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**B cell/stromal cell crosstalk in health, disease, and treatment:  
follicular lymphoma as a paradigm**

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## Summary

Stromal cells organize specific anatomic compartments within bone marrow (BM) and secondary lymphoid organs where they finely regulate the behavior of mature normal B cells. In particular, lymphoid stromal cells (LSCs) form a phenotypically heterogeneous compartment including various cell subsets variably supporting B-cell survival, activation, proliferation, and differentiation. In turn, activated B cells trigger in-depth remodeling of LSC networks within lymph nodes (LN) and BM. Follicular lymphoma (FL) is one of the best paradigms of a B-cell neoplasia depending on a specific tumor microenvironment (TME), including cancer-associated fibroblasts (CAFs) emerging from the reprogramming of LN LSCs or poorly characterized local BM precursors. FL-CAFs support directly malignant B-cell growth and orchestrate FL permissive cell niche by contributing, through a bidirectional crosstalk, to the recruitment and polarization of immune TME subsets. Recent studies have highlighted a previously unexpected level of heterogeneity of both FL B cells and FL TME, underlined by FL-CAF plasticity. A better understanding of the signaling pathways, molecular mechanisms, and kinetic of stromal cell remodeling in FL would be useful to delineate new predictive markers and new therapeutic approaches in this still fatal malignancy.

## 1. Introduction

B cells initially differentiate within the bone marrow (BM), before reaching the periphery as BCR-expressing immature B cells, able to gain secondary lymphoid organs (SLO). Recognition of their cognate antigen drives then naïve B-cell activation, proliferation, selection, and differentiation into memory B cells and plasma cells, ultimately homing to the BM as long-lived antibody-producing cells. All stages of B-cell life rely on strong interactions with specific subsets of stromal cells, organized as discrete microanatomic areas controlling B-cell fate through direct B-cell supportive functions and through the recruitment and polarization of other immune cell subsets. In turn, the differentiation and functional plasticity of B-cell interacting stromal cells are influenced by their contact with B cells. In agreement, the development of B-cell malignancies profoundly affects the B-cell/stromal cell bidirectional crosstalk, leading to a co-evolution of both partners and resulting in malignant B-cell growth. Follicular lymphoma (FL) is the most frequent indolent lymphoma<sup>1</sup> and is one of the best paradigms of a B-cell malignancy strongly dependent on a permissive tumor microenvironment (TME) including FL cancer-associated fibroblasts (FL-CAFs).<sup>2-4</sup> FL results from the clonal expansion of germinal center (GC) B cells, even if malignant transformation is initiated during early B-cell development in the BM, by aberrant repair failure of V(D)J recombination. The resulting t(14;18) translocation promotes high expression of the antiapoptotic protein BCL2, providing survival advantage to B cells during GC reaction<sup>5</sup>, a place where BCL2 is normally actively repressed by the GC-specific transcriptional machinery. Indeed, up to 50% of GC B cells undergo apoptosis every 6 hours unless they are positively selected.<sup>6</sup> B cells carrying t(14;18) translocation recirculate as atypical memory B cells considered as FL precursors and detected in the peripheral blood of most healthy individuals.

<sup>7,8</sup> These pre-FL cells are enriched as non-proliferating GC B cells in hyperplastic lymph nodes (LN), thus mimicking the low proliferation rate of FL B cells.<sup>9</sup> Transformation into overt FL is a very rare event, associated with the accumulation of numerous secondary genetic hits following a complex evolutionary dynamics from premalignant stage to FL diagnosis and progression.<sup>10,11</sup> The current view of FL pathogenesis is based on the concept of long-lived cancer precursor cells (CPCs) exhibiting driver genetic alterations and that follow divergent intraclonal evolution, creating a landscape of genetically distinct subclones.<sup>8,12,13</sup> CPCs are responsible for late relapses or transformation into aggressive lymphoma.<sup>14</sup> Importantly, FL is a disseminated disease, characterized by a frequent BM involvement <sup>15,16</sup>, a property shared with t(14;18)<sup>pos</sup> pre-FL cells.<sup>17</sup> How the spatial and functional heterogeneity of stromal cell niches modulates FL B-cell survival, growth, subclonal evolution, and drug resistance remains essentially unknown. Moreover, the signaling pathways, molecular mechanisms, and kinetics of stromal cell reprogramming in FL have been poorly defined. Finally, a better understanding of FL B-cell/FL-CAF interplay would be useful to delineate new predictive markers and new therapeutic approaches in this still fatal malignancy.

## **2. Functional heterogeneity of the stromal cell niches of normal mature B cells**

BM constitutes the primary site for the maintenance and differentiation of hematopoietic stem cells (HSCs) and for B-cell lymphopoiesis. It has long been assumed that different stromal cell niches dynamically control these processes. Seminal papers have recently proposed a molecular atlas of the BM stromal cells at the single cell resolution, providing clues on how various stromal cell subtypes could interact with HSCs and differentiating B-cell subsets by producing soluble factors, such as CXCL12 and IL-7, and signals involved in cell adhesion and

retention, such as VCAM-1 or Nidogen-1.<sup>18,20</sup> In addition, differentiation trajectories within these newly identified stromal cell subtypes were inferred from single cell RNA sequencing (scRNA-seq) data, and were shown to be affected in case of acute myeloid leukemia.<sup>19</sup> Finally, a combination of scRNA-seq and spatial transcriptomics was used to define a spatial map of BM niches, confirming the existence of perisinusoidal and periarteriolar niches orchestrating different aspects of hematopoiesis and B-cell differentiation.<sup>21</sup> An endosteal niche including osteoblasts and lining Podoplanin/gp38<sup>pos</sup> fibroblasts was also identified.

Besides its key hematopoietic function, the BM is a functional reservoir for mature immune cells.<sup>22</sup> Long-lived plasma cells are the best-characterized mature lymphocyte subset residing in the BM, localizing close to CXCL12-producing stromal cells. However, BM contains also significant numbers of resident memory B cells, which can rapidly differentiate into plasma cells locally upon stimulation.<sup>23</sup> Interestingly, reactive GC, including mature follicular dendritic cells (FDCs) and follicular helper T cells (Tfh), can be rarely found within BM, in the context of autoimmune diseases, infections, or malignancies, and exhibit a non-paratrabeular localization.<sup>24</sup> The precursors and differentiation pathways of these ectopic BM FDCs are unknown. Moreover, how differentiating and mature B cells contribute to the plasticity of BM stromal cells has never been explored.

