Exploring BAFF: its expression, receptors and contribution to the immunopathogenesis of Sjögren’s Syndrome

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ABSTRACT

Sjögren’s syndrome (SS) is an autoimmune condition characterized by exocrine gland destruction and systemic complications associated with lymphocytic infiltration of many organs, autoantibody production and immune complex deposition. Genetic, environmental and viral factors play a role in disease aetiology; however the exact mechanisms driving the immunopathogenesis of SS remain uncertain. Here we discuss a role for B-cell activating factor (BAFF), whereby B cell hyperactivity and increased BAFF secretion, both observed frequently in patients and animal models of the disease, can be explained by the expression of cell specific or ‘pseudo’ BAFF-receptor and/or ‘pseudo’ BAFF in several immune cell types. Understanding the role of BAFF heterogeneity in SS pathogenesis could help to facilitate new treatment strategies for patients.

Key words: B-cell activating factor (BAFF); BAFF-receptor; Sjögren’s syndrome
INTRODUCTION

Sjögren’s syndrome (SS) is a chronic autoimmune disorder affecting approximately 0.1–0.4% of the general population with a female-to-male ratio of 9:1 usually diagnosed in the fourth and fifth decades of life [1]. Clinically, SS is typified by ocular and oral dryness developed as a consequence of the autoimmune process. It may occur either alone, as primary (p)SS, or secondary to other autoimmune disease, often rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) or systemic sclerosis, as secondary (s)SS. Clinical, laboratory and histological features can be used to classify the systemic manifestations of SS as peri-epithelial or tissue-specific (including liver, lung and kidney) or extra-epithelial, including vasculitis, peripheral neuropathy, kidney glomerulonephritis and myositis [2]. In addition, there is an increased risk of developing non-Hodgkin’s B cell lymphoma [1, 3]. Both humoral and cellular arms of innate and adaptive immune responses are involved in disease pathogenesis [1, 4, 5] which is characterized by infiltration of the salivary and lacrimal glands by T and B lymphocytes, dendritic cells (DCs), macrophages and other mononuclear cells leading to tissue destruction [4]. B cell hyperactivity is a dominant feature of SS, manifested by hypergammaglobulinemia, multiple autoantibody production and cryoglobulins [1]. Autoantibodies against components of ribonucleoproteins, such as anti-Ro52, anti-Ro60 and anti-La, are included in the diagnostic criteria for SS and correlate with early disease onset, increased disease duration, parotid gland enlargement, extra glandular manifestations and lymphocytic glandular infiltration, features seen in 60-70% of SS patients [2, 4]

B CELLS AND BAFF AND THEIR ROLE IN pSS PATHOGENESIS

Introduction to BAFF

B cell activating factor (BAFF; also known as B lymphocyte stimulator, BLyS) and a proliferation-inducing ligand (APRIL) are members of the tumour necrosis factor (TNF) superfamily of soluble and membrane-bound proteins that regulate immune responses [6,
BAFF and APRIL are cytokines that share biological functions, they promote B-cell survival and maturation and are expressed as membrane bound or soluble proteins [6]. BAFF is produced by many cell types including antigen presenting cells (B cells, monocytes/macrophages, DCs, plasmacytoid DCs, follicular DCs), neutrophils, epithelial cells (EC) and activated T lymphocytes [8]. BAFF messenger ribonucleic acid (mRNA) has also been detected in bone marrow-derived stromal cells, astrocytes, and fibroblast-like synoviocytes in response to pro-inflammatory cytokines [8, 9]. BAFF is a type II membrane-bound protein (mBAFF) that is released from cells via proteolytic cleavage mediated by metalloproteases from a furin protease site and released in a soluble form [8, 10]. Soluble (s)BAFF can exist as trimers or multimers (BAFF-60-mers) as well as in glycosylated or non-glycosylated forms [6].

