The BAFFling problem of B cell-activating factor in nonalcoholic fatty liver disease

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Received: 18 October 2012 / Accepted: 12 December 2012 / Published online: 19 February 2013
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Nonalcoholic fatty liver disease (NAFLD) has emerged as a global health problem together with the obesity and diabetes epidemic. Currently, the spectrum of NAFLD is defined histologically as nonalcoholic fatty liver alone or simple steatosis (NAFL or SS) and nonalcoholic steatohepatitis (NASH) with or without fibrosis. Histologic details about steatosis and inflammation, cytologic ballooning, and Mallory-Denk bodies help characterize the disease spectrum. However, a noninvasive alternative to histology is presently unavailable and is an area of active investigation.

Obesity, insulin resistance, inflammation, and oxidative stress play significant roles in the development and progression of NAFLD (Fig. 1). The long-term outcome of NAFLD is influenced by the histologic spectrum (development of cirrhosis in up to 3–5 % of SS vs. 15–20 % of NASH patients). Thus, the distinction between SS and NASH is important; however, it requires a liver biopsy. Noninvasive means to differentiate the spectrum of NAFLD is being actively explored. In the current issue of *Hepatology International*, Miyake et al. have presented data on B cell-activating factor (BAFF) in an attempt to identify blood-based markers to distinguish SS from NASH.

The B cell-activating factor (BAFF, also known as BLyS, TALL-1, CD257) is a tumor necrosis factor (TNF) superfamily (TNFSF13B) member that promotes the expansion and differentiation of the B cell population leading to increased serum immunoglobulin levels [1, 2]. BAFF is an important regulator of peripheral B cell

maturation, survival, immunoglobulin production and immunoglobulin class-switch recombination (CSR), a biological mechanism by which activated B cells (plasma cells) change their antibody production from one isotype to another, for example, from IgM to IgG [3].

BAFF is mainly produced and secreted by myeloid cells (macrophages, monocytes, and dendritic cells) and also by nonlymphoid cell types and epithelial cells [3–5]. It is expressed as a type II transmembrane protein (biologically active 17-kDa molecule), and levels of BAFF are upregulated by interferon (IFN)- γ , interleukin (IL)-10, and CD40 ligand produced during inflammation and/or chronic infections [6].

The biological role of BAFF is mediated by three specific receptors (Fig. 2). BAFF receptor (BAFF-R) and transmembrane activator-calcium modulator and cyclophilin ligand interactor (TACI) are high-affinity receptors, while B cell maturation antigen (BCMA) is a low-affinity receptor [7–9]. BAFF is synthesized as a membrane-bound protein and is released as soluble BAFF by proteolysis. Soluble BAFF can then either remain as a homotrimer or transform into a capsid-like assembly of 20 trimers (60-mer) following oligomerization (Fig. 2). Downstream signaling is mediated through TNF receptor-associated factors (TRAFs). The recruitment of TRAF3 to trimeric BAFF-R activates the alternative nuclear factor- κ B2 (NF- κ B2) signaling pathway. In contrast, the recruitment of TRAF2 or TRAF6 to trimeric TACI initiates the classical NF- κ B1 pathway.

Recent evidence points to an emerging role of BAFF in adipocyte biology [10–13]. Alexaki and colleagues [10] identified BAFF-R in human adipocytes from visceral adipose tissue (VAT). Further, Hamada et al. [11] demonstrated that BAFF-treated mice had higher TNF- α , IL-6, and resistin gene expression in VAT, while adiponectin

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Fig. 1 Putative role of B-cell activating factor (BAFF) in the pathogenesis of nonalcoholic fatty liver disease (NAFLD). *NAFL* non alcoholic fatty liver, *SS* simple steatosis, *NASH* non alcoholic steatohepatitis

gene expression decreased, contributing to adipocyte insulin resistance. In addition, BAFF was shown to directly affect the glucose uptake and phosphorylation of insulin receptor substrate-1 in adipocytes. This underlines the role of BAFF in impaired insulin sensitivity via inhibition of insulin signaling pathways and alterations in adipokine production.

Increased serum BAFF levels have been linked to autoimmune disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjogren's syndrome, systemic sclerosis, etc., as well as allergic diseases, infections, and malignancies, suggesting the potential role of BAFF in different diseases. Interestingly, BAFF has also been associated with other liver diseases such as hepatitis C [14], primary biliary cirrhosis (PBC) [15], and autoimmune hepatitis where corticosteroid therapy markedly reduced serum BAFF levels in AIH [16]. Also, elevated serum BAFF levels were associated with advanced interface hepatitis in PBC patients [15].

