B-Cell Activating Factor in IBD

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B-cell activating factor (BAFF), a member of the tumor necrosis factor (TNF) superfamily. BAFF is predominantly produced by myeloid cells (monocytes, macrophages, dendritic cells and neutrophils), and its main role is regulation of mature B cell survival and differentiation into antibody-producing plasma cells. Overproduction of BAFF has been observed in various autoimmune diseases, most notably in systemic lupus erythematosus (SLE), where BAFF-inhibitor belimumab was approved for treatment.

B-cell activating factor inflammatory bowel disease

1. Role of B-Cells in IBD

Despite myriad of distinct biological pathways have been implicated in its pathophysiology, it is generally believed that IBD is a result of a maladaptive immune response to gut-resident commensal bacteria in a genetically susceptible host [1]. Inflammation in CD seems to be mainly driven by T_h1 responses, whereas T_h2 responses dominate the pathobiology of UC [2]. Nevertheless, additional lymphocytes, such as innate lymphoid cells and T_h17 cells have also arisen as key players in the pathogenesis of IBD [3]. Specifically, abnormal pro-inflammatory $CD4^+$ T-cell responses mediated by effector T_h1, T_h2, or T_h17 cells disrupt homeostasis and causes IBD by outweighing anti-inflammatory $CD4^+$ T-cell responses orchestrated by T regulatory (T_{reg}) cells [4]. Even though T-cell system is predominant in studies concerning the IBD pathogenesis and therapeutic approach, emerging data suggest a role of B-cell lineage in IBD as well. Firstly, humoral homeostasis seems to be impaired in IBD. For instance, it has been shown that production of functional, dimeric immunoglobulin A (IgA) is impaired in patients with IBD [5]. As IgA exerts local anti-inflammatory effects by coating commensal bacteria after undergoing transepithelial translocation in gut, its depletion favors gut inflammation [6]. Moreover, B-cell expression of the pro-inflammatory cytokine IL-8, as well as production of mucosal IgG in gut are upregulated in IBD, thereby further promoting inflammation [7][8]. Accordingly, expression of both IL-8 and TLR-2 in IBD patients positively correlated with CD activity [8][9][10].

In murine IBD model, poorly regulated B-cells have been shown to exacerbate inflammation by blocking T_{reg} cell function [11][12]. Moreover, B-cells promote ileitis in UC by producing epithelial cell-specific autoantibodies [11][13]. Mucosal IgG in IBD can be directed against microbial elements, such as anti-saccharomyces-cerevisiae antibodies (ASCA) and anti-flagellin antibodies, or autoantigens, such as anti-neutrophil cytoplasmic antibodies (ANCA) and anti-epithelial antibodies [14][15]. Notably, the role of anti-granulocyte macrophage colony-stimulating factor (anti-GM-CSF) in IBD is fairly complex, yet the presence of anti-GM-CSF in the setting of IBD is associated with ileal phenotype and intricated behavior of the disease [16]. The latter observation is in line with preclinical data, as NOD2

KO mice treated with anti-GM-CSF antibodies develop transmural ileitis subsequent to NSAID exposure [16]. Alterations of the B-cell lineage in IBD are less obvious, and more complex for that matter, than those associated with derangement of T-cell system [17]. Acknowledgement of poor understanding of the complexity of B-cell responses in IBD allows us to evaluate recently failed therapeutic attempts in UC involving the CD20-targeting agent rituximab more critically [18]. Namely, negative outcomes of therapeutic approaches including rituximab should not discourage from considering B-cells as potential therapeutic target in IBD, especially since unresponsiveness to rituximab can be also observed in certain cases of B-cell-related autoimmune disorders such as rheumatoid arthritis (RA) and vasculitis [19][20]. For example, in certain group of patients, paradoxical pro-inflammatory manifestations can occur subsequent to rituximab administration [21][22]. While dysfunctional B-cell lineage can promote autoimmunity via autoreactive, long-lived plasma cells, regulatory B-cells can attenuate inflammation too. For instance, anti-CD20-treated mice deficient in peripheral B-cells failed to undergo spontaneous recovery and even developed chronic disease in a model of murine autoimmune encephalomyelitis [23][24]. In addition, B-cells may produce anti-inflammatory IL-10 but may also promote the anti-inflammatory effect of T_{reg} cells [25]. Even more perplexing is the fact that tissue resident plasma cells do not express CD20 and thus cannot be targeted by rituximab [26]. In the setting of IBD, in vitro experiment showed that plasma cells subset expanded in the mucosa of IBD patients and was resistant to rituximab-induced apoptosis [27]. Nevertheless, evidence of rituximab in IBD is conflicting, as some studies showed that rituximab could improve colonic inflammation, whereas case reports showed that rituximab could trigger colitis [28][29][30][31]. In fact, a retrospective cohort study showed that patients on rituximab have a sixfold increased risk of developing IBD compared to the general population [32]. Finally, a phase II randomized controlled trial, in which effects of rituximab on UC patients was assessed, showed no significant effect on inducing remission in moderately active UC not responding to oral steroids with possible short-term response that was not sustained [28].

