The B-cell Activating Factor/A Proliferation-Inducing Ligand System

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It cannot present MZ B-cell populations without discussing the B-cell Activating Factor/A Proliferation-Inducing Ligand System (BAFF/APRIL) system. Without a doubt, one of the most important molecules for the survival and differentiation of B-cells is BAFF. BAFF, also known as B lymphocyte stimulator (BLyS), is part of the tumor necrosis factor (TNF) family and is encoded by the TNFSF13B gene.

Keywords: marginal zone (MZ) B-cells ; B-cell activating factor (BAFF)

1. The BAFF/APRIL System

It cannot present MZ B-cell populations without discussing the B-cell Activating Factor/A Proliferation-Inducing Ligand System (BAFF/APRIL) system. Without a doubt, one of the most important molecules for the survival and differentiation of B-cells is BAFF. BAFF, also known as B lymphocyte stimulator (BLyS), is part of the tumor necrosis factor (TNF) family and is encoded by the *TNFSF13B* gene [1]. BAFF possesses three receptors found across all B-cell populations; they are BAFF-R, TACI and B-cell maturation antigen (BCMA) [2]. The latter two are also shared with the BAFF analog APRIL, encoded by the *TNFSF13* gene, with which it shares a strong homology [2].

BAFF is a transmembrane protein that can be expressed as trimers at the surface of DCs, monocytes, macrophages, activated T-cells and B-cells, neutrophils, and the stroma of secondary lymphoid organs; alternatively, BAFF can be cleaved by a furin protease and released in a soluble form [1]. Interestingly, BAFF in its soluble form can associate with 20 other BAFF trimers and form a 60-mer, a giant virus capsid-like structure that confers different signals when compared to its trimer form [3][4][5]. APRIL can only be found in a soluble form, also in trimers, since its membrane domain is cleaved in the Golgi apparatus as part of its maturation process. Interestingly, APRIL can also complex itself with heparan sulfate proteoglycans (HSPG) such as perlecan, and then bind to its receptors [6]. Furthermore, BAFF and APRIL can form heterotrimers that possess different affinities with receptors of the BAFF/APRIL system [7]. However, the precise involvement of these heterotrimers in immune responsiveness remains to be elucidated.

As previously described, BAFF-R signaling is important for MZ cell fate decision by activating the NF-kB pathway and delivering survival signals [8], and possibly by upregulating NOTCH2 expression [8][9][10]. TACI signaling, on the other hand, is mainly involved in MZ antibody production and CSR (see below) [11]. Lastly, BCMA signals play an important role in plasma cell survival and differentiation [2]. TACI signaling has been shown to reduce the activation threshold of MZ by cross-linking between the TLR pathway and the phosphatidylinositol 3-kinase (PI3K)- protein kinase B (AKT)- mechanistic target of rapamycin (mTOR), PI3K-AKT-mTOR pathway [1][12]. Furthermore, following the binding of BAFF/APRIL to TACI, recruitment of the TNF receptor associated factor (TRAF) ensues, involving TRAF2 and TRAF6, while BAFF-R signaling involves TRAF2 and TRAF3 [1]. Interestingly, TRAF3 has been shown to negatively regulate CREB, possibly modifying the transcriptional program of the B-cell to a more activated state, as the expression of CREB-induced molecules, such as NR4As, are generally related to anti-inflammatory and activation control roles [13][14]. Thus, the BAFF/APRIL system is involved in the shaping of MZ pools and their effector functions. The fact that these factors are often found to be in excess in the context of inflammation is likely to perturb MZ B-cell populations' homeostasis.

2. HIV Infection and the Dysregulation of the B-Cell Compartment

Even if HIV does not infect B-cells directly, the early and persistent inflammation associated with this infection—despite highly active antiretroviral therapy (HAART)—affects virtually all arms of the immune system, including the B-cell compartment [15].

It has been shown that BAFF levels in the blood of HIV infected individuals are in excess when compared to healthy individuals, which correlates with hyperglobulinemia and breakage of tolerance [16]. It has been shown that excess BAFF persists despite HAART in several different cohorts, as well as in simian immunodeficiency virus (SIV)-infected macaques and HIV-transgenic (Tg) mice [17][18][19][20][21][22]. As such, BAFF is one of several reliable markers of inflammation that correlates with the chronic inflammation associated with HIV infection. There are several reasons that can explain this increase in BAFF levels in HIV-infected individuals, some of which are viral factors and others of which are non-viral factors. First of all, some viral proteins detected despite HAART, such as negative regulating factor (Nef)—an accessory protein that has a key role in HIV infection—or gp120 of the HIV envelope (Env), are capable of directly up-regulating BAFF expression by MoDCs and monocytes, respectively [18][23]. Furthermore, TLR ligands and/or type I interferons (IFNs) such as interferon alpha (IFNα), abundantly produced during viral infections, lead to the production of BAFF [23][24][25]. Excess BAFF can also be caused by non-viral factors such as elements of microbial translocation, e.g., lipopolysaccharides (LPS), shown to promote BAFF expression by MoDCs [18].

Hyperglobulinemia, especially hypergammaglobulinemia (high polyclonal IgG titers in blood) is one of the main characteristics of HIV-associated B-cell deregulation, and is even one of the first ever described in people living with HIV [15][26]. Hyperglobulinemia is caused by the non-specific polyclonal activation of the B-cell compartment as a result of the excessive inflammation associated with the HIV infection context [15]. This state is fueled by the excess of pro-inflammatory cytokines such as IFN-α and TNF-α, which are produced in response to the viral infection itself [18][27]. Microbial translocation associated with massive HIV replication in the GALT also participates in the hyperactivation of the B-cell compartment via PRRs [28][29]. As mentioned above, excessive BAFF signals also favor polyclonal B-cell activation, notably that of innate-like B-cells such as MZ and MZp.

Notably, hyperglobulinemia is also associated with the presence of autoreactive antibodies. Interestingly, excess BAFF has been associated with the production of autoreactive antibodies in autoimmune diseases such as systematic lupus erythematous (SLE), rheumatoid arthritis (RA) and Sjögren syndrome (SS) [30]. This is suggested to be mainly due to the BAFF delivery of survival signals having the capacity to bypass apoptotic signals that would otherwise eliminate autoreactive B-cells during their selection in the periphery [30].

HIV infection is also characterized by the loss of circulating memory B cells, despite HAART [31][32][33]. This phenomenon could be partly explained by the downregulation of expression of BAFF-R by memory B-cells, which is essential for delivering the survival signals needed to keep these cells alive. Furthermore, in the HIV context, memory B-cells also express apoptosis markers such as CD95 (Fas), forkhead box o3 (FOXO3a) and TNF-related apoptosis inducing ligand (TRAIL), which are involved in cell death [34][35][36]. This loss of memory B-cells also affects memory generated in response to childhood vaccination antigens, further nourishing the immune incompetence observed in people living with HIV (PLHIV) [37][38].

Another important factor is the loss of $CD4^+$ T-cells, the main targets for HIV. As previously described, memory B cells result from a long process that takes place in the GC, one that requires the implication of $CD4^+$ T-cells, notably T_{fh}. Without these cells, efficient T-dependent responses cannot take place. In fact, in HIV-Tg mice and BAFF-Tg mice, the formation of GC is impaired and FDC networks reduced, with lowered expression of CD40L by activated $CD4^+$ T-cells [39][40][41][42]. Similar observations were seen in the context of human HIV infection [43][44][45][46].

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