BAFF binding to BAFF-R triggers the so-called non-canonical NF-κB signalling pathway and facilitates peripheral B cell survival and differentiation, germinal centre formation, plasma cell survival and IgG and IgE class switching [11]. Engagement of the BAFFR induces the recruitment of intracellular tumor necrosis factor receptor (TNFR)-associated factor (TRAF)-3 and TRAF-2 to the intracellular domain of the BAFFR molecule. Binding of TRAF3 to the BAFFR reverses the inhibitory effect of unbound/cytoplasmic TRAF3 on the alternative nuclear factor-κB2 (NF-κB2) signalling pathway and releases NIK (NF-κB-inducing kinase) which phosphorylates IKK1 leading to activation of non-canonical NFκB [8]. BAFFR signalling is associated with signalling via the BCR and both are critical for peripheral B cell survival and differentiation, germinal centre formation, plasma cell survival and IgG and IgE class switching [12].

Both sBAFF and mBAFF are biologically active, inducing a range of functions in a variety of cell types. Primarily, sBAFF binds to B cells and promotes their survival and proliferation. Indeed the level of BAFF might set a threshold for naïve B-cell selection, autoreactive B cells
have a higher dependence on BAFF compared to naïve mature B cells and experimental models show that overexpression of BAFF in lymphoid tissues is associated with mature B cell hyperplasia and the development of SLE and SS-like symptoms [13, 14]. Alternatively, BAFF stimulation in other cell types induces enhanced epithelial cell survival, interleukin (IL-2) and interferon gamma (INF-γ) production by CD4+T cells and peripheral blood mononuclear cell proliferation which is inhibited by blocking the BAFF-R [10]. BAFF expression is increased in the presence of type I interferons, IFNγ, IL-10 and granulocyte colony-stimulating factor as well as by Toll-like receptor (TLR)3, TLR4 or TLR9 stimulation [8, 15].

Splice variants of BAFF have been described, including delta (Δ)BAFF, first identified in macrophages and mouse and human derived myeloid cell lines [16, 17]. ΔBAFF binds to BAFF in disulfide-bonded heteromultimers and limits BAFF proteolytic cleavage from the cell surface [17]. Furthermore, soluble forms of BAFF/ΔBAFF heteromultimers bind poorly to BAFF receptors in comparison to heteromultimers of BAFF; therefore suppressing BAFF through competitive association. Also, ΔBAFF cellular expression down-regulates BAFF ability to be shed in the extracellular space. Δ4BAFF, an alternative-splice isoform, acts as a transcription factor to enhance BAFF production in auto-immunity and cancer [18] and psi BAFF (ΨBAFF) resulting from the incomplete splicing of intron sequences; creating a long non-functional transcript in humans [19]. Δ5BAFF has been reported in mice [18]. Soluble BAFF binds to three receptors that are present on several immune cell types, BAFF-receptor (R) (also known as TNFR superfamily member 13C and BR3 [6]), TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor, also known as TNFR superfamily member 13B) and BCMA (B-cell maturation antigen, also known as tumor necrosis factor receptor superfamily member 17) [7, 8] BAFF-R is expressed on all B cells (but not plasma cells) and on central and effector memory (but not naïve) T cells [20], especially upon their activation, and interacts with BAFF exclusively [8]. BAFF-R has also been described in the human macrophage-like cell line
THP-1 cells upon stimulation and on the TF-1 human monocytic cell line [21]. BCMA binds APRIL with higher affinity than BAFF, while TACI binds both ligands. BAFF binding to its receptors will elicit signal transduction through several pathways, while BAFF binding to TACI has an inhibitory role on BAFF activity [11].

Thus BAFF binding to the group of BAFF receptors is a complex mix of interactions comprising membrane and soluble forms that are able to stimulate cells in different ways, both via membrane-bound BAFF receptors and via membrane bound BAFF [8]. B cells derived from a murine plasmacytoma cell line were stimulated more potently via mBAFF compared to sBAFF and also, the mBAFF co-stimulated T cells through their BR3 receptor, signifying that mBAFF plays a role in cell-to-cell communication [10]. Soluble forms of BAFF receptors, TACI-Fc and BAFF-R-Fc, are able to stimulate murine bone marrow-derived macrophages, and human myeloid cell lines THP1 and U937 via so called ‘reverse signalling’ [21]. mBAFF binding to sBAFF-R promoted the expression of inflammatory mediators while reducing cytoskeletal movement associated with phagocytosis and transmigration [21]. Understanding these interactions is important for identifying the role of BAFF in the pathogenesis of SS. The known actions of BAFF from current literature are summarized in Figure 1.