Within SLO, lymphoid stromal cells (LSCs) pattern discrete anatomical niches and orchestrate adaptive immune response by supporting lymphocyte recruitment, survival, activation, and differentiation.<sup>25,26</sup> Mature LSCs are phenotypically defined by their expression of gp38, in the absence of hematopoietic, epithelial, and endothelial markers.<sup>27</sup> In mouse adult SLO, perivascular cells have been proposed as the local precursors of LSCs even if competing views exist concerning their specific origin, including gp38<sup>neg</sup> mural cells and gp38<sup>pos</sup>CD34<sup>pos</sup>

adventitial cells.<sup>28–30</sup> Historically, the two best-defined LSC subsets are CD21/CD35<sup>pos</sup> FDCs, populating the light zone (LZ) of the GC and regulating guidance and selection of high-affinity B cells, and CD21<sup>neg</sup> fibroblastic reticular cells (FRCs), residing outside the follicles and supporting antigen delivery, naive lymphocyte and mature dendritic cell recruitment, and T-cell survival and activation.<sup>31</sup> However, new strategies of cell-fate mapping, high-resolution imaging, and scRNA-seq have recently revealed a higher level of diversity in LSCs, reflecting their various functions and anatomical location.<sup>32</sup>

In particular, the genetic targeting of CXCL13-expressing cells has been used to characterize B-cell interacting reticular cell (BRC) subsets.<sup>33</sup> Two subsets of FDCs could be highlighted, sitting in GC LZ and dark zone (DZ), respectively. Classical LZ FDCs are known to recruit and sequester CXCR5-expressing GC B cells and Tfh through the production of high amounts of CXCL13 and to retain intact antigens for extended period of times by continuous recycling.<sup>34</sup> LZ GC B cells, called centrocytes, compete with each other for the capture of antigens from LZ FDCs through a specific immune synapse architecture allowing stringent affinity discrimination.<sup>35</sup> Antigenic peptides could then be presented by high-affinity centrocytes to cognate Tfh that in turn trigger GC B-cell recycling to the DZ for further rounds of proliferation/somatic hypermutations. GC B cells ultimately differentiate into memory B cells and plasma cells, exiting the GC with a different kinetic of preferential output. Besides BCR activation, which is a primary determinant of GC B-cell fate, LZ FDCs have been suggested to contribute to GC B-cell survival through a combination of membrane and soluble factors including VCAM-1, Notch ligands, BAFF/TNFRSF13B, IL-15, Wnt5a, or Shh<sup>36–41</sup>, but the precise roles of these molecules remain unknown. LZ FDCs also regulate apoptotic B-cell clearance through the production of MFGE8, promoting GC B-cell phagocytosis by tingible body

macrophages.<sup>42</sup> Conversely, DZ FDCs are characterized by their low expression of CD21/CD35 and their high production of CXCL12. CXCL12 is involved in the localization of CXCR4<sup>hi</sup> proliferating centroblasts into the DZ, and play a determinant role in the efficacy of the GC response by orchestrating BRC topology and resulting B-Tfh crosstalk.<sup>33,43,44</sup> Of note, the glycosaminoglycan-binding property of CXCL12 is critical for the correct GC organization, likely reflecting local retention of CXCL12 by DZ FDCs.<sup>43</sup> DZ and LZ FDCs share similar morphology and expression of the transcription factor SOX9<sup>32</sup>, suggesting a common origin, but subset specification of LZ and DZ FDCs was found to be predetermined in the steady state.<sup>33</sup> Besides FDCs, BRCs also comprise marginal reticular cells (MRCs), interfollicular reticular cells (IFRCs), T-B border reticular cells (TBRCs), and medullary reticular cells (MedRCs), all located outside the GC. MRCs, primarily sitting at the edge of the follicle, lining the subcapsular sinus, capture and transfer immune complexes to B cells.<sup>45</sup> Of note, they have also been proposed as precursors of FDCs during inflammation-induced LN remodeling.<sup>46</sup> TBRCs express both CXCL13 and CCL19/CCL21 and support naïve B-cell survival by producing high amounts of BAFF.<sup>47</sup> In agreement, ablation of CCL19-expressing cells *in vivo* reduces substantially B-cell viability within LN, whereas FDC loss has a minor impact on B-cell homeostasis.<sup>47,48</sup> Some TBRCs producing APRIL, IL-6, and CXCL12 were also shown to support plasmablast exit from the GC and differentiation into plasma cells.<sup>49</sup> IFRCs are transcriptionally close to TBRCs, and express high amounts of the cholesterol-25-hydroxylase (Ch25h), a crucial enzyme in the production of 7 $\alpha$ ,25-hydroxycholesterol<sup>32</sup>, the ligand of the EB12 receptor guiding activated B cells and T cells and favoring their interaction at the T-B border and interfollicular areas.<sup>50</sup> Finally, MedRCs form a dense meshwork throughout medullary cords, express high amounts of leptin receptor, and guide plasma cell migration and survival by producing BAFF, IL-6, CXCL12, and



APRIL together with an intermediate level of CXCL13.<sup>51</sup> Apart from BRC subsets, the last well characterized LSC population is that of T-cell zone reticular cells (TRCs) producing high amounts of CCL19/CCL21. Importantly, even if they were initially identified for their crucial role on T-cell behavior, TRCs promote the recruitment of naïve CCR7<sup>pos</sup> B cells and ensure their guided trafficking from the paracortex to B-cell follicles. Altogether, B cells are engaged in a sequential crosstalk with virtually all LSC subsets that differentially regulate each step of their activation and differentiation within SLO. However, this detailed characterization of LSC heterogeneity has been performed in mice and very few data are available on human LSC diversity, plasticity, and function. Very recently, we proposed that CD49a/Integrin  $\alpha$ 1 could be used to sort human immune cell-interacting gp38<sup>pos</sup> FRCs and gp38<sup>neg</sup> perivascular cells displaying features of LSC precursors, allowing further molecular and functional studies.<sup>52</sup> Such approach could be useful to analyze LSC remodeling during inflammation and cancer. Importantly, B cells have also a huge impact on LSC dynamics in response to inflammatory stimuli. Within GC, the production of tumor necrosis factor- $\alpha$  (TNF) and lymphotoxin  $\alpha$ 1 $\beta$ 2 (LT) by B cells is required for FDC maturation and maintenance and is dependent on stimulation by FDC-derived CXCL13.<sup>53,54</sup> B cells are crucial not only for FDC organization. In particular, B cell-derived LT, upregulated in response to IL-4 stimulation, is involved in the proliferation and robust transcriptional remodeling of FRCs in response to viral infection<sup>55,56</sup> and in the stretching and maturation of TBRCs into CXCL13-expressing stromal cells in response to the early swelling of GC within follicles.<sup>57</sup> Conversely to FRCs, modest changes have been described in the FDC transcriptional program in response to infection.<sup>33</sup> Importantly, other cell partners have a strong impact on TRC proliferation and differentiation. CLEC-2 expressed by migratory dendritic cells interacts with gp38 on the surface of TRCs and

promotes the relaxation of their actomyosin cytoskeleton.<sup>58</sup> TRCs then stretch and elongate, the reticular network relaxes, and LN swell to accommodate the rapid increase of lymphocyte number following immune response initiation.<sup>58,59</sup> TRC relaxation is later followed by TRC proliferation.<sup>59</sup> LT deficiency in B cells or dendritic cells results in a premature contraction of the FRC network. Additionally, IL-17 produced by locally differentiating Th17 cells triggers metabolic reprogramming of TRCs required to support their proliferation and survival.<sup>60</sup> In addition, IL-17 drives the differentiation of IL17Rc<sup>pos</sup> pulmonary stromal cells from bronchus-associated lymphoid tissues into gp38<sup>pos</sup>CD21/35<sup>neg</sup>CXCL12<sup>pos</sup> follicular stromal cells allowing GC formation in the absence of both FDC and LT<sup>pos</sup> B cells.<sup>61</sup> B cells are thus engaged in a bidirectional crosstalk with both FRCs and FDCs and cooperate with other cell partners to trigger their differentiation and activation during physiological immune response, in particular through the production of LT.

