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Fibroblast subtypes in tissues affected by autoimmunity: with lessons from lymph node fibroblasts

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The recent advent of single-cell technologies has fast-tracked the discovery of multiple fibroblast subsets in tissues affected by autoimmune disease. In recent years, interest in lymph node fibroblasts that support and regulate immune cells has also grown, leading to an expanding framework of stromal cell subsets with distinct spatial, transcriptional, and functional characteristics. Inflammation can drive tissue fibroblasts to adopt a lymphoid tissue stromal cell phenotype, suggesting that fibroblasts in diseased tissues can have counterparts in lymphoid tissues. Here, we examine fibroblast subsets in tissues affected by autoimmunity in the context of knowledge gained from studies on lymph node fibroblasts, with the ultimate aim to better understand stromal cell heterogeneity in these immunologically reactive tissues.

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Introduction

The heterogeneity of fibroblasts in secondary lymphoid tissues has been long appreciated, in part because of the notably distinct anatomic compartments populated by T versus B cells and aided by the finding of monoclonal antibodies that recognized compartment-specific stromal antigens. While studying the thymic stroma in the 1980's, van Ewijk *et al.* generated a panel of monoclonal antibodies. This panel included the ER-TR7 antibody, which stained vascular structures in the thymus but more robustly stained fibroblasts that comprised a reticular network in the T zones of lymph nodes and spleen [1,2]. In the early 1990's, Farr and colleagues generated the antibody clone 8.1.1 to study thymic epithelial cells, and found that 8.1.1 labelled T zone reticular cells similarly to ER-TR7 [3]. Using expression cloning, they identified the antigen as gp38, now also known as podoplanin, that is used as a defining marker of the reticular cells now referred to as fibroblastic reticular cells [4]. Although reticular cells also resided in B cell follicles, ER-TR7 and 8.1.1 notably did not stain these cells, pointing to the compartment-specific nature of fibroblasts in lymphoid tissues. In the B cell follicles, the distinct meshwork of fibroblast reticular cells, known as follicular dendritic cells (FDCs) based on their morphology, also attracted considerable attention due to their capacity to bind immune complexes and interact closely with the B cells. The FDCs, although initially thought to be of the hematopoietic lineage, are now understood as originating from mesenchymal stem cells based on lineage tracing experiments and radioresistance patterns, and are stained by antibodies such as FDC-M1 (now known to recognize MFG-E8) and FDC-M2 (complement factor C4) [5,6]. In the late 1990's, FDCs were shown to be primary expressors of CXCL13, the ligand for CXCR5, while T zone FRCs, among other cells, expressed CCL19 and CCL21, the ligands for CCR7 [7]. This furthered the understanding of positional specificity for reticular cells that now included expression of distinct lymphocyte support factors and laid the foundation for subsequent studies.

Studies in the mid-2000s began to focus in on and characterize lymph node stromal cells in greater detail. These studies, often with the addition of flow cytometric analysis that traded in positional information for more granular protein expression information, led to further delineation of stromal subsets within the B cell and T cell compartments. During this period, marginal reticular cells (MRCs) in the follicles were identified and T zone FRCs were better characterized [4,8,9]. It became clear that there was heterogeneity even within the T zone, as high

VEGF expression marked a subset of FRCs that were enriched in vascular-rich regions [10]. Sorting and transcriptomic analysis along with accelerating interest in stromal cells in the last eight years further expanded our understanding of FRC subsets and potential functions, including the identification of PDPN-neg fibroblasts that resemble pericytes, cortical reticular cells, BP3-CD34$^+$ cells that have a perivascular location in the medulla, medullary fibroblasts, and the understanding that FRCs, like synovial fibroblasts, can express cadherin 11 (CDH11) [11,12••,13–15]. More recently, Rodda *et al.* used single-cell RNAseq to examine lymph node stromal cells, identifying 3 subsets of T zone reticular cells and 2 subsets that were enriched in the medulla, in addition to delineating the FDCS, MRCs, perivascular cells, and CD34$^+$ cells [16••].