In this issue of *Hepatology International*, Miyake et al. have demonstrated that NASH patients had higher serum levels of BAFF compared to those with SS in their article "B cell activating factor is associated with the histological severity of nonalcoholic fatty liver disease." Further, cytologic ballooning and advanced fibrosis in NAFLD patients were associated with higher serum levels of BAFF. No such association was noted with hepatic steatosis, inflammation, NAFLD activity score (NAS), and other histologic features. Similarly, serum BAFF levels had no biochemical association with other inflammatory markers or with the presence or absence of ANA in patients with NAFLD.

Obesity, insulin resistance, inflammation, and oxidative stress play a significant role in the development and progression of NAFLD. Emerging evidence suggests that

Fig. 2 Schematic illustration of B-cell activating factor (BAFF) signaling pathway. It is initiated through binding of soluble BAFF trimer to BAFF receptor (BAFF-R), TNF receptor-associated factors (TRAFs), transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) and B cell maturation antigen (BCMA). These interactions mediate downstream signaling through alternate and classical nuclear factor-κB (NF-κB) pathways

BAFF may relate to these pathophysiologic links in NAFLD. However, in this study, no association or correlation of BAFF was found with the body mass index or visceral fat area. Although it is intriguing not to see an association of BAFF with obesity, insulin resistance, and inflammatory and autoimmune markers, these can presumably be related to the following: (1) type II error given a small study population ($n = 96$, 76 with NASH) with an even smaller sample of SS ($n = 20$); (2) a wide range of serum BAFF values with a lot of overlap in BAFF values among variables studied resulting in a large variance and standard deviations limiting its utility to discriminate SS and NASH; (3) multiple medications for diabetes, hyperlipidemia, and hypertension confounding serum inflammatory marker studies and limiting studies to evaluate the effect on insulin resistance; and (4) no well-defined range of normal serum BAFF levels which can introduce a lot of variation in data interpretation and analysis.

Interestingly, high serum BAFF levels were associated with ballooning hepatocytes and advanced fibrosis. "Ballooning" is a frequently used yet ill-defined term in liver morphology indicating hepatocyte degeneration associated with enlargement, swelling, rounding, and characteristic reticulated cytoplasm and generally regarded as a form of apoptosis [17]. The intermediate filament (IF) cytoskeleton plays a major role in the stabilization and topographical organization of a cell and its organelles. In hepatocytes, IFs consist of type I keratin (K) 18 and type II K8 noncovalently assembled in an equimolar ratio [18–20]. "Ballooned" hepatocytes on immunohistochemical staining

Fig. 3 Proposed model for role of B-cell activating factor (BAFF) in characteristic histologic changes of hepatocyte ballooning and hepatic fibrosis. These changes can also increase the potential for hepatocellular carcinoma (HCC). *EC* endothelial cell, *ECM* extracellular matrix

with antibodies against K8 and K18 revealed a deranged IF network [21]. Inflammation and oxidative stress lead to hepatocyte ballooning and apoptosis and have been shown to result in elevated circulating cytokeratin 18 (CK-18) [22]. Inflammation and oxidative stress also contribute to hepatic fibrosis, and serum BAFF levels have been shown to be associated with advanced fibrosis, as observed in this study.

Although this study was not designed to investigate the putative mechanism of these associations, a proposed pathophysiologic link can be nuclear factor kappa light-chain enhancer of activated B cells (NF-κB). Chronic inflammation and oxidative stress can induce an alternate pathway of NF-κB through BAFF and result in downstream effects of hepatocyte ballooning and activation of hepatic stellate cells promoting fibrosis. The mechanism of BAFF signaling and the proposed pathway are illustrated in Figs. 2 and 3. This line of evidence can be explored in future investigations. It will also be reasonable to evaluate the role of BAFF and insulin resistance in nondiabetic NAFLD patients.

Finally, what is the utility of serum BAFF as a diagnostic tool in NAFLD based on the current study? An ideal biomarker is highly specific, sensitive, predictive, robust, generalizable, easily available, and affordable. Serum BAFF in this study has a low specificity of 50 % with a good sensitivity of 93.4 %, positive predictive value of 87.6 %, negative predictive value of 66.7 %, and diagnostic accuracy of 84.3 %. Additionally, serum BAFF levels do not even reflect the specificity to liver diseases as serum BAFF levels were

increased in chronic hepatitis C, AIH, and PBC. Augmented BAFF signaling can contribute to the development and progression of chronic diseases such as NAFLD. Further studies are needed to evaluate, establish, and validate the role of BAFF in NAFLD compared to other populations including appropriate controls. Efforts can then be directed in the development of a diagnostic panel with either BAFF alone or a combination of other markers such as cytokeratin-8/18. BAFF also appears to be an attractive treatment target. Recently, belimumab, a humanized monoclonal antibody against BAFF, has been approved by the US Food and Drug Administration for the treatment of SLE [23, 24]. This drug or similar strategies targeting BAFF signaling can be a promising approach in the treatment and monitoring of NAFLD. Future studies will continue to explore the development of noninvasive markers in the diagnosis and monitoring of NAFLD and potential novel therapies.