### **3. General organization of FL stromal cell niches**

FL B cells exhibit the general hallmark of centrocytes and accumulate primarily within LN follicles whereas BM infiltration, found in 40-70% of FL patients at diagnosis, is an important adverse factor in FL clinical risk-stratification scores.<sup>15,62,63</sup> Macroscopically, FL LN retain well-defined follicles, where FDCs and Tfh are found admixed with malignant B cells without DZ/LZ organization, and a surrounding extrafollicular zone, exhibiting a dense network of FRCs and CD8 T cells. However, whereas LN expansion is rapid but transient during normal immune response, remaining confined by the capsule limit, FL LN are chronically enlarged, with frequent capsule disruption and invasion of the adipose perinodal tissue by ectopic GC-like structures (Figure 1A-D). Moreover, FL LN are uniformly invaded by tumor follicles in the

cortex, paracortex, and medullary areas. Importantly, a huge intra-tissular heterogeneity could be found both within and outside follicles, including for the density, phenotype, and organization of FDC and FRC networks (Figure 1E-G). How the specific anatomic and phenotypic properties of stromal cells impact their reprogramming during FL lymphomagenesis and support malignant B cells with specific subclonal and/or transcriptomic features has not been explored.

Invaded FL BM do not exhibit a diffuse infiltration by tumor cells, that are found as nodular aggregates including mature LSCs and PD-1<sup>pos</sup>CD4<sup>pos</sup> T cells. Conversely to reactive GC, malignant follicles essentially display paratrabecular localization (Figure 2). LN FL-FDCs progressively lose expression of CD21, CD23, and CD35, a process associated with the strongly reduced expression of LT by malignant FL B cells compared to normal GC B cells.<sup>64,65</sup> Conversely, mature FDCs expressing CD21 and producing CXCL13 could be ectopically detected in the center of BM FL B-cell aggregates, distant from the bone.<sup>66</sup> FRC-like cells are also identified within these BM follicle-like structures. These data suggest that ectopic localization of FL B cells within BM requires FDCs, whereas FL LN B cells lose their dependency towards LZ FDCs and/or become dependent on functionally different LSC subsets. Besides sharing lymphoid-like properties, BM and LN FL stromal cells display common extracellular matrix composition features including upregulation of secreted protein acidic and rich in cysteine (SPARC), a matricellular protein involved in collagen deposition and organization.<sup>67</sup> However, gene expression profile analysis has underlined key differences in the phenotype of FL-CAFs within BM and LN niches.<sup>68</sup> In agreement, BM FL B cells are also characterized by a lower cytological grade, a decreased proliferation, a modified phenotype with reduced CD10 expression, and an altered gene expression profile compared with LN FL B cells.<sup>68,69</sup> Moreover,

somatic hypermutation analysis and targeted deep sequencing have demonstrated that different FL B-cell subclones could be detected within LN *versus* BM, and suggest that FL originates in the LN and infiltrates BM early in the course of the disease, allowing further accumulation of BM-specific mutations.<sup>69–71</sup> Yet, no study has been designed to specifically interrogate the consequences of the differences in FL-CAF phenotype in LN *versus* BM on FL B-cell genetic heterogeneity.

#### **4. Functional heterogeneity of FL stromal cell niches**

CAFs exert key protumoral functions including direct impact on tumor cell survival, proliferation, and dissemination and indirect effects on tumor organization and anti-tumor immunity, altogether promoting tumor growth and drug resistance. FL-CAFs have been initially characterized at the functional and transcriptomic levels after short term *in vitro* expansion. Even if such approach could be associated with culture-related artifacts and with a loss of stromal cell heterogeneity, it is interesting to notice that culture-adapted human mesenchymal stromal cells obtained from BM (BM-MSC) and adipose tissue (ASC) retain the main transcriptomic and functional differential features of their native counterparts, demonstrating an imprinting of the tissue origin on stromal cell properties.<sup>72</sup> In agreement, several deregulated pathways have been identified in *in vitro*-expanded FL-CAFs and further confirmed *in situ* in both BM and LN FL tissues (Figure 3). In particular, FL-CAFs were proposed as main organizers of FL cell niche. First, FL-CAFs overexpress CCL2, detected at high levels in FL BM plasma, and recruit monocytes, further converted into proangiogenic and anti-inflammatory macrophages, at least in part through Notch-dependent signaling.<sup>73</sup> Interestingly, FL tumor-associated macrophages (FL-TAMs) have been shown to trigger FL B-

cell activation and survival through the transpresentation of IL-15, able to activate STAT5 in B cells and to collaborate with Tfh-derived CD40L signaling.<sup>74</sup> Conversely to normal B cells, FL BCR harbor in more than 80% of cases unusual N-glycosylation sites occupied by immature oligomannose residues.<sup>75</sup> This modification is an early event in FL pathogenesis and is retained across relapse and transformation events.<sup>76</sup> The lectin DC-SIGN specifically recognizes FL N-glycosylated BCR and triggers its delayed but long-lasting aggregation and activation.<sup>77</sup> DC-SIGN is inducible by IL-4, a cytokine overexpressed by FL-Tfh, and is thus overexpressed on FL-infiltrating myeloid cells.<sup>78</sup> IL-4 also increases IgM expression on FL B cells thus further favoring BCR/DC-SIGN crosstalk. Strikingly, FL-LSCs contribute to the polarization of FL-Tfh by favoring the early commitment of PD1<sup>dim</sup>CXCR5<sup>pos</sup>CD4<sup>pos</sup> cells, corresponding to pre-Tfh cells, into IL-4<sup>hi</sup> producers, in a Notch and ICAM1/LFA1-dependent manner<sup>79</sup>. Altogether these data highlight FL-CAFs as central coordinators of the FL-Tfh/FL-TAM/B-cell tripartite crosstalk. Besides CCL2, FL-CAFs also overexpress IL-8, thus favoring the recruitment and survival of protumoral neutrophils.<sup>80</sup> Whereas PGE2 has been proposed as upregulated in FL-CAFs<sup>81</sup> and despite the accumulating evidence showing a role for CAFs in immune escape and resistance to immunotherapy in solid cancers<sup>82</sup>, no data are currently available on their immunosuppressive activity in FL.

