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Microbial Translocation and B Cell Dysfunction in Human Immunodeficiency Virus Disease

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Abstract: The gut mucosal barrier disrupted in HIV disease, resulting in increased systemic exposure to microbial products such as Lipo Polys Accharide (LPS). The association of enhanced microbial translocation and B cell dysfunction in HIV disease is not fully understood. High dose and short term exposure of microbial Toll-Like Receptor (TLR) agonists were used as vaccine adjuvants, however, low dose and long term exposure of TLR agonists could be harmful. The characteristics of B cell dysfunction in HIV disease included B cell, especially memory B cell depletion, enhanced levels of autoimmune antibodies and impaired vaccine or antigen responsiveness. This review discusses and explores the possibility of the effect of microbial translocation on memory B cell depletion and impaired vaccine responses in HIV infection. By determining the mechanisms of B cell depletion and perturbations in HIV disease, it may be possible to design interventions that can improve immune responses to vaccines, reduce selected opportunistic infections and perhaps slow disease progression.

Key words: Microbial translocation, dysfunction, B cell, HIV disease, vaccine, Lipo Polys Accharide (LPS), Toll-Like Receptor (TLR)

INTRODUTION

HIV epidemiology: Human Immunodeficiency Virus (HIV) is a lentivirus that attacks the human immune system and causes Acquired Immunodeficiency Syndrome (AIDS). The incidence of HIV in the United States is approximately 56, 300 people each year, with the prevalence of HIV infection in the US of about 1,100,000 people (Hall *et al*., 2008; MMWR, 2006). Approximately 18,000 people with AIDS die each year in the US. There are four major routes of HIV transmission including sex, needles, breast feeding and from mother to her baby at birth (Tsibris and Hirsch. 2010; Grivel *et al*., 2010). However, until now there is not drug available to completely eliminate HIV virus.

AIDS is a life-threatening condition that can lead to opportunistic infections, cardiovascular and metabolic diseases and cancers. HIV infection leads to the disease of AIDS approximately two to ten years after infection. There are around two to ten years from HIV infection to AIDS. Antiretroviral treatment greatly reduces the mortality and the morbidity of HIV infection (Tsibris and Hirsch. 2010; Grivel *et al*., 2010). Antiretroviral treatment limits virus under detectable in peripheral blood, other tissues such as lymph nodes, brain and tears still contain varying levels of virus.

Innate and adaptive immunities: There are two types of immune responses in the human system, the innate and adaptive immune responses. The innate immune system has the function to immediately and non-specifically respond to invading pathogens, including inflammation, complement system and cellular innate responses. For example, dendritic cells produce interferon-alpha in response to virus infection and interferon-alpha has the function of killing the virus (Yoshikai, 2006). When innate immunity cannot eliminate pathogens, adaptive immunity plays a role to control infection. Adaptive immune response defends the host from infection by a specific manner. This means that certain cells of the adaptive immune system recognize and respond to specific pathogens and have specific memories, next time these memory cells can attack the same invading pathogens with a fast and strong response. Innate immunity defenses are immediate and short lasting. Adaptive immunity defenses mount often 1-2 weeks and last longer (Yoshikai, 2006).

Toll-like receptor and its ligands: Toll-Like Receptor (TLR) families are responsible for the recognition of Pathogen-Associated Molecular Patterns (PAMPs) expressed by pathogens and distinguishable from host molecules. TLRs recognize structurally conserved molecules derived from microbes. PAMPs activation links to the innate immune system, results in the production of proinflammatory cytokines and the expression of antimicrobial genes. Activation of

PAMPs also plays a key role in shaping adaptive immune response. There are more than 10 families of TLR ligands found until now; these TLR ligands include DNA of bacteria, RNA of the virus and Lipo Poly Saccharide (LPS) produced by most Gram-negative bacteria and Gram-positive bacteria. TLR ligands have the function of maintaining normal immune function, however, too much TLR ligands may result in immune activation and cause disease pathogenesis. A certain and low level of TLR ligands in human body is a consequence of living in a non sterile environment, however, the systemic heightened level of TLR ligands are believed to be a consequence of the impaired mucosal integrity, especially in the gut (Abreu, 2010; Fukata and Abreu, 2009).