In the last two decades, synovial fibroblasts in rheumatoid arthritis (RA) have been increasingly recognized as active participants in joint inflammation and injury and encompassing heterogeneous phenotypes. Synovial fibroblasts were observed in the rheumatoid synovium that share characteristics with those in lymphoid tissues [17–19], and this paralleled the development of the understanding that tissue inflammation can drive the adoption of lymphoid tissue reticular cell phenotype [20,21]. Recently, high dimensional analysis of human synovial fibroblasts using single cell RNAseq and mass cytometry (CyTOF) have helped to define multiple fibroblast subsets in the inflamed synovium. Here, we examine synovial fibroblast subsets in the context of insights gained from studies on lymph node fibroblasts, with the goal of better conceptualizing the heterogeneity in both tissues.

Lymph node and synovial stromal subsets: are there parallels?

Synovial fibroblasts can be divided into two general categories based on anatomic location. The lining fibroblasts, together with macrophages, produce and turn over the synovial fluid and provide an epithelial-like layer that separates the fluid from the sublining, albeit without a basement membrane. Sublining fibroblasts are interspersed within and likely responsible for generating the extracellular matrix that constitutes the bulk of the mass of the sublining tissue under homeostatic states. Lining fibroblasts are marked by CD55$^+$PRG4$^+$ and Thy1(CD90)^{lo}, in contrast to sublining fibroblasts that exhibit CD55-PRG4- and Thy1(CD90)$^+$ [18,22••,23,24••,25••,26••]. Similar to lymph node FRCs, both lining and sublining fibroblasts in human and mouse synovium are PDPN$^+$ and FAPa$^+$ [22••,26••,27] (Table 1), suggesting a degree of resemblance among these fibroblast populations. Sublining fibroblasts resemble lymph node FRCs in expressing Thy1, albeit at higher baseline levels, and both FRCs and sublining fibroblasts further upregulate Thy1 upon an inflammatory challenge [22••,26••,28,29] (Table 1). Synovial sublining fibroblasts undergo proliferative expansion upon inflammation, much like FRCs do upon lymph node inflammation and swelling [22••,26••,30] (Table 1). In RA synovium, a subset of sublining fibroblasts exhibit MHCII^{hi} CD34- Thy1$^+$ (mirroring the CD34-Thy1+ murine sublining cells), and both express inflammatory cytokines and chemokines, much like FRCs as a whole. In particular, one of the sublining fibroblast subtypes express high levels of IL-6 and CXCL12 [22••,26••], reminiscent of the constitutive and widespread stromal IL-6 and CXCL12 expression by FRCs throughout lymph nodes [12••,15] (Table 1).

While tertiary lymphoid structures can form in rheumatoid synovium, they are relatively rare in frequency, and T and B cells typically accumulate in spherical aggregates wherein both cell types interspersed without distinct regions such as in the lymph node. In single cell RNA-seq examination of synovium, there was no obvious population that resembled the largest FRC subset, the T zone FRCs (TRCs), in expressing CCL21 or CCL19 or the T zone and follicular stromal marker BP-3. However, MHCII^{hi} CD34- sublining cells resemble the CCL19^{hi} subset of TRCs that populate the majority of the T zone, as they are high expressers of extracellular matrix components (and CD34$^{-/lo}$). In expressing interferon response genes and MHCII, they also resemble the CXCL9$^+$ subset of TRCs that may represent IFN-activated CCL19^{hi} TRCs [16••,26••] (Table 1). Thus, the sizable population of synovial sublining fibroblasts resemble TRCs (Figure 1).

Anatomically, synovial lining fibroblasts share similarities with lymph node marginal reticular cells (MRCs) that sit at the back border of the B cell follicles just under the floor of the subcapsular sinus (Figure 1). Notably, both lining fibroblasts (in mice) and MRCs are unique from other fibroblasts in their tissues in expressing high levels of RANKL (Table 1). RANKL is a driver of osteoclastogenesis and of macrophage development more generally, and the RANKL expression by both lining fibroblasts and MRCs may reflect their shared function in their unique anatomic locations in this regard. Osteoclast activation by lining fibroblast-derived RANKL would be consistent with their role in mediating bone and cartilage damage in inflammatory arthritis [22••], and MRC-derived RANKL is important for maintenance of CD169+ sinusoidal macrophages [33•] that play important roles in limiting viral dissemination [34]. Interestingly, Wilms' Tumor1 (WT1)+ mesothelial cells, epithelial-like cells that line cavity surfaces such as the peritoneum, resemble synovial lining cells and MRCs in their lining function and their ability to modulate macrophages and B cells [31,32•]. The WT1+ mesothelial cells along with WT+ fibroblasts were recently shown to maintain peritoneal macrophages via retinoic acid