**Experimental models of SS**

Several animal models of SS exist, each specific for an abnormality but none representing all the characteristics associated with patients with pSS. We review here only the BAFF related animal models.

The BAFF-transgenic mouse model is characterized by B cell hyperplasia with transitional (T) II B cell and marginal zone-like B cell infiltration of the salivary glands. However, the absence of female sex predominance, autoantibodies, the accumulation of marginal zone B
cells elsewhere in addition to the salivary glands, and the absence of T cell infiltration differentiate this model from the classical features of the human disease [22].

BAFF-transgenic mice lacking lymphotoxin-beta/delta have altered splenic histology, being characterized by a lack of marginal zone B cells, display enlarged peripheral lymph nodes and are unable to provide T cell-dependent immune responses [23]. BAFF-transgenic mice lacking TNF have expanded TII and marginal zone B cell populations, enhanced T-independent immune responses and an elevated incidence of B cell lymphomas [24]. Both BAFF and CD40 play an important role in B cell survival and differentiation. The adaptor molecule Act1 is a negative regulator of BAFF and CD40 mediated B cell survival. The CD40-Act1 and BAFF-Act1 double knockout mouse model of SS has reduced enlargement of lymph nodes and spleen compared to Act1-deficient mice [25]. Complete loss of Act-1 or B cell over-signaling resulted in SS-like pathology. BALB/C mice lacking Act1 develop systemic autoimmunity similar to SLE and SS [26].

In the ΔBAFF transgenic model described by Gavin et al. [17] it was observed that ΔBAFF reduced B cell activation and opposed BAFF activity. Reduced B cell frequencies were observed in these mice in the TII and later stages of B cell development. These stages were thought to be the point at which BAFF exerts its biological effect on B cell development [17]. Immunization with trinitrophenyl-Ficoll or trinitrophenyl-hemocyanin (used to induce B cell antibody responses) resulted in reduced B cell numbers and T cell-dependent immune responses, but not T cell-independent responses in ΔBAFF transgenic mice compared to wild-type and BAFF transgenic mice [17]. Interestingly, Gavin et al. [17] observed that residual B cells in BAFF-/- mice were not affected by ΔBAFF expression. The ratio of BAFF to ΔBAFF produced by primary myeloid cells could depend on the mode of their activation. IFN stimulation of salivary gland epithelial (SGE) cells from SS patients was associated with increased BAFF and to a lesser extent ΔBAFF levels, an increased BAFF:ΔBAFF ratio could perpetuate autoimmunity [27].
**BAFF in patients with SS**

In pSS BAFF expression is elevated and acts as a link between innate immune activation (possibly linked to infection initiating disease onset) and chronic autoimmune B cell activation. Over activation of B cells in patients is linked to the higher frequency of non-Hodgkin’s B cell lymphomas found in pSS patients compared with the general population [3]. BAFF has been shown to influence the development of SS in both animal models and patients where its expression is induced by type I and type II IFNs [4, 28, 29]. BAFF is critical for B cell survival in the periphery [30], however in pSS BAFF is also produced in secondary and tertiary lymphoid organs containing germinal centres (GC) [1]. BAFF can be secreted by human SGE cells following type I IFN stimulation and viral infection, these cells activate B cells by the local secretion of BAFF but can also present autoantigens [1, 15]. Abundant BAFF expression is a consequence of the reduced levels of B cell apoptosis in SS salivary gland cells, and leads to excessive B cell activation and increased risk of lymphoma [1, 31].

**Nocturne and Mariette** [4] found that GC-like structures occur within the glandular epithelium in pSS patients. The epithelial expression of specific homing molecules, such as CXCR5 and its ligand CXCL13, promote GC-like structure development and organisation. Activation of B cells within these structures drives the production of the characteristic autoantibodies in pSS patients [4]. However controversy exists surrounding the role of BAFF in this process. Li, et al. [32] observed increased BAFF expression in SGE cells in SS patients treated with oral interferon (IFN) and also upon in vitro stimulation by IFN-α, but not IFN-γ or TNF-α. BAFF accumulating adjacent to transitional and marginal-zone–like B lymphocytes, is thought to provide the stimulus for the differentiation of transitional type I (TI) B cells into TII B cells [33]. However, BAFF levels in the peripheral blood and saliva of pSS patients vary between studies [9, 31]. A correlation between serum and saliva BAFF levels and autoantibody production in patients with pSS has been described [9]. In other studies,
BAFF expression levels in SGE cells were either normal or lower than in the serum [27]. Such discrepancies could reflect the existence of different subgroups of pSS patients.