More recently, *in situ* analysis of FL-CAFs has highlighted a strong upregulation of CXCL12 expression in FL-FDCs, FL-FRCs, and FL BM stromal cells with a parallel increase of CXCL12 level in FL BM plasma.<sup>66</sup> Moreover, heparanase, an endoglycosidase increasing the bioavailability of heparin-binding factors like CXCL12, is strongly expressed in about 50% of FL.<sup>83</sup> CXCL12 triggers FL B-cell activation, migration, and adhesion. Within FL follicles, this upregulation of CXCL12 parallels the disappearance of CD21<sup>pos</sup> FDCs. The lack of specific marker for DZ FDCs

precludes any definitive conclusion on whether this remodeling of malignant follicles actually corresponds to an expansion of the DZ FDC network. However, unlike LZ FDCs and TBRCs, DZ FDCs were proposed to not require LT and TNF for the maintenance of CXCL12 expression and network morphology<sup>44</sup>, thus providing an argument in favor of a DZ FDC origin for CXCL12<sup>hi</sup> follicular stromal cells supporting LT<sup>lo</sup> FL B cells. In order to further delineate the properties of FL-CAFs *in situ* we recently analyzed the gene expression profile of sorted gp38<sup>pos</sup>CD21<sup>pos</sup> FDCs, gp38<sup>pos</sup>CD49a<sup>pos</sup>CD21<sup>neg</sup> LSCs, including FRCs and DZ FDC-like cells, and their putative gp38<sup>pos</sup>CD49a<sup>neg</sup> local LSC precursors in FL LN and reactive SLO.<sup>52</sup> Interactome analysis demonstrated that FL B cells had a higher capacity to interact with CD21<sup>neg</sup> LSCs than with CD21<sup>pos</sup> FDCs, providing a molecular support for the disruption of LZ FDC network within FL follicles. Moreover, we confirmed the deregulation of CXCL12 and highlighted an overexpression of CCL19/CCL21 by FL-CAFs. Interestingly, FL-LSC precursors already displayed a specific gene expression profile, suggesting an early commitment towards tumor supportive phenotype. A more detailed study of the heterogeneity of FL-CAF precursors remains to be performed, taking into account the spatial specificities of FL niches. In fact, besides MRCs and perivascular cells, pre-adipocytic cells, already shown to migrate into newborn LN and differentiate into a variety of LSCs<sup>84</sup>, are an interesting putative precursor of FL-CAFs supporting the formation of the perinodal FL follicles found in the surrounding fat. Moreover, the question of the local precursors of BM FL-CAFs and whether endosteal, perisinusoidal, and/or periarteriolar stromal cells could be involved remain completely open.

Interestingly, FL B cells express higher levels of *CCR7* and *CXCR4* than normal CC.<sup>52</sup> Together with their reduced expression of the GC-confinement receptors *S1PR2* and *P2RY8*, and their increased expression of the *S1PR1* egress receptor<sup>52</sup>, these data suggest that FL B cells are

prone to interact with FL-LSCs both within and outside follicles, thus contributing to their disseminated profile. An important unsolved question remains the direct and indirect impacts of the modifications of extracellular matrix composition, organization, and stiffness, which are largely dependent on stromal cells, on FL growth. Recently, relevant 3D *in vitro* models have suggested that mechanical forces resulting from compressive stress and cell contractility, two processes finely regulated by FRCs, may influence integrin and BCR signaling in GC B-cell lymphomas, with functional consequences on cell proliferation and drug resistance.<sup>85</sup>

Of note, new strategies of scRNA-seq combined with spatial transcriptomic/multiparametric imaging will make it possible to better define FL-CAF precursors and differentiation trajectories and to draw a more complete picture of how each CAF subset specifically interacts with malignant B cells and with the other components of TME, how this crosstalk is dynamically affected during the course of the disease, and how it could provide relevant stratification markers and therapeutic targets.

## **5. FL stromal niche commitment, heterogeneity, and dynamics**

FL-CAFs have emerged as highly heterogeneous and plastic stromal cell subsets, raising the question of the cellular interactions, molecular mechanisms, and kinetic of their reprogramming, with a major clinical interest for understanding the primary TME alterations supporting pre-FL stage and early CPC as well as the treatment-induced TME plasticity.

Within FL LN, a first challenging issue is to understand how FL-CAFs accommodate the chronic LN enlargement associated with lymphoma growth. The proportion of dendritic cells is strongly reduced in FL<sup>86</sup> and FL-CAFs display a reduced expression of gp38<sup>66</sup>, suggesting that the CLEC-2/gp38 loop is not the main driver of the chronic FRC network expansion in FL.

Moreover FL B cells downregulate LT<sup>65</sup> and the Th17/Treg balance is specifically skewed towards Treg differentiation<sup>87</sup>, whereas FL-Tfh poorly express Th17-related markers, including *IL-17*, *IL-26*, and *RORC*.<sup>87,88</sup> These data argue against a role for B cell-derived LT and T cell-derived IL-17 in FL-FRC proliferation. In agreement, FL LN are characterized by a disorganized and partly disrupted collagen-based reticular network.

Malignant B cells have been initially proposed as the main drivers of the modifications of FL stromal cell phenotype and gene expression profile. In particular B-cell derived TNF triggers CCL2 and IL-8 expression in LN and BM stromal cells and supports the differentiation of BM-MSCs towards FL-supportive FRC-like cells *in vitro*.<sup>73,80</sup> Moreover, our recent RNA profiling of FL-CAF subsets highlighted a putative role for B cell-derived TGFβ<sup>52</sup>, a factor already identified as upregulated within FL cell niches<sup>90</sup> where it impacts intratumoral T-cell function.<sup>91,92</sup> Interestingly, TNF/LT and TGFβ synergize to induce FL-CAF markers, including *CXCL12*, *CCL19*, and *CCL2*, on LN LSC precursors. Moreover, we could demonstrate a correlation between *TGFB1* and *CCL21* expression across large series of FL patients.<sup>52</sup>

Importantly, non-malignant cells also contribute to FL-CAF reprogramming. Whereas FL B cells are not able to upregulate CXCL12 when cocultured with stromal cells, FL-Tfh induce CXCL12 in an IL-4-dependent manner.<sup>66</sup> Accordingly, a correlation was found between CXCL12 and p-STAT6, a surrogate marker of IL-4 production, in a large series of FL LN. TNF/LT and IL-4, both overexpressed in FL-Tfh, synergize to trigger a transglutaminase<sup>hi</sup>gp38<sup>lo</sup>VCAM-1<sup>hi</sup> CXCL12<sup>hi</sup> phenotype in stromal cell precursors and FRC-like cells *in vitro*, thus closely mimicking the phenotype of FL-FRCs *in situ*. In fact, TNF/LT upregulate STAT6 and IL4R expression in stromal cells, suggesting differentiated LSCs respond more efficiently to IL-4 compared to undifferentiated stromal cells. FL-Tfh also overexpress IFN-γ<sup>89</sup>, able to induce indoleamine-2,3



dioxygenase (IDO) in human FRC-like cells *in vitro*.<sup>93</sup> By catalyzing the tryptophan metabolism, IDO inhibits CD4<sup>pos</sup> and CD8<sup>pos</sup> T-cell but also normal and malignant B-cell proliferation. It is tempting to speculate that FL tissues are organized in discrete areas where different subsets of FL-Tfh and FL-stromal cells variably regulate FL B cell/FL immune microenvironment interplay.

