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Editorial

Mannose-binding lectin and susceptibility to human retrovirus infections

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One of the major goals for the future of medicine is the prediction of susceptibility, resistance, increased transmission risk, infection, and disease on an individual basis to provide personalized medical, drug-based treatment. To do this, relevant information must be available.

Mannose binding lectin (MBL) is a liver-derived pluripotent serum lectin and molecule of the innate response system. It binds with high affinity to mannose or other sugar components on the surface of viruses, bacteria, and yeasts and mediates phagocytosis or activates the lectin pathway of the complement system[1]. MBL function is associated with its serum concentration and is regulated by expression of the promoter and structural gene single nucleotide polymorphisms (SNP).

The wild allele is called *MBL*A,* and three mutations have been described in the structural region of the molecule (codons 52, 54, and 57), from which three allelic variants are derived: *MBL*D*, *MBL*B,* and *MBL*C*, respectively[2]. The occurrence of these variants has been associated with MBL serum deficiency and, consequently, to susceptibility/resistance to infection by various pathogens, including human immunodeficiency virus (HIV)-1[1].

The mutation in the promoter region of the MBL gene has shown that serum MBL concentrations are also modulated by transcriptional levels[2]. Nucleotide substitutions in positions -550 (G to C) and -221 (G to C) provide the variants H (G)/L (C) and Y(G)/X(C), respectively. Promoter variants such as HY, LY, and LX haplotypes alter plasma levels and are currently associated with high, medium, and low levels of circulating MBL, respectively[3]. Because of a linkage disequilibrium among some variants, only seven haplotypes of MBL (HYPA, LYQA, LYPA, LXPA, LYPB, LYQC, and HYPD) have been identified[3]. The importance of the allele dimorphism resides mainly in the fact that the promoter region is known to influence MBL concentration. As a result, the -221 promoter polymorphism provides a stronger response than the -550 SNP, resulting in higher MBL plasma concentrations.

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Biomarkers are defined as biological molecules found in the blood or other organic fluids or tissues that indicate the presence of a normal process, abnormal process, condition, or disease. MBL has been pursued as a biomarker to help understand the pathogenesis of the human retroviruses, HIV-1, human T-cell lymphotropic virus (HTLV)-1, and HTLV-2 in the Amazon region of Brazil.

HIV-1 is probably the most important emerging pathogen in recent history for humankind and has resulted in global behavioral changes owing to the impact on the health of humans with acquired immune deficiency syndrome (AIDS) that is associated with this viral infection. HIV-1 is responsible for a disease that places the human species in a dangerous epidemiological situation in remote parts of the world that are plagued by poverty, undernourishment, and political instability. The pathogenesis of HIV-1 is complex and influenced by both viral and host factors. Recently, studies have focused attention on the role of *MBL* gene variants and their serum concentrations on the progression of AIDS in HIV-1-infected subjects[4].

HTLV-1 and HTLV-2 were the first viruses of the family *Retroviridae* found to infect humans and share several molecular and biological properties with HIV-1. HTLV-1 is endemic in diverse geographical regions worldwide and associated with several diseases, including adult T-cell leukemia/lymphoma (ATLL) and a neurodegenerative disorder named tropical spastic paraparesis/HTLV-1 associated myelopathy (TSP/HAM)[5]. A large number of HTLV-1-infected individuals remain asymptomatic, suggesting that the infection alone is not sufficient to cause disease. Furthermore, the outcome of HTLV-1 infection is still unclear, but genetic factors seem to be important[6].

The initial investigations regarding the association between *MBL* gene polymorphisms and susceptibility to HIV-1 infection included 145 HIV-1-infected subjects and 99 healthy controls. The alleles *MBL*A*, *MBL*B,* and *MBL*D* were present in 69%, 22%, and 9% of patients and 71%, 13%, and 16% of 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[7].