BAFF is also associated with monocyte activation. Monocytes isolated from peripheral blood of pSS patients produced significantly higher amounts of sBAFF and IL-6 than monocytes from healthy donors, even in the absence of stimulation [34]. The expression levels of BAFF-R and transcription factors regulating IL-6 were also significantly elevated in pSS monocytes compared with normal monocytes [34].

B Cell Subsets in pSS
Several studies describe abnormal B cell phenotypes in patients with pSS compared with other rheumatic disease controls and healthy donors [33, 35]. This incorporates reduced memory, including CD27+IgD- switched and CD27+IgD+ unswitched memory B cells, and increased mature 2/B mature 2 transitional (Bm2/Bm2') and regulatory B cells (CD19+/CD24hi/CD38hi/IL-10+ cells) cells [35-37]. Altered B cell subpopulations have also been correlated with disease activity. Increased transitional B cells negatively correlated with ESR and serum IgG levels [38] and increased regulatory B cells were observed in clinically inactive SS patients. A more detailed examination of B cell phenotype correlated with clinical features of SS patients and response to BAFF stimulation could help to understand their role in disease pathogenesis.

BAFF/BAFF-R HETEROGENEITY
How does BAFF production by different cell types affect B cell function?
Although BAFF is widely associated with the pathogenesis of pSS, there is no definitive study to associate BAFF defects with disease development. Moreover, conflicting data exist regarding BAFF and BAFF-R serum expression levels in pSS patients. High levels of BAFF were described in the serum and salivary glands of SS patients, strongly suggesting a crucial role in the proliferation of B cells [39]. However, several reports show that the
expression of BAFF-R on peripheral blood B and T cells is reduced in patients with pSS compared to healthy controls [31]. Other studies have found a negative correlation between serum sBAFF levels and BAFF-R expression levels on B cells [9]. Mariette et al. [40] found that BAFF levels correlated with the level of autoantibodies in patients with pSS. BAFF-R expression has been observed in some lymphomas but not others, in addition BAFF is differentially expressed and detected more frequently on the lymphoid component of lymphoplasmacytic lymphomas but not plasmacytic cells [41].

To date it has been difficult to determine whether BAFF produced by different cell types have unique, non-overlapping biological effects [10] and conflicting reports regarding BAFF/BAFF-R expression could point to the existence of cell-specific BAFF/BAFF-R molecules, which we will call ‘pseudo-BAFF/BAFF-R’, that could alter the normal function and response to BAFF.

**Pseudo-BAFF/BAFF-R: a possible mechanism to explain BAFF/BAFF-R heterogeneity**

It is possible that the autocrine cell-specific interaction between BAFF and BAFF-R is unique for every cell type. Different cells could express slightly different BAFF-R and produce a multitude of BAFF splice variants. Based on the ratio of different cell-specific BAFF variants (which we will call "pseudo" BAFF) and BAFF-R variability (called “pseudo BAFF-R”), cells could respond differently to the circulating BAFF levels. Thus BAFF produced by monocytes (as a combination of different splice variants) binding to BAFF-R expressed on B cells could induce a different outcome compared to B cell BAFF binding B-cell BAFF-R. We propose a possible mechanism of BAFF regulation in Figure 2.

In the context of the autoimmune abnormalities associated with SS, it is reasonable to consider the possibility that BAFF is being secreted in high concentrations from different types of immune cells, such as T cells (activated via TLR), EC, DC, natural killer cells, monocytes, macrophages and other immune cell types, which can be found in glandular environments, as proposed in Figure 2. It is recognized that viral-based antigens may condition the adaptive immune responses and also trigger B cell hyperactivity by increasing BAFF secretion or BAFF-R expression. It is also known, for example, that T cells and NK
cells produce BAFF upon IL-2 stimulation [42]. Increased levels of B cell BAFF could activate pseudo-BAFF receptor on non-B cell immune cells in pSS. One hypothesis is that pseudo-BAFF receptor on these cells could have a lower activation threshold and may be prone to activation in glandular environments therefore contribute to pathology. It will be interesting to investigate the effects of cell specific (pseudo)-BAFF on B cell activation in the context of health and autoimmunity.