The hypothesis that specific genetic alterations directly impact the capacity of malignant FL B cells to drive the development of specific TME patterns has emerged only recently (Figure 4). Initially, loss-of-function mutations of the H3K27/H3K18 acetyltransferase CREBBP, detected in about 50% of FL patients, were associated with a decrease of MHC class II expression resulting in reduced CD4<sup>pos</sup> and CD8<sup>pos</sup> T-cell infiltration and proliferation.<sup>94</sup> Interestingly, CREBBP alterations are considered early events potentially playing a major role in the initiation of FL tumors.<sup>95</sup> Human FL tumors are heavily mutated, with numerous subclones harboring different patterns of genetic alterations. In addition, they could essentially be analyzed once, at the diagnosis, making it difficult to infer the direct impact of each single genetic event on B-cell/TME crosstalk over the course of the disease. To fill this gap, genetically-engineered mouse models have been proposed in the past few years, studying how the deregulation of a single genetic target synergizes with BCL2 overexpression to promote FL-like tumors. These models are not optimal, in particular since they are using essentially the vavP promoter to deregulate BCL2, leading to BCL2 overexpression in all hematopoietic cells, and do not mimic the rare occurrence of FL-promoting mutations. However, they have been shown useful to figure out the impact of FL recurrent mutations on GC reaction and early lymphomagenesis. Recently, gain of function mutations of the histone methyltransferase EZH2, occurring early during transformation in 20-30% of FL and initially

thought to display B-cell intrinsic protumoral effects<sup>96</sup>, were proposed to uncouple GC B cells from the critical Tfh checkpoint whereas switching them to FDC dependency.<sup>97</sup> EZH2-mutated GC B cells downregulate many genes linked to Tfh signaling, fail to engage Tfh, thus limiting recycling towards the DZ, and survive in the LZ as proliferating centrocytes overexpressing LT, TNF, and BAFFR, all involved in GC B-cell/FDC crosstalk. Such model seems thus to mimic well the early stages of FL initiation, and perhaps also what happens ectopically in FDC-rich invaded FL BM. However, it also gives clues on the development of overt FL since EZH2-mutated human FL feature greater association with intact FDC network as compared to unmutated FL, suggesting that early events could imprint later FL development and evolution. Whereas EZH2 mutations are proposed to directly impact FL stroma, other recurrent alterations could indirectly promote LSC reprogramming. This is in particular the case for loss-of-function mutations/deletions of TNFRSF14/HVEM, that are found in about 40% of FL patients, disrupt the HVEM/BTLA inhibitory loop, and accelerate FL development in the *vavP-BCL2* mouse model.<sup>98</sup> HVEM/BTLA paracrine interaction is lost in most FL B cells by either HVEM mutations or BTLA transcriptional repression, favoring a cell-autonomous B cell activation by reinforcing BCR signaling in both mouse and human cells. Moreover, Tfh express huge amount of BTLA, and BTLA engagement in Tfh reduces TCR signaling and CD40L mobilization at the immunological synapse, thus diminishing Tfh help to GC B cells.<sup>99</sup> HVEM mutations thus favor B cell/Tfh crosstalk and outgrowth of premalignant B cells. Accordingly, Tfh infiltration and STAT6 phosphorylation are higher in HVEM<sup>lo</sup> human FL tumors.<sup>98</sup> Interestingly, FRC and FDC activation could be detected in HVEM-deficient mouse lymphomas, potentially related to the upregulation of TNF and LT expression by Tfh. Likewise, HVEM specifically decreases LT expression by human Tfh *in vitro* without impacting their survival or CXCL13 and IL-21

expression. Altogether HVEM mutations strongly impact FL TME features including FL-CAF network organization. Recently, other genetic alterations were associated with FL-Tfh reprogramming. Even if the resulting stromal cell phenotype has not been studied, the major effect of Tfh on LSC activation and plasticity suggests that a comparative analysis of FL-CAF phenotype in response to different genetic backgrounds would be of great interest. Point-activating mutations in the mTORC1 activator *RRAGC* are associated with a decrease in Tfh infiltration in both *vavP-Bcl2*; *RagC<sup>mut</sup>* mice and FL patients harboring *RRAGC* mutations<sup>100</sup>, whereas Cathepsin S (*CTSS*) alterations detected in 20% of FL patients, upregulate MHC class II antigen presentation and are associated with a higher CD4<sup>pos</sup> T cell infiltration whereas CD8<sup>pos</sup> T cells are excluded from the GC in mutated mice.<sup>101,102</sup> Again, FL patients with deregulated *CTSS* had a higher intrafollicular CD4<sup>pos</sup> T cell infiltration, supporting a stronger dependency on Tfh cell help. Interestingly, both *RRAGC* mutations, conferring independence from Tfh, and *CTSS* mutations, modulating Tfh/CD8 T cell balance, were found mutually exclusive with *HVEM* mutations.<sup>100,102</sup> However, the net impact of harboring various combinations of *EZH2*, *CREBBP*, *HVEM*, *RRAGC*, *CTSS*, *MLL2*, and the other less characterized genetic alterations on TME modifications is unknown and very difficult to model, in particular since numerous subclones harboring different mutational profiles coexist within each FL biopsy.<sup>103</sup>

In fact, the relationship between B-cell subclonal and transcriptional heterogeneity in FL is not completely solved. Tracking subclonal divergences through the analysis of BCR diversification reveals that B-cell subclones do not massively differ at the transcriptional levels<sup>12,104</sup> suggesting that other drivers of phenotypic diversity are stronger than genetic events. However other studies propose either that copy number variations could represent an

important layer of transcriptional heterogeneity and drug-response<sup>105</sup> or that patients exhibiting divergent BCR evolution between 2 distant tumor sites also exhibit divergent tumor gene expression and cell surface protein profiles.<sup>106</sup> An interesting finding is that FL tumor B cells are not, at the single-cell level, frozen in a specific GC stage of differentiation and could thus not be directly compared with the different subsets of normal GC B cells recently identified.<sup>104</sup> Yet, FL B cell transcriptomic profile within a single biopsy dynamically spans a continuum of transitional states between proliferating GC-like and quiescent memory-like states, with rare cells carrying a plasma cell-like profile.<sup>107</sup> It is likely that, together with tumor genetics, this transcriptional plasticity impacts FL B cell intra-tissular localization and interactions with TME, including with various specialized subsets of LSCs.