More recently, the MBL plasma concentrations according to genotype were investigated[8]. The differences between the AA (113.41 ± 55.95ng/mL) and AO (53.30 ± 51.49ng/mL)

genotypes ($p < 0.0001$) and AA and OO (66.58 ± 55.06ng/mL) genotypes ($p < 0.001$) were statistically significant, but not those between the AO and OO genotypes ($p = 0.17$).

The prevalence of mutations in the -550 (H/L) and -221 (X/Y) MBL gene promoter regions and their impact on HIV-1 infection were investigated in a population of 128 HIV-1 seropositive and 97 seronegative individuals, and there were no differences in the allele and haplotype frequencies between seropositive and seronegative status[9]. $CD4^+$ T-lymphocyte counts were lower in the seropositive individuals carrying haplotypes LY, LX, and HX, as compared to those carrying the HY haplotype. The mean plasma viral load was higher in the seropositive individuals with haplotypes LY, LX, and HX than in those carrying the HY haplotype. When promoter and exon 1 mutations were matched, a significantly higher viral load was observed in HIV-1 infected individuals carrying haplotypes correlated to low serum levels of MBL. The study showed that haplotypes related to medium and low MBL serum levels might directly influence disease progression in patients. Therefore, the identification of haplotypes within the promoter region of the MBL gene in HIV-1 infected persons should be further evaluated as a prognostic tool for AIDS progression.

Regarding HTLV, the frequencies of *MBL*A*, *MBL*B,* and *MBL*D* were 63%, 22%, and 15% in seropositive individuals and 70%, 14%, and 16% in healthy controls, respectively[10]. Genotype differences were statistically significant ($\chi^2 = 11.57$, $p = 0.04$); genotype BB was present in 9.6% of HTLV-infected individuals compared with 1% of controls ($\chi^2 = 7.151$, $p = 0.019$). A significant difference in genotype frequencies between HTLV-1 and HTLV-2 infections was observed, but this could be attributed to the significantly higher number of HTLV-1-infected subjects. The odds ratio for the presence of the *BB* genotype was 10.453 (95% confidence interval [CI] = 1.279-85.40, $p = 0.019$). There was an association between MBL polymorphisms and HTLV infection.

The subsequent analysis of allele frequencies at position -550 did not show significant differences between the HTLV-infected and control groups[11], but there was a significant difference at position -221. The comparative analysis of haplotype frequencies was not significant. However, there was a higher prevalence of genotype LYLX (25.3%) associated with medium and low MBL serum levels in the HTLV-infected individuals, and the presence of genotype LYLX was associated with an increased risk of HTLV infection (odds ratios [OR]= 3,2498, 95% CI = 1.38-7.7605, $p = 0.0096$). There was no association between proviral load and the promoter polymorphism; however, when the promoter and exon 1 mutations were matched, a significantly higher proviral load was detected in the HTLV-infected individuals carrying haplotypes correlated with low serum MBL levels.

The article by Paiva & Casseb[12], in the present issue of the *Journal of the Brazilian Society of Tropical Medicine* (RSBMT), is an open field for the future application of biomarkers that would help in the control of human retrovirus (HIV-1, HIV-2, HTLV-1, and HTLV-2) transmission. MBL, as a component of the innate mechanism of the immunological response, could also be of interest following virus infection or its dissemination to other host cells. The human retroviruses of interest here are well adapted to the host and follow an usual pattern of transmission through sexual means. The present review is rich in such examples that have primarily contributed to the global dissemination of the viruses.

Apart from belonging to the same virus family, HIV and HTLV share biological properties, but behave differently in their replicative outcome. Experience with HTLV led to a faster description of HIV following the increase in the prevalence of AIDS. The descriptive epidemiology of HTLV-2 among epidemiologically isolated groups[13] also led to a better understanding of the effect of integration, latency, and productive infection on the perpetuation and maintenance of these viruses in their hosts, through vertical and horizontal patterns of transmission that contributed to their success as human infectious agents and pathogens. Finally, the appropriate comprehension of the host's immunological and genetic mechanisms could help, in the future, to control the virus replication and prevent the spread.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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