**Do cell specific forms of BAFF/BAFF-R exist?**

Reports detailing splice variants of BAFF are available. An Ensembl search revealed that the BAFF gene has been associated with 6 splice variants, 59 orthologues, 3 paralogues, is a member of 1 Ensembl protein family and is associated with 42 phenotypes. A BLAST search of the ΔBAFF sequence alignment (*Accession number: AAP83164.1*) showed that *Homo sapiens* and other species display conservative regions but have some distinct changes in base pair sequences [19]. BAFF-R variants are also described: 5 Homo sapiens BAFF-R sequences have been listed in the EMBL-EBI European Nucleotide Archive and a His159Tyr mutation in BAFF-R has been linked to early-onset SS patients with MALT lymphomas [43]. It remains unclear whether these variants of BAFF/BAFF-R are cell specific or are able to exert differential functional effects.

There is evidence to support the idea that variations exist in cell specific BAFF/BAFF-R interactions. For example, B cells induce epithelial cell apoptosis in SS [30], however, the 17kDa form of BAFF enhanced epithelial cell survival upon binding to the BAFF-R/BR3 receptor [44]. Clonal analysis indicated that monoclonal B cell lineages could spread from one glandular site to another site during the course of SS disease progression [45] and T follicular helper cells provided a local source of BAFF (BLyS) in GCs, aiding affinity maturation [46]. It is therefore reasonable to question whether BAFF from different cell types can influence BAFF-R expression on newly differentiated mature/transitional and Ig class-switched B cells in pSS. It is possible that in SS B cell BAFF acts in both an autocrine
manner, stimulating B cells via the BAFF-R triggering B cell autoantibody production and also in a paracrine manner, potentially stimulating BAFF production from other immune cell subtypes present in the glandular environment. It is also possible that excessive antibody production could be mediated by the interaction between pseudo-BAFF and pseudo-BAFF-R produced and expressed by non-B cell immune cell types; creating an even more autoantibody-saturated environment and exacerbating SS.

Role of Lipid Rafts in B cell activation in SS patients
Membrane bound BAFF and BAFF-receptors both play an important role in activating a range of cell types and it is likely that their activation could be affected by plasma membrane lipid rafts. Lipid rafts are sphingolipid-cholesterol-enriched membrane microdomains that are associated with immune cell signalling and function [47]. Under certain conditions, membrane–associated molecules can be excluded or incorporated into lipid rafts; in addition the modification of critical residues in raft-associated proteins can disrupt their membrane localization and inhibit cell activation [47]. Such changes can impact lymphocyte function, for example, BCR-mediated signalling depends on BCR-proximal signalling proteins being located in lipid rafts, thus changes in lipid raft dynamics could lead to aberrant B cell responses. To date only one study has investigated lipid rafts in B cells from SS patients, B cell activation via antigen and BAFF/BAFF-R binding prolonged BCR/lipid raft association in patients with pSS compared to controls, increasing signalling and preventing the recruitment of negative regulators of activation [36]. Also evidence from studies in patients with SLE supports that lipid raft abnormalities influence B cell intracellular signalling and function. B cells from SLE patients have reduced levels of protein tyrosine kinase Lyn (encoded by gene LYN) and altered translocation of proximal B cell signalling molecules to lipid raft domains, Lyn mediates Syk (spleen tyrosine kinase) activation, but in the absence of Lyn, Syk complexes are retained in the membrane, resulting in enhanced activation of nuclear factor of activated T cells and B lymphocyte hyperactivity [48]. Recent work has shown that cross-talk between BCR and BAFF-R signalling leads to phosphorylation of Syk which mediates
essential BCR and BAFF-R-associated survival signals [49]. In aggressive non-Hodgkin Lymphoma, the CD40 Signalosome, defined as a macrodomain anchored in lipid-rafts by CD40, accounted for signaling pathway dysregulation and uncontrolled B cell growth. Antibodies to CD40 L (CD-154) are currently being tested in lymphoma and SS, suggesting that the lipid raft anchored-Signalosome might be a potential therapeutic target for NH lymphomas and SS [50].