As a disseminated disease, spatial heterogeneity is another level of heterogeneity in FL, with a specific emphasis on BM *versus* LN niches. *CCL19* and *CXCL13* are highly expressed within FL BM and correlate with *TNF* expression, suggesting common driver mechanisms for the development of BM FRC-like/FDC-like stromal cells (unpublished personal data). Conversely, BM *CXCL12* is not correlated to *TNF* level and, as previously described in FL LN, is associated with *IL-4* expression.<sup>66</sup> FL B cells and immune TME have thus been proposed to cooperate in the induction of BM FL-CAF polarization. Importantly, very few T cells with a full Tfh phenotype could be detected in FL BM and CD4/CD8 ratio was found increased only in heavily involved BM<sup>108</sup>, whereas the level of *CXCL12* is already increased in non-involved BM plasma. This discrepancy has been recently solved by the demonstration that FL B cells produce extracellular vesicles that could be internalized by BM stromal cells, making them more efficient to support BM FL B-cell survival and quiescence, at least in part through the production of *CXCL12*.<sup>68</sup> This study further suggests that differences in LN *versus* BM FL

stromal cell phenotypes and mechanisms of reprogramming could drive locally specific patterns of molecular interactions with malignant B cells and contribute to tumor spatial heterogeneity. Interestingly, TGF $\beta$  signaling was identified as one of the underlying pathway supporting BM stromal cell activation by FL B cell-derived extracellular vesicles.<sup>68</sup> A scRNA-seq study comparing distant FL LN from the same patients further highlights a specific correlation between site-to-site tumor heterogeneity and Tfh cell abundance, raising the question of the underlying stromal cell functional features.<sup>106</sup> Having discussed how malignant B cells and their stromal niche dynamically co-evolve to support FL initiation and progression, a remaining bullet point is the question of the clinical consequences of this crosstalk on patient behavior and treatment.

## **6. Clinical impact of FL B cell/stromal cell crosstalk**

In agreement with the key role of TME in FL pathogenesis, the majority of biomarker studies have proposed predictive parameters reflecting TME composition and organization rather than tumor genetic landscape.<sup>3</sup> These studies gave controversial conclusions, with a huge impact of the treatment schedule on the predictive value of each identified biomarker. Moreover, whereas T cell and myeloid cell subsets have been extensively associated with patient outcome, no study has been designed to specifically challenge the predictive value of FL-CAF heterogeneity. LZ FDCs, easily detectable by their specific expression of CD21/CD23, have been variably connected with FL prognosis and a meta-analysis of the literature recently identified high FDC density as associated with poor outcome.<sup>109</sup> Importantly, none of these biomarker studies includes tumor genetics in the interpretation of the data. The demonstration that numerous recurrent alterations alter TME composition and organization,

together with the spatial heterogeneity of B cells and TME limit the clinical impact of these studies on patient stratification and follow-up.

Considering FL treatment, FL-CAFs should be considered not only for their putative interest as therapeutic targets but also for their impact on resistance to treatments targeting tumor B cells and immune response. A first strategy would be to target B-cell retention within their supportive niche or FL-CAF downstream molecular effectors. Interestingly, both the disruption of CXCL12/CXCR4 axis and the use of BCR inhibitors have been shown to impair B-cell interactions with stromal cells.<sup>110</sup> An intriguing hypothesis is that some specific genetic hits favoring B-cell/stromal cell interplay, such as *EZH2* mutations, could sensitize FL B cells to therapeutic approaches aiming at abrogating B-cell/stromal cell interactions. Whether the reprogramming of B-cell/TME crosstalk contributes to the clinical efficacy of *EZH2* inhibitors against *EZH2* mutated FL remains to be explored. It will require sequential biopsies of LN and BM in order to capture the kinetic of B-cell/TME co-evolution under treatment. Moreover, a better understanding of epigenetic and metabolic pathways underlying FL-CAF commitment and plasticity would provide new therapeutic opportunities. Finally, CAFs have been proposed to strongly impact the response to immunotherapies, including immune checkpoint inhibitors and CAR-T cells, notably by creating a physical barrier maintaining anti-tumor T cells at the periphery of the tumor in collagen-rich areas, and by recruiting and activating Treg, whereas inhibiting CD8<sup>pos</sup> T cell and NK cell cytotoxicity.<sup>111</sup> Blocking of TGF $\beta$  in a mouse model recapitulating immune-excluded phenotype was shown to synergize with anti-PDL1 antibodies by facilitating the penetration of T cells into the center of the tumor thus converting tumors from an excluded to an inflamed phenotype.<sup>112</sup> The enrichment for TGF $\beta$  signaling

within FL tumor niches and the exclusion of CD8 T cells from FL follicles raise the question of the targeting of CAFs or CAF-derived extracellular matrix proteins in FL.

Whereas several 3D models have been recently developed for drug screening in lymphoma, the introduction of LSCs/FL-CAFs in these approaches is mandatory to take into account the major role of B-cell/CAF crosstalk in malignant B-cell survival and drug resistance. Recently, a 3D collagen spheroid model incorporating adipose-derived stromal cells has been used to support survival of primary B cells in aggressive lymphoma and was shown useful to evaluate therapeutic compounds.<sup>113</sup> Such approach would be highly valuable in FL, in particular with additional incorporation of Tfh-mimicking signals, such as CD40L and IL-4.

## **7. Concluding remarks**

Functionally and spatially specialized stromal cell subsets collectively contribute to each stage of normal mature B-cell recruitment, homing, survival, activation, proliferation, selection, and differentiation in both LN and BM. These cells are the local precursors of tumor-infiltrating stromal cells in B-cell lymphomas but they have surprisingly received very little attention in FL, until CAFs were recently identified as a major component of tumor-promoting microenvironment in solid cancers. In fact, rapid advances have been made recently in the molecular characterization of CAF diversity even if their origin and commitment/polarization pathways remain poorly defined. In FL, tumor heterogeneity relies on a coevolution of FL B cells and TME, whose dynamic has only been partly deciphered in the absence of sequential sampling of patients in early stage, late stage, relapse, and progression. In particular the nature of CPC and minimal residual disease stromal niches is of major interest and can hold therapeutic potential in FL, where clinical evolution is marked by cycles of remissions and

relapses, which will be gradually less sensitive to treatment. The clinical impact of this new research avenue remains to be explored through well-designed controlled trials including state-of-the-art ancillary studies repositioning B-cell heterogeneity within its ecosystem.

**Conflict-of-interest disclosure**

The authors declare no other competing financial interest.



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## Figure Legends

### Figure 1. Human stromal niche organization within FL lymph nodes

**A)** Normal reactive lymph node with an intact capsule (yellow dotted line) and a well-delimited medullary zone (white dotted line). FRCs are stained by anti-collagen IV antibody (COLLIV, yellow) and FDCs by anti-CD21 antibody (CD21, red). Nuclei are counterstained with DAPI (blue). Scale bar, 5mm.

