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An Opinion About the Importance of MBL in HIV/HHV-8 Coinfection

INTRODUCTION

The prevalence of human herpesvirus 8 (HHV-8) varies according to different geographic regions and subpopulations [1-3], however, HHV-8 infection has increased in people living with HIV/AIDS (PLHA) compared to HIV negative individuals [4-7].

Most of the primary infections caused by HHV-8 are asymptomatic, with viral syndrome characterized by fever, fatigue, lymphadenopathy, diarrhea, and skin rash [8]. However, after the emergence of HIV/AIDS there was a higher incidence of diseases associated with HHV-8 infection, in which the main manifestations are from the excess of cytokines, such as Castleman's multicenter disease, and the formation of tumors, as primary effusion lymphoma and Kaposi's sarcoma (KS) [9,10]. HHV-8 is associated with all forms of Kaposi's sarcoma (KS), the classic, endemic, iatrogenic, and epidemic or HIV/AIDS-associated form [6,11,12], being the necessary etiological agent, but insufficient for the development of clinical manifestations [4,5,10].

With the HIV/AIDS epidemic, the incidence of KS increased dramatically and presented a more aggressive clinical course, with progression to death, due to the spread of lesions to internal organs. Since 1996, combination antiretroviral therapy was used to reverse HIV-associated immunosuppression, reducing the risk of developing KS [2,11,12]. Although the introduction of therapy has largely altered the natural history of HIV infection, KS is still one of the most common malignancies in PLHA [5,10,13].

Therapy reduced the incidence of KS by approximately 80%, as well as the morbidity and mortality caused by this disease, but KS persist more frequent in PLHA than in the general population. The incidence of KS is approximately 1 in 100,000 in the general population, and 1 in 20 PLHA About 50% of coinfected men who have sex with men develop KS within 5 to 10 years of acquiring coinfection, even in countries where the prevalence of KS is considered low [3,14]. Studies have reported that KS may develop in treated PLHA, with controlled viral load HIV and CD4 T-cell counts greater than 350 cells/mm^3, where up to 40% of these patients require antineoplastic chemotherapy in combination with antiretroviral therapy [5,10,13].

Control of HHV-8 infection and early stages of KS development are mediated by innate and adaptive immunity responses [15–18]. In this context, mannose-binding

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lectin (MBL) plays a key role in innate immune defense of the host as a pattern recognition receptor by binding with high affinity to the patterns of carbohydrate residues present on the surface of viruses or virus-infected cells, especially when humoral immunity is not fully functional, as in immunosuppressed populations [19–21]. Thus, MBL contributes to activation of the complement system lectin pathway in an antibody-independent mechanism, and may promote opsonophagocytosis, modulate inflammation and induce cell lysis [17,21–25].

MBL protein is comprised of multimers of an identical polypeptide chain comprising four regions, the cysteine-rich N-terminal region, a collagenous domain, a helical spiral hydrophobic region called the neck, and a carbohydrate recognition domain [24,26]. It has the ability to recognize sugar units such as N-acetyl-D-glucosamine, mannose, N-acetyl-manosamine, fucose and glucose, expressed by different microorganisms and structures, and activate the complement system lectin pathway through association with serine proteases MASP-1, MASP-2 and MASP-3 [26–28].

MBL protein expression is genetically determined and variations in plasma concentrations can also be attributed to MBL2 gene polymorphisms, which may cause defects in the polymerization of the molecule leading to functional deficiency and/or serum levels [26,27,29–33]. Functional deficiency of plasma MBL concentrations has been associated with various infections or progression of clinical manifestations [20,34–38]. Regarding PLHA, research has shown an association between functional deficiency of MBL plasma concentrations and susceptibility to HIV infection, as well as faster disease progression [22,39–42], while other studies have not found this association with infection, HIV viral load or TCD4 count [23,43].

MBL is known to bind directly to viruses of several families, such as dengue, Ebola, influenza, HIV, among others, and this interaction leads to neutralization by deposition of complement C3 and C4 in the virus, preventing the interaction of the virus with the host cell and leading to further phagocytosis or viral lysis [41,44–47].

Regarding the Herpesviridae family, MBL has been reported to bind to HHV-2 surface glycoproteins, although it is not specifically known what this structure would be [35]. While cytomegalovirus (CMV) has glycoproteins that are potential targets for MBL binding and may prevent viruses from entering host cells; another possibility is that MBL could recognize CMV glycoproteins on the surface of a cell infected with this virus and consequently induce complement-mediated cell destruction [48,49].

Thus, studies have suggested that deficient MBL concentrations may be a risk factor for symptomatic HHV-2 infection and CMV reactivation; however, it is not yet known how MBL could help control HHV-8 infection and/or the development of KS [50–52]. On the other hand, HHV-8 presents in the viral envelope a mannose carbohydrate structure, glycoprotein B (gB), which could be a potential target for MBL binding [53,54].

Morais et al (2019), reported that MBL plasma concentration median were significantly lower in the coinfected patient and a possible explanation would be the consumption and reduction of this protein, involving the opsonization of HIV and HHV-8, leading to the reduction of plasma MBL [55]. Because of these results, studies related to MBL plasma concentrations evaluating the HHV-8 latent or latent cycle, quantify of the HHV-8 viral load or measure the activity of MBL in the complement system become essential and may help to understand the role of MBL in the development of KS in HIV/HHV-8 coinfected patients.

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