TLR ligands can be found in bacteria, fungi and also viruses and provide, via TLR binding, early recognition of microbial invasion. TLR1, TLR2 and TLR6 are triggered by peptidoglycan and other microbial products, TLR3 by double-stranded RNA, TLR4 by Lipo Poly Saccharide (LPS), TLR5 by flagellin, TLR7 and TLR8 by imidazoquinolines and TLR9 by unmethylated CpG DNA (Barton and Medzhitov 2003). All TLRs, except TLR3, activate the adaptor Molecule (MyD88) -dependent pathways that culminate in the activation of nuclear factor-kB (NF-kB) transcription factors, as well as the Mitogen-Activated Protein Kinases (MAPKs) extracellular signal-regulated kinase (ERK), p38 and c-Jun N-terminal Kinase (JNK) (Barton and Medzhitov 2003; O'Neill, 2000; 2002a; 2002b). These transcription factors function in concert to promote inflammatory responses (e.g., IL-6, IL-10 and TNF-a) (Lamping *et al*., 1998; Shen *et al*., 2008; Soboll *et al*., 2006). HIV itself is also functional as TLR ligands since RNA sequences derived from the HIV genome are capable of signaling through TLR 7 and TLR 8 (Meier *et al*., 2007).

Human B lymphocytes and TLRs: Human B lymphocytes produce antibodies against invading pathogens that are key to induce a humoral immune response. Human B cells express high levels of TLR1, TLR6, TLR9 and TLR10, intermediate levels of TLR7 and low levels of TLR2 and TLR4 (Hornung *et al*., 2002). Most B cell studies focus on TLR9, the main TLR on human B cells, which binds to bacterial DNA (Mansson *et al*., 2006; Chuang *et al* ., 2002; Jiang *et al*., 2007; Martinson *et al*., 2007; Vollmer *et al*., 2004). It has been demonstrated recently that switched and IgM-positive memory B cells constitutively express Toll-Like Receptor 9 (TLR9) (Bernasconi *et al*., 2003) and it has been suggested that the repeated stimulation through unmetylated CpG may function to continuously and specifically restimulate B cells and maintain serologic memory in the absence of traditional protein antigens (Bernasconi *et al*., 2002). In the model, serum IgG antibodies constitute the specific memory (with B cell receptor signals) built up by previous experience and vaccination and IgM antibodies may represent first-line memory, indispensable against pathogens never encountered before and T cell Independent (TI) antigens. On the other hand, naïve B cells are also reported to proliferate and produce IgM (not IgG) in response to CpG ODN (TLR9 ligand) alone from our previous study and others (Jiang *et al*., 2007; Bekeredjian-Ding *et al*., 2005). Furthermore, IgG class switch DNA recombination is induced among human naïve B cells in response to CpG ODN and IL-10 (He *et al*., 2004). Thus, TLRs may play a role in the autoimmune diseases those are present in HIV infection. However, the role of TLRs in autoimmune diseases is not clear and is controversial (Lamphier *et al*., 2006; Papadimitraki *et al*., 2006). Importantly, TLR ligands enhance antigen-specific B cell responses through B Cell Receptor (BCR) stimulation (Poeck *et al*., 2004). However, It remains to be demonstrated whether TLRs are important in specific recall reactions induced by either infection or vaccination (TLR ligands as adjuvants).

Chronic immune activation in HIV infection: HIV infection induces broad immune perturbation, including dysfunction and loss of CD4+ T cells and B cells (Grossman *et al*., 2002). Although the HIV virus infects CD4+ T cell, monocytes/macrophages and dendritic cells, the exact mechanisms of loss of CD4+ T cells, key cells to achieve adaptive humoral and cellular immune responses, are still not fully understood. In HIV infection, there is increasing consensus that immune activation is central to disease pathogenesis (Giorgi *et al*., 1993). Recent studies suggest that increased microbial products from the damaged gut in chronic HIV infection are at least partially responsible for chronic immune activation (Brenchley *et al*., 2006; Jiang *et al*., 2009). High levels of the Toll-like receptor 4 ligand, Lipo Poly Saccharide (LPS) and bacterial ribosomal 16S RNA are found in the plasma of individuals with chronic HIV infection. Levels of LPS and 16S rDNA are correlated with indices of immune activation and predict the magnitude of immune restoration after 48 weeks of antiretroviral treatment.