**B)** FL lymph node with capsule disruption (yellow arrows) and invasion of the medulla (white arrows) by malignant follicles. FRCs are stained by anti-collagen IV antibody (COLLIV, yellow) and FDCs by anti-CD21 antibody (CD21, red). Nuclei are counterstained with DAPI (blue). Scale bar, 5mm.

**C-D)** FL lymph node with perinodal follicular expansion in surrounding adipose tissue. FRCs are stained by anti-collagen VI antibody (COLLIV, green) and FDCs by anti-CD21 antibody (CD21, yellow). **(C)** Scale bar, 5mm; **(D)** Scale bar, 1mm. White arrow highlights a perinodal follicle. Capsule is indicated by yellow dotted line.

**E-F-G)** FDC heterogeneity in FL. FRCs are stained with an anti-collagen IV antibody (COLLIV, yellow) and FDCs by an anti-CD21 antibody (CD21, green). **(E)** intact FDC network; **(F)** variably disrupted FDC network; **(G)** lack of FDC network.

### Figure 2. Human stromal niche organization within FL bone marrow

**A)** Invaded FL bone marrow showing FRC-like cells stained with anti-transglutaminase antibody (green), FDC-like cells with anti-CD21 antibody (red), and FL B cells with anti-CD20 antibody (blue). Dotted lines indicate the bone. Box indicates the area magnified in lower panel. Scale bars, 100  $\mu$ m

**B)** Invaded FL bone marrow showing FRC-like cells stained with anti-transglutaminase antibody (green), FDC-like cells with anti-CXCL13 antibody (red), and FL B cells with anti-CD20 antibody (blue). Dotted point line indicates the bone. Scale bar, 100  $\mu$ m

### Figure 3. B-cell/stromal cell interactions within FL cell niches

FL cancer associated fibroblasts (FL-CAF) form a heterogeneous compartment overexpressing factors involved in direct FL B-cell activation and in the recruitment and activation of other

components of tumor supportive cell niche such as tumor associated macrophages (TAM) and T follicular helper (Tfh). In FL bone marrow, FL B cell-derived extracellular vesicles (EVs) contribute to the early commitment of BM mesenchymal stromal cells (BM-MSK) towards FL permissive stromal niche ultimately including mature lymphoid stromal cells and CD4<sup>pos</sup> T cells admixed with malignant B cells within nodular aggregates.

**Figure 4. Main genetic alterations affecting B/CAF/Tfh crosstalk in FL**

Schematic representation on the main individual recurrent B-cell intrinsic genetic alterations affecting the crosstalk between immune and stromal TME and FL (pre)malignant B cells to promote lymphomagenesis.

