially important mechanism that significantly contributes to HIV genetic variability with serious implications for diagnosis, drug treatment and optimal vaccine development (Sanabani et al., 2010).

2. HIV-1 infection in the Brazilian Amazon region

The molecular epidemiology of HIV-1 strains circulating in the Northern region of Brazil is poorly known (Table 1). The State of Para has 43.3% of the cases. Until June 2006, there were 5919 infected individuals, in which 80.4% were men and 19.6% were women (Brasil, 2008). The prevalence of the infection in the State of Amapa is still low, although the region borders French Guiana and a great number of indigenous populations move freely between the two countries. The cities of Belem (State of Para), Manaus (State of Amazonas) and Macapa (State of Amapa) can be considered as the main entry of HIV-1 in northern Brazil. The city of Belem has one of the largest ports in the Brazilian Amazon and receives a great input of tourists throughout the year, while the city of Macapa is located next to several Indian tribes and borders countries such as Guyana, which generates a large population movement between two locations. The city of Belem shows the highest diversity of subtypes of HIV-1 in Brazil, having been identified the subtypes B, F, D, C and recombinant CRF02_AG subtype reflecting in this way, the same epidemiological profile found in almost all regions of Brazil (Sabino et al., 1996; Morgado et al., 1998; Ramos et al., 1999, Tanuri et al., 1999; Vicente et al., 2000) and from South America (Marquina et al., 1996; Navas et al., 1999; Avila et al., 2002; Castro et al., 2003).

The population group studied presented epidemiological characteristics which indicated that the heterosexual transmission of HIV-1 associated with sexual promiscuity, was the main way of virus dissemination. HIV-1 occurred mostly in the group of individuals who

reported having only primary and secondary education, as well as those with a heterosexual behavior. There was no statistically correlation between sex, educational level, sexual orientation and risk behavior for HIV-1, with subtypes B and F infection.

Subtype C was identified in Belem and phylogenetic analysis supports the hypothesis that the virus was imported from the Southeast and Southern Brazil. Additionally, the recombinant CRF02_AG subtype, circulating in Belém-PA probably was reported for the first time in the Amazon region and reinforces the importance of epidemiological surveillance for the virus in the country.

In Belem four subtypes were described in relation to *env*: B (88.3%), F (8.3%), D (1.7%), and C (1.7%); subtype B was the only one found in Macapa. In relation to the *pro* segment, there were four distinct subtypes in Belem: B (88.3%), F (9.3%), D (1.2%), and CRF02_AG (1.2%). In Macapa, subtypes B (97.1%) and F (2.9%) were detected. Six strains were characterized as mosaics: two were B^{env}/F^{pro} (1.6%), two F^{env}/B^{pro} (1.6%), one C^{env}/B^{pro} (0.85%), and one B^{env}/D^{pro} (0.8%) (Machado et al., 2009).

When compared to the State of Amazonas, there is a higher concentration of cases of disease in Manaus (capital), which holds approximately 90% of cases (Fundação de Medicina Tropical do Amazonas, 2006). Manaus has greater human genetic diversity because of their indigenous origin and sociocultural strong influence of migration from the Northeast region of Brazil since the 1800's when colonization occurred more intensely because of the business cycles of the rubber extractive exploratory projects, settlement of forest areas its transformation into an industrial area (Carneiro Filho, 1998).

There is evidence that the HIV / AIDS in the city of Manaus evolved with different patterns of distribution and expansion, whose characteristics define its consolidation in the initially affected districts still in the emergency epidemic, spreading later to other spaces receptive City (Silva et al., 2009).

In Manaus, it was found almost equal proportions of HIV-1 strains belonging to subtype B (51.6%) and F (48.4%), a finding that differs from previous results from studies conducted in urban areas of southeastern Brazil (Vicente et al., 2000).

Region	State	Subtypes	Gene(s)	References
North	Pará	B, F, D e C	*env*	Machado *et al*., 2009
	Pará	B, F, D, CRF02_AG	*pro*	Machado *et al*., 2009
	Pará	B^{env}/F^{pro}, F^{env}/B^{pro}, C^{env}/B^{pro}, B^{env}/D^{pro}		Machado *et al*., 2009
	Amapá	B	*env*	Machado *et al*., 2009
	Amapá	B e F	*pro*	Machado *et al*., 2009
	Amazonas	B, F e B/F	*env*	Vicente *et al*., 2000

Table 1. Geographic distribution of subtypes of HIV-1 in northern Brazil.