2. Pathophysiological Background of BAFF in IBD

Even though BAFF is widely considered as a cytokine affecting B-cells primarily, and to a lesser extent T-cells, BAFF has been also shown to affect innate immunity by multiple effector arms [33]. Namely, it has been well documented that BAFF improves human monocyte survival, upregulates proinflammatory cytokine secretion, and positively regulates secretion of multiple costimulatory molecules [34]. These findings may be important for explaining the role of BAFF in IBD, as genome-wide association studies have highlighted the importance of host innate immune responses to microbes in the pathogenesis of IBD [31]. Single nucleotide polymorphisms associated with increased risk of developing IBD were identified in genes encoding microbial sensing and clearance, as well as integrating antimicrobial adaptive immune responses [35]. Accordingly, evidence suggests that macrophages and dendritic cells residing in gastrointestinal system have important interactions with the microbial environment, resolution of mucosal inflammation, proinflammatory tissue injury, and induction of adaptive immune responses [36][37][38]. Despite the presence of BAFF is most commonly associated with the induction of autoimmune inflammation, alternative function including induction of B regulatory cells that protect the intestinal mucosa from inflammatory injury has also been explored [39]. It was recently demonstrated that mice with DSS-colitis exhibit a persistent decrease in colonic CD5(+) regulatory B-cells (B_{reg}), suggesting that persistent altered mucosal B-cell population

caused by chronic gut inflammation may be involved in the pathogenesis of IBD [40]. These conclusions were corroborated in a small-sample clinical study, as UC patients had significantly reduced frequencies of CD5(+) B_{reg} in peripheral blood and intestinal tissues, accompanied by lower serum IL-10 levels [41]. In the same study, Mayo clinic scores, CRP, and ESR in UC patients negatively correlated with the frequency of B_{reg} and the IL-10 concentration. Nevertheless, as we further discuss, BAFF serum levels positively correlate with clinical disease activity and inflammatory biomarkers, thus indicating that the role of BAFF in IBD is primarily proinflammatory [42]. Finally, the strongest evidence indicating contribution of BAFF to IBD pathogenesis is data from colonic biopsies from UC and CD patients [42]. In colonic bioptates of both UC and CD patients, mRNA and BAFF protein expression were higher than in the control group. Furthermore, in inflamed regions of UC mucosa, upregulation of BAFF was predominant in mononuclear cells residing in lamina propria [42].

Finally, an important link connecting BAFF with IBD is the Nuclear Factor kappa-light-chain-enhancer of activated B-cells (NFκB), protein complex involved in control of transcription of DNA in almost all mammalian cells [43]. In response to various pro-inflammatory stimuli, NFκB activates and leads to in the increased expression of adhesion molecules and chemokines by endothelial cells and in the tissue, thus favoring the recruitment and activation of effector immune cells [44]. Multiple line of evidence suggests important role of NFκB activation in IBD pathogenesis [45][46]. Activation of NFκB is detected in both epithelial cells and macrophages from IBD patients and relates to the intensity of inflammation [47]. Furthermore, administration of antisense phosphorothioate oligonucleotides to the p65 subunit of NFκB has been shown to suppress colitis in mice model of TNBS-induced colitis [48]. Finally, effectiveness of corticosteroid treatment in IBD flares is in part owing to steroid-induced decrease of NFκB activation [49]. As BAFF is capable of activating NFκB in lymphoid and myeloid cells via both canonical and non-canonical pathway, thus promoting intestinal inflammation, it is plausible that NFκB is the missing link between BAFF and IBD [50].

3. Clinical Implications of BAFF in IBD

In light of the prominent role of BAFF in B-cells and autoimmunity, Zhang et al. sought to explore the putative role of BAFF in management of IBD [42]. The principal aim of that pivotal study was to determine the value of BAFF to discriminate patients with IBD from healthy controls and patients with IBS by measuring BAFF serum and fecal levels, as well as its mucosal expression. An additional aim was to establish whether there is a correlation between BAFF and disease activity in IBD patients. It was demonstrated that BAFF expression is increased in serum, feces and colonic mucosa of patients with IBD when compared to controls. Moreover, in comparison to IBS patients, significantly higher fecal BAFF concentrations were observed in patients with IBD, regardless of disease activity, with fecal BAFF concentrations in IBS patients being identical to those of healthy controls. In fact, for BAFF fecal levels above cut-off of 325 pg/mL, respectively. Even higher sensitivity (90%) was observed for discrimination between active IBD and IBS/healthy controls, which is in line with strong positive correlations observed between BAFF and disease activity, TNF-α and IL-1β in patients with UC. The discriminative power of serum BAFF had comparable specificity (93%), but markedly lower sensitivity (55%) than fecal BAFF. Nevertheless, it appears that, following the reduction in disease activity, BAFF serum levels return to values similar to that of healthy subjects

rapidly, unlike BAFF levels in feces which persist much longer. Thus, it is plausible that serum BAFF may be utilized in monitoring the disease activity.