Figure 1

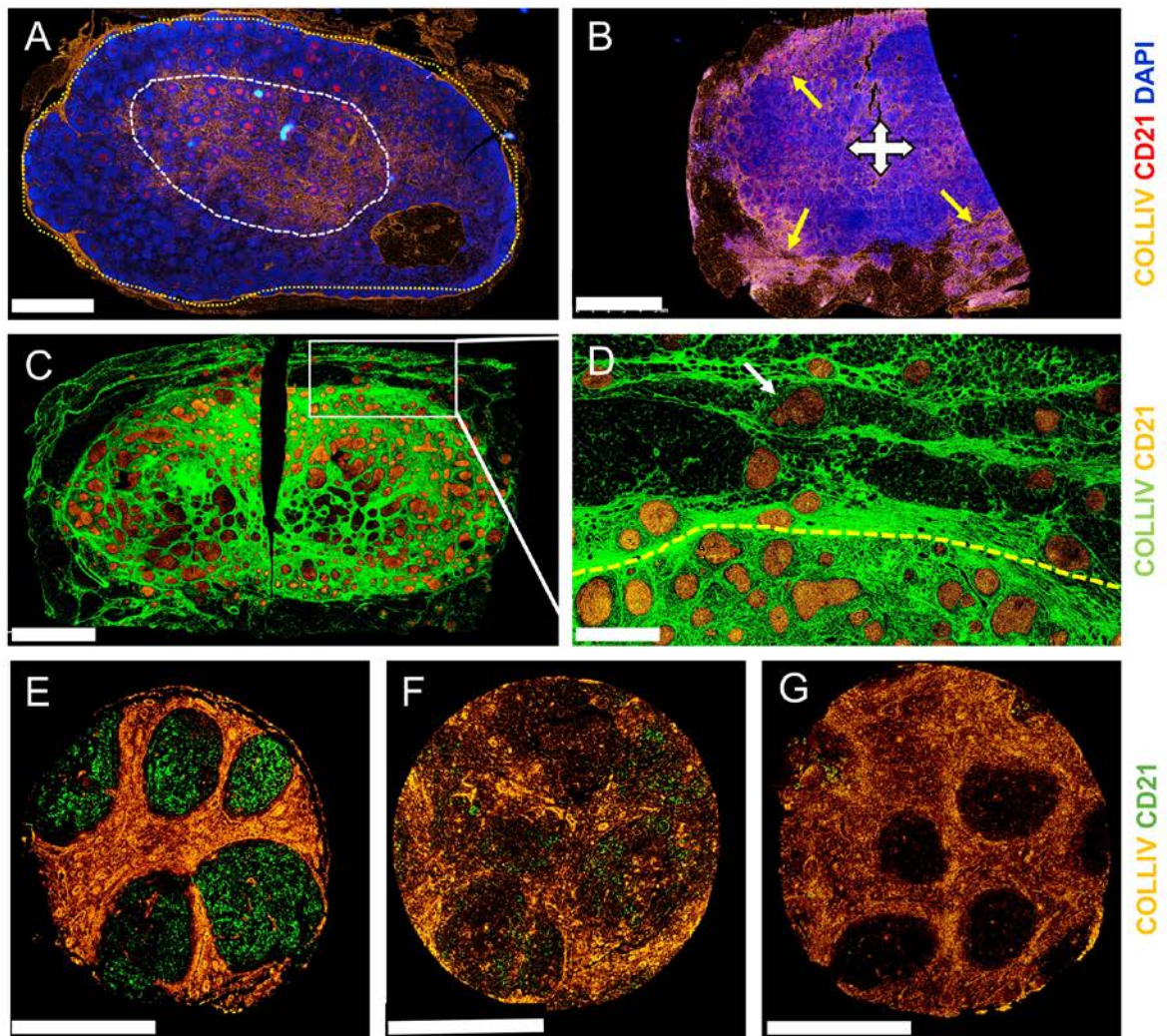


Figure 2

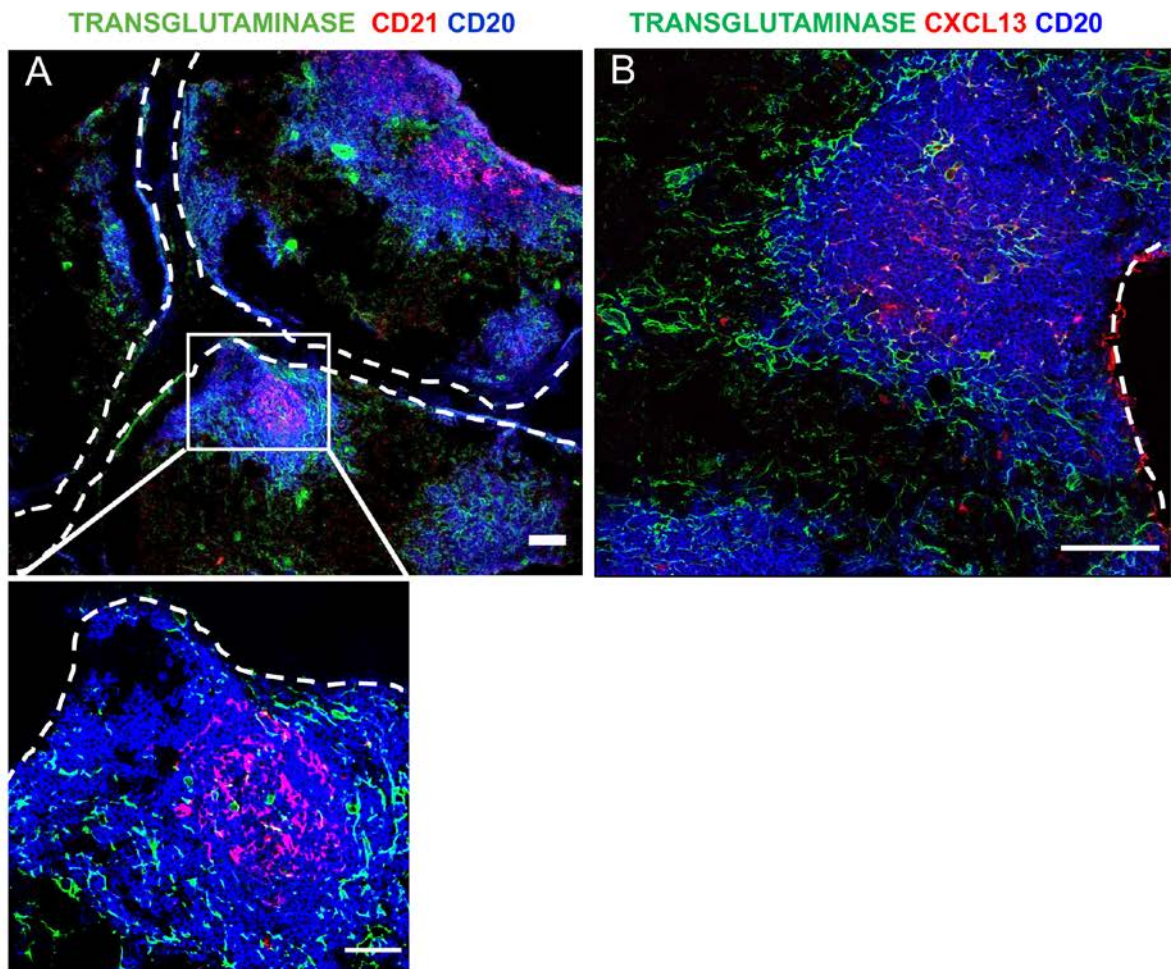
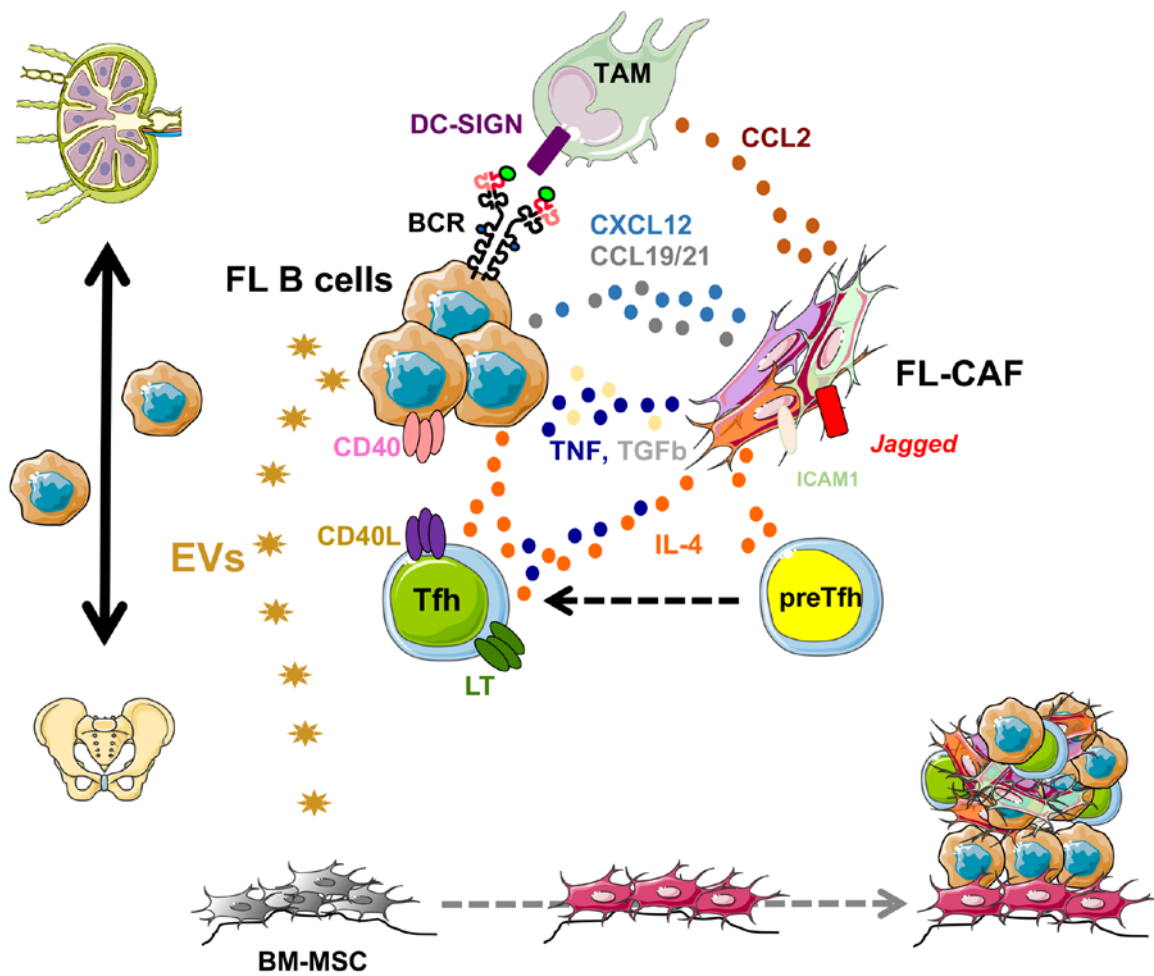


Figure 3



**Figure 4**