B cell perturbations in HIV disease: B cells are antibody-producing cells; antibodies have the function of killing pathogens. Perturbations of the B cells will result in infection or autoimmune diseases. In HIV disease, there are three main B cell perturbations including polyclonal B cell activation, peripheral memory B cell depletion and impaired recall antibody responses (Titanji *et al*., 2005; 2006; Milito *et al*., 2000;

2004; Guan *et al*., 2009). Although the lack of CD4+ T cell help may explain some of these deficiencies, there also appear to be intrinsic defects in B lymphocytes that can be demonstrated in functional assays that do not require T helper cells (Malaspina *et al*., 2003). The functional defects that have been described in B cells from HIV-infected persons include impaired proliferation responses (to B cell antigen receptor stimulation, CD40L and CpG ODNs), reduced antibody production following vaccination, B cell hyperactivation and hypergammaglobulinemia and increased susceptibility to spontaneous apoptosis (Conge *et al*., 1998; Malaspina *et al*., 2008; Moir *et al*., 2004). B cell hyperactivation in HIV disease may lead to the increased susceptibility of these cells to apoptosis and may also contribute to impaired immune responsiveness.

The effects of B cell depletion and impaired HIV-specific antibodies on SIV/HIV pathogenesis and disease progression are not clear and the results are contradictory (Mao *et al*., 2005; Miller *et al*., 2007; McKay *et al*., 2003; Mestecky *et al*., 2004; Gaufin *et al*., 2009). However, B cells are depleted and functionally impaired in pathogenic SIV-infected rhesus macaques, but not in non-pathogenic African green monkeys (Titanji *et al*., 2005; Dykhuizen *et al*., 1998; Holznagel *et al*., 2002; Steger *et al*., 1998). Non-pathogenic SIV-infected animal models also do not demonstrate gut damage or increased systemic levels of microbial products (Brenchley *et al*., 2006; Pandrea *et al*., 2007). B cell apoptosis is rare in non-pathogenic SIV-infected monkeys in the absence of gut enteropathy, B cell apoptosis is present in pathogenic SIV-infected monkeys with microbial translocation, suggesting that B cell death may be induced by HIV infection and microbial translocation.

B cells may also be activated and functionally impaired by HIV itself. It was demonstrated that B cells from HIV-infected viremic patients carry replication-competent virus on their surface through CD21, a complement receptor. It was also found that virus bound to B cells could efficiently infect activated CD4 T cells and cause B cell dysfunction (Moir *et al*., 2001; 2000). There are other mechanisms involved in HIV-associated B cell dysfunction. HIV interacts with CXCR4 (Feng *et al*., 2006) on the B cell surface and induces B cell apoptosis. HIV-1 nef protein can activate and stimulate B cells to differentiate (Chirmule *et al*., 1994; Swingler *et al*., 2003) as reflected by polyclonal activation (hyperimmunoglobulinmia) in HIV infection (Milito *et al*., 2004; Nagase *et al*., 2001). In contrast, a recent study by Qiao *et al.* (2006) shows that HIV nef protein directly inhibits B cell functional class switches. However, the mechanisms of HIV-associated B cell defects are not completely understood.