It will be important to consider whether lipid rafts are enhancing signalling in the over-active B cells found in patients with SS and whether changes in lipid rafts can influence BAFF-R signalling.

**CONCLUSION**

SS is a chronic autoimmune disorder whose pathogenic mechanisms are not fully understood. Hyperactive B cells are strongly associated with pSS pathogenesis and BAFF is strongly implicated in the process of aberrant B cell maturation. Evidence suggests that different forms of BAFF exist and may contribute to pathology. It is possible that variant forms of BAFF so called ‘pseudo-BAFF’ and its ‘pseudo receptors’ exist. These are acting promiscuously and may increase B cell derived BAFF or even ‘pseudo- BAFF’ expression in a positive feedback manner, at least in glandular environments. In order to address this question it is necessary to better characterize BAFF and BAFF-R expression in different immune cell types. Additional genetic and proteomic sequencing analyses are needed to further characterize the role of BAFF in the disease pathogenesis and will hopefully generate potential therapeutic targets in the future.
LIST OF ABBREVIATIONS

APRIL; a proliferation-inducing ligand, BAFF; B-cell activating factor, BAFF-R; B-cell activating factor receptor, BCMA; B-cell maturation antigen, BCR; B cell receptor, BLYS; B lymphocyte stimulator, DC; dendritic cell, EC; epithelial cells, GC; germinal centres, IL; interleukin, INF; interferon, LYN; tyrosine protein kinases encoded by gene LYN, mRNA; messenger ribonucleic acid, mBAFF; membrane-bound BAFF, RA; rheumatoid arthritis, sBAFF; soluble BAFF, SGE; salivary gland epithelial, SS; Sjögren's syndrome, pSS; primary Sjögren's syndrome, SLE; systemic lupus erythematosus, Syk; Spleen tyrosine kinase, TACI; transmembrane activator and calcium modulator and cyclophilin ligand interactor, TNF; tumour necrosis factor, TNFR; tumour necrosis factor receptor, transitional T TLR; Toll-like receptor, TI/II; transitional I/II,

COMPETING INTERESTS

The authors declare that they have no competing interests

AUTHORS' CONTRIBUTIONS

NT performed the review of the literature, drafted the manuscript and prepared the figures, ECJ and CC designed, coordinated and helped to draft the manuscript, DAI provided critical review. All authors read and approved the final manuscript.

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REFERENCES


**Figure Legends**

**Figure 1: Current understanding of BAFF production and function by immune cells.**

1) Viral, environment and/or genetic susceptibility predisposes individuals,
2) membrane (m)BAFF expressed on different immune cell types,
3) T cells acting on monocytes to increase BAFF production,
4) delta BAFF (ΔBAFF) forms heteromultimers with mBAFF and inhibits its release and function.
5) mBAFF is cleaved from cell surface to produce soluble (s)BAFF existing as trimers or oligomers,
6) sBAFF binds to cell surface receptors, BAFF-receptor (BAFF-R, also called BR3), B cell maturation antigen (BCMA) and transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI). sBAFF binding to TACI is inhibitory and
7) known activities of BAFF binding to BAFF-R on different cell types.

(B cell (BC), T cell (TC), plasmacytoid dendritic cell (pDC), follicular dendritic cell (fDC), epithelial cell (EC), macrophage (Mφ), monocyte (Mn), neutrophil (Neu), natural killer cell (NK). Of BAFF coloured purple; showing the same form is being released from different cell types).

**Figure 2: Possible mechanism of cell specific or pseudo-BAFF action in pSS pathogenesis.**

1) Viral, environment and/or genetic susceptibility predisposes individuals,
2) Upon innate immune activation B cells release BAFF which binds to BAFF receptors on B cells (BAFF-R, BCMA, TACI) inducing activation and antibody production,
3) non-B cells release cell specific ‘pseudo-BAFF’;
4) ‘pseudo-BAFF’ binds to BAFF receptors on B cells and stimulate hyper Ig production associated with SS. Pseudo-BAFF from each cell type indicated by different colours synonymous with their hypothetical specific source. (B cell (BC), T cell (TC), plasmacytoid dendritic cell (pDC), follicular dendritic cell (fDC), epithelial cell (EC), macrophage (Mφ), monocyte (Mn), neutrophil (Neu), natural killer cell (NK).)