References

- Moore PA, Belvedere O, Orr A, et al. BLyS: member of the tumor necrosis factor family and B lymphocyte stimulator. *Science*. 1999;285:260–263.
- Schneider P, MacKay F, Steiner V, et al. BAFF, a novel ligand of the tumor necrosis factor family, stimulates B cell growth. *J Exp Med*. 1999;189:1747–1756.
- Mackay F, Browning JL. BAFF: a fundamental survival factor for B cells. *Nat Rev Immunol*. 2002;2:465–475.
- Moisini I, Davidson A. BAFF: a local and systemic target in autoimmune diseases. *Clin Exp Immunol*. 2009;158:155–163.
- Ng LG, Mackay CR, Mackay F. The BAFF/APRIL system: life beyond B lymphocytes. *Mol Immunol*. 2005;42:763–772.
- Morimoto S, Nakano S, Watanabe T, et al. Expression of B-cell activating factor of the tumor necrosis factor family (BAFF) in T cells in active systemic lupus erythematosus: the role of BAFF in T cell-dependent B cell pathogenic autoantibody production. *Rheumatology*. 2007;46:1083–1086.
- Mackay F, Schneider P, Rennert P, Browning J. BAFF AND APRIL: a tutorial on B cell survival. *Annu Rev Immunol*. 2003;21:231–264.
- Martin F, Chan AC. B cell immunobiology in disease: evolving concepts from the clinic. *Annu Rev Immunol*. 2006;24:467–496.
- Sutherland AP, Ng LG, Fletcher CA, et al. BAFF augments certain Th1-associated inflammatory responses. *J Immunol*. 2005;174:5537–5544.
- Alexaki VI, Notas G, Pelekanou V, et al. Adipocytes as immune cells: differential expression of TWEAK, BAFF, and APRIL and their receptors (Fn14, BAFF-R, TACI, and BCMA) at different stages of normal and pathological adipose tissue development. *J Immunol*. 2009;183:5948–5956.
- Hamada M, Abe M, Miyake T, et al. B cell-activating factor controls the production of adipokines and induces insulin resistance. *Obesity (Silver Spring)*. 2011;19:1915–1922.
- Kim YH, Choi BH, Cheon HG, Do MS. B cell activation factor (BAFF) is a novel adipokine that links obesity and inflammation. *Exp Mol Med*. 2009;41:208–216.
- Pelekanou V, Kampa M, Kafousi M, et al. Expression of TNF-superfamily members BAFF and APRIL in breast cancer:

- immunohistochemical study in 52 invasive ductal breast carcinomas. *BMC Cancer*. 2008;8:76.
14. Toubi E, Gordon S, Kessel A, et al. Elevated serum B-Lymphocyte activating factor (BAFF) in chronic hepatitis C virus infection: association with autoimmunity. *J Autoimmun*. 2006;27:134–139.
 15. Migita K, Ilyassova B, Kovzel EF, et al. Serum BAFF and APRIL levels in patients with PBC. *Clin Immunol*. 2010;134:217–225.
 16. Migita K, Abiru S, Maeda Y, et al. Elevated serum BAFF levels in patients with autoimmune hepatitis. *Hum Immunol*. 2007;68:586–591.
 17. Yip WW, Burt AD. Alcoholic liver disease. *Semin Diagn Pathol*. 2006;23:149–160.
 18. Denk H, Stumptner C, Zatloukal K. Mallory bodies revisited. *J Hepatol*. 2000;32:689–702.
 19. Omary MB, Ku NO. Intermediate filament proteins of the liver: emerging disease association and functions. *Hepatology*. 1997;25:1043–1048.
 20. Omary MB, Ku NO, Toivola DM. Keratins: guardians of the liver. *Hepatology*. 2002;35:251–257.
 21. Zatloukal K, Stumptner C, Fuchsbichler A, et al. The keratin cytoskeleton in liver diseases. *J Pathol*. 2004;204:367–376.
 22. Tamimi TI, Elgouhari HM, Alkhouri N, et al. An apoptosis panel for nonalcoholic steatohepatitis diagnosis. *J Hepatol*. 2011;54:1224–1229.
 23. Navarra SV, Guzman RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet*. 2011;377:721–731.
 24. Vincent FB, Morand EF, Mackay F. BAFF and innate immunity: new therapeutic targets for systemic lupus erythematosus. *Immunol Cell Biol*. 2012;90:293–303.