3. Genetic background of HIV-1 infected subjects

The pathogenesis of human immunodeficiency virus 1 infection is very complex and of course influenced by both viral and host factors (Cohen et al., 1997). Studies have focused the attention about the role of *MBL* gene variants and its serum concentration on the progression of AIDS in HIV-1-infected subjects (Garred et al., 1997; Prohászka et al., 1997).

Mannose-binding lectin (MBL) is a liver-derived pluripotent serum lectin that has a role in the host's innate immune system (Turner, 2003) by binding with high affinity to mannose or other carbohydrate components existent in viruses, bacteria and yeast (Kuipers et al., 2003). However, MBL function is directly associated with its serum concentrations which are determined by the interplay between promoter and structural gene mutations (Madsen et al., 1995; Jüliger et al., 2000).

Three mutations have been described in the structural region of the molecule (codons 52, 54 and 57) from which are derived three allelic variants named *MBL*D*, *MBL*B* and *MBL*C*, respectively. On the other hand, the wild allele is called *MBL*A* (Madsen et al., 1994). The occurrence of these variants have been associated with MBL serum deficiency and consequently to susceptibility/resistance to infection by various pathogens, including HIV-1 (Drogari-Apiranthitou et al., 1997; Garred et al., 1997; Prohászka et al., 1997; Luty et al., 1998; Hibberd et al., 1999; Peterslund et al., 2001; Klabunde et al., 2002; Roy et al., 2002; Song et al., 2003).

It was investigated the association between *MBL* gene polymorphism and the susceptibility to HIV-1 infection (Vallinoto et al., 2006). The study of 145 HIV-1-infected subjects and 99 healthy controls showed the presence of alleles *MBL*A*, *MBL*B* and *MBL*D*, whose frequencies were 69%, 22% and 09% among patients and 71%, 13% and 16% among healthy controls, respectively. The presence of the variant *MBL*B* was associated with higher plasma viral load levels, suggesting the importance of the *MBL* gene polymorphism in the clinical evolution of HIV-1-infected patients.

The prevalence of mutations in the -550 (H/L) and -221 (X/Y) mannose-binding lectin (MBL) gene promoter regions and their impact on infection by human immunodeficiency virus 1 (HIV-1) was investigated in a population of 128 HIV-1 seropositive and 97 seronegative patients (Vallinoto et al, 2008). The allele identification was performed through the sequence-specific primer polymerase chain reaction method, using primer sequences specific to each polymorphism. The evolution of the infection was evaluated through CD4+ T-lymphocyte counts and plasma viral load. The allele and haplotype frequencies among HIV-1-infected patients and seronegative healthy control patients did not show significant differences. CD4+ T-lymphocyte counts showed lower levels among seropositive patients carrying haplotypes LY, LX and HX, as compared to those carrying the HY haplotype. Mean plasma viral load was higher among seropositive patients with haplotypes LY, LX and HX than among those carrying the HY haplotype. When promoter and exon 1 mutations were matched, it was possible to identify a significantly higher viral load among HIV-1 infected individuals carrying haplotypes correlated to low serum levels of MBL. The current study shows that haplotypes related to medium and low MBL serum levels might directly influence the evolution of viral progression in patients. Therefore, it is suggested that the identification of haplotypes within the promoter region of the MBL gene among HIV-1 infected persons should be further evaluated as a prognostic tool for AIDS progression.

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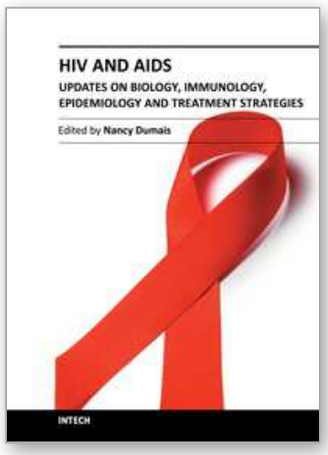
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The continuing AIDS pandemic reminds us that despite the unrelenting quest for knowledge since the early 1980s, we have much to learn about HIV and AIDS. This terrible syndrome represents one of the greatest challenges for science and medicine. The purpose of this book is to aid clinicians, provide a source of inspiration for researchers, and serve as a guide for graduate students in their continued search for a cure of HIV. The first part of this book, â€œFrom the laboratory to the clinic,â€ and the second part, â€œFrom the clinic to the patients,â€ represent the unique but intertwined mission of this work: to provide basic and clinical knowledge on HIV/AIDS.

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