Microbial translocation may play an important role in HIV-associated B cell perturbations. Loss of memory B cells and reduced production of antigen-specific antibody is seen in the majority of chronic HIV infection even though the humoral system is subject to repeated and long-term stimulation through TLR agonists released from the gut (Brenchley *et al*., 2006; Titanji *et al*., 2006; Milito *et al*., 2004). This is not only due to desensitization since at the same time there is a B cell polyclonal activation as reflected by increased total IgM and IgG levels (Milito *et al*., 2004; Nagase *et al*., 2001). Short-term exposure to TLR ligands (e.g., CpG ODNs) enhances immune responses and has adjuvant effects (Jiang *et al*., 2007; Malaspina *et al*., 2008; McCluskie and Krieg, 2006; Krug *et al*., 2001; Jiang *et al*., 2005). However, chronic systemic exposure to microbial TLR ligands in HIV disease may have deleterious effects. Nevertheless, humoral immune dysfunction is present differently in HIV disease as reflected by enhanced ex vivo B cell apoptosis with reduced antigen-specific antibody production and polyclonal activation, as compared to other diseases occurring with microbial translocation (e.g., Inflammatory bowel disease) where the autoimmune disease appears to play an important role in immunopathogenesis and gut damage (Kazemi-Shirazi *et al*., 2002; Roggenbuck *et al*., 2009). As neither CD4/B lymphopenia nor cell-mediated immune deficiency is recognized concomitants of untreated inflammatory bowel disease (Melmed *et al*., 2010), it would appear that the virus maintains a central role in cellular and humoral immunodeficiency in HIV infection.

The loss of memory B cells may be related to increased susceptibility of these cells to apoptosis: Spontaneous B cell apoptosis *ex vivo* as measured by binding of annexin V is increased in acute and chronic HIV infection (Titanji *et al*., 2005; Samuelsson *et al*., 1997). Several cell death signaling pathways has been implicated in HIV infection, such as TNFα/TNFR, TRAIL and Fas/FasL (Lichtner *et al*., 2004; Gasper-Smith *et al*., 2008; Katsikis *et al*., 1997; Stylianou *et al*., 2002; Petrovas *et al*., 2005; Mueller *et al*., 2001 Nunnari *et al*., 2005). Moreover, studies by Susan Moir and others indicate that enhanced CD95/Fas expression on B cells in treatment-naïve HIV+ donors is related to B cell apoptosis by exogenous Fas ligand in vitro (Moir *et al*., 2004). Fas is expressed at low levels on the surface of naïve B cells and enhanced levels in memory B cells (Miyawaki *et al*., 1992; Schattner and Friedman 1996). In contrast with Fas expression, the expression of Fas ligand is reported to be much more restricted and often requires cell activation. Monocytes or macrophages are capable of producing Fas ligand after activation by opsonizedzymosan or HIV infection in

vitro (Badley *et al*., 1996; Brown and Savill, 1999). Importantly, in vivo treatment of anti-Fas ligand Ab (RNOK203) reduces cell death in circulating B cells from SIV-infected individuals and increases antibody responses to viral proteins (Salvato *et al*., 2007). Thus, a Fas/FasL-induced cell signal may be involved in B cell death in HIV infection.

Enhanced memory B cell apoptosis may result in impaired antibody responsiveness to vaccination in HIV infection.

A remaining gap in knowledge is the effect of antiretroviral therapy on microbial translocation and B cell restoration. Data from previous studies have shown that the levels of LPS and the 16s RDNA in plasma are significantly reduced after initiation of antiretroviral therapy, but never decrease to normal even among patients with restored normal CD4 counts (Brenchley *et al*., 2006). Consistent with this, B cell recovery was slower than CD4 T cell recovery after antiretroviral therapy and was also never restored to normal (Milito, 2004; Terpstra *et al*., 1989). Although the data relating to HIV-specific IgA are conflicting, it remains clear that the majority of chronically HIV-infected individuals do not mount vigorous HIV-specific IgA antibody responses either locally at mucosal sites or systemically (Mestecky *et al*., 2004; Broliden *et al*., 2001 Clerici *et al*., 2002; Devito *et al*., 2000a; 2000b).

Although short-term administration of HAART may improve antibody responses (Melvin and Mohan, 2003), long-term administration is still unable to maintain protective levels of antibodies against vaccination antigens like measles, tetanus, influenza and pneumococcus (Titanji *et al*., 2006; Hart *et al*., 2007). It suggests that low levels of microbial translocation and HIV RNA in patient plasma after HAART may contribute to the incomplete recovery of antibody responses. The further studies should be designed to be better understood the mechanisms of memory B cell apoptosis in HIV disease. This knowledge would be valuable to improve vaccine responsiveness, decrease opportunistic infections and slow down disease progression.

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