Clinical distinction between IBD and IBS is of utmost importance, as these two conditions can present similar symptoms, but have very different underlying pathophysiology and, more importantly, severity of consequences [51]. In the absence of additional symptoms indicating on IBD, such as rectal bleeding and systemic illness, it is very challenging to distinguish between the two. On the other hand, although it is a common practice, it is not cost-effective to use colonoscopy as a part of diagnostic algorithm in the workup of patients suspected of having IBS [52] [53]. Moreover, colonoscopy is associated with serious complications such as bleeding and perforations, adverse events related to the anesthesia, and increased discomfort of patients [54]. Hence, it would be beneficial to use sensitive and specific biomarker for IBD/IBS differentiation. So far, calprotectin has been used for this purpose with relative success owing to sufficient sensitivity, yet what calprotectin lacks is adequate specificity [55].

In this sense, Fu et al. compared the efficacy of fecal BAFF, calprotectin and fecal occult blood test (FOBT) to find the “best non-invasive marker” [56]. The study showed that for discriminating IBD from IBS, fecal BAFF ≥ 227.3 pg/mL yielded 84% sensitivity and 100% specificity, calprotectin ≥ 50 µg/g yielded 76% sensitivity and 93% specificity whereas FOBT yielded 65% sensitivity and 93% specificity. Moreover, combination of BAFF with calprotectin yielded 94% sensitivity and 93% specificity, thus increasing the accuracy of differential diagnosis. Notably, fecal BAFF concentration exhibited stronger correlation with endoscopic inflammatory score in comparison to calprotectin in both UC (r = 0.69, $p < 0.0001$ vs. $r = 0.58$, $p < 0.0001$) and CD ($r = 0.58$, $p < 0.0001$ vs. $r = 0.52$, $p = 0.0003$). Accordingly, a separate study confirmed that fecal BAFF is more sensitive and specific in predicting UC activity and severity than fecal calprotectin [57]. On a separate note, neither fecal BAFF nor calprotectin showed significant correlation with Crohn’s Disease Activity Index (CDAI) in CD patients, yet they both showed correlation with Mayo score in patients with UC ($r = 0.415$ and 0.365, respectively). Furthermore, Xie et al. explored whether BAFF can discriminate patients with IBD and malignancy from other gastrointestinal diseases among population of patients presenting with abdominal discomfort [58]. It was demonstrated that fecal BAFF was able to accurately distinguish patients with either IBD or tumor from patients without any of these, giving a sensitivity of 85% and specificity of 91%. On the other hand, BAFF was also able to discriminate IBD from patients without it with sensitivity of 89% and specificity of 77%. An important finding of this study is that BAFF was found to be temperature-stable for 7 days and equally distributed in the feces, thus implying that for BAFF measurement no specific storage conditions are required and only a small number of samples are needed to accurately measure it. Altogether, the above-noted results imply that BAFF could be used as a complementary biomarker in diagnostic workup of patients with suspected IBD and that it may also be utilized as a sensitive surrogate for assessment of endoscopic inflammation in IBD. Nevertheless, further research is warranted to elucidate in deep the values of fecal BAFF in IBD clinical scenery, such as whether fecal BAFF can be used to predict relapse in IBD patients in remission, as shown in calprotectin [59].

Usefulness of BAFF in the setting of IBD has been explored in pediatric population as well. The problem of IBD diagnosis and follow-up represents an even bigger challenge children then among the adults. Firstly, colonoscopy is not easily accepted by children nor caregivers compared to adults [60]. Moreover, currently no consensus was

established with regard to the definition of remission in pediatric IBD. The term “clinical remission” is the most widely accepted term defined by composite scores based on clinical parameters (abdominal pain, rectal bleeding, stool frequency and consistency, number of stools per 24 h, nocturnal stools, activity level, weight). Notably, laboratory findings (ESR and albumin) are used in the wPCDAI score exclusively. As multiple studies showed that there is a discrepancy between the clinical remission and the laboratory, endoscopic and histologic findings, there is a need for a comprehensive approach, including clinical, imaging, histologic and laboratory parameters [61][62][63]. In a recent prospective study, Fodor et al. found no differences in serum BAFF between IBD, IBS, and healthy group, yet they found that fecal BAFF was higher in the IBD group in comparison to IBS and healthy group [64]. In comparison of different types of IBD, it was shown that BAFF is higher in pediatric patients with UC compared to CD patients. ROC curve analysis for fecal BAFF showed that with cut-off of 16 pg/mL, sensitivity and specificity for discrimination between IBD and IBS in pediatric population is 51% and 93%, respectively. The observed lack of sensitivity could be owing to the fact that only mild cases of IBD were included and limited number of participants. Finally, as fecal BAFF was the highest in patients with increased calprotectin levels, the authors proposed that fecal BAFF may be a promising marker in the evaluation of the remission status in pediatric IBD.

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