Table 1

Fibroblast subtypes in lymph nodes, inflamed synovium, skin, and salivary glands

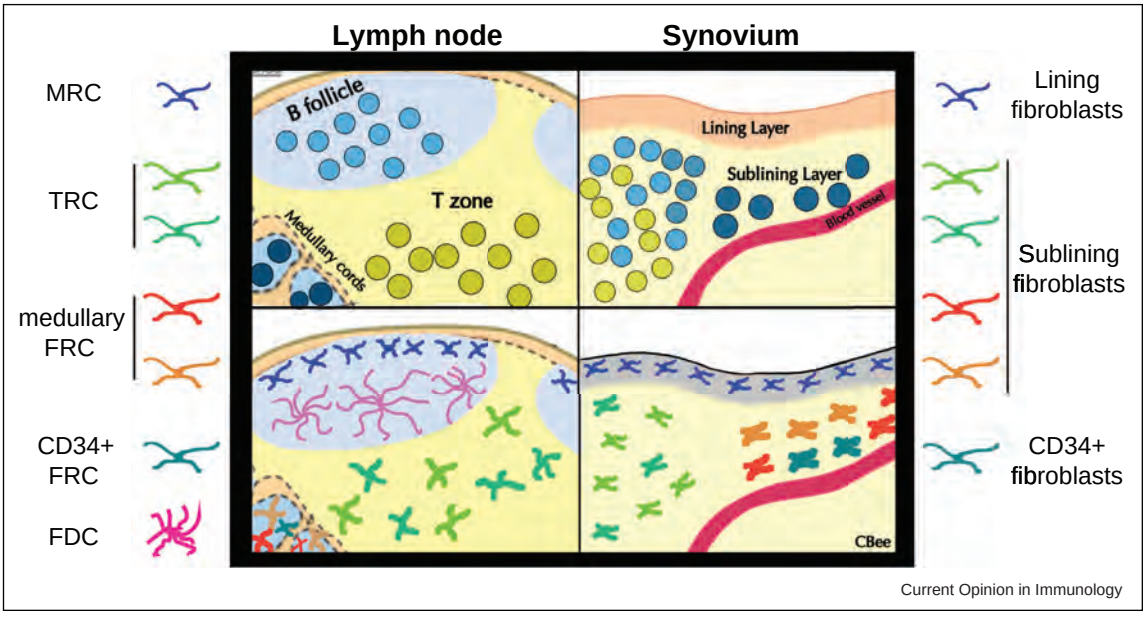
Lymph Node						Synovium				Skin			
Fibroblast Subtype	Phenotype	Function	Inflammatory State	Ref.	Fibroblast Subtype	Phenotype	Function	Inflammatory state	Ref.	Fibroblast Subtype	Phenotype	Function	Inflammatory state	Ref.
Pericytes	PDPN− Thy1+ Itga7+ Acta2+	- perivascular - endothelial support - prevent bleeding from HEVs - modulate HEV integrity and function	- upregulate peripheral tissue-restricted antigen expression and PD-L1 after Poly:C treatment in mice.	[11,16••,28]	**Pericytes**	PDPN-Thy1+	- perivascular - endothelial support		[24••,25••]	**Pericytes**	PDPN + Thy1+ CD34− SMA + PDGFRβ +	- perivascular - endothelial support		[48]
CD34+ reticular cells	PDPN + CD34 + CDH11+ Thy1 +/− Sca1+/−	- in the capsule and perivascular in medulla - can differentiate into FRC-, MRC-, and FDC-like cells and pericytes		[11,13,16••]	**CD34+**	PDPN+ Thy1+ CD34+ HLA-DR$^{hi/lo}$ FAPα+	- sublining fibroblasts	- when activated pathologically, promote inflammatory cell infiltration in mice	[22••,24••,26••]	**CD34+**	PDPN+/− Thy1−	- dermal fibroblasts	- decreased in systemic sclerosis and murine wounds - transition to CD34- PDPN + fibroblasts and αSMA + myofibroblasts during fibrosis by TGF-β activity.	[42]
T-zone reticular cells (TRCs)	PDPN + CCL21+ CCL19$^{lo/hi}$ IL7+ CXCL12+ CDH11+ Thy1$^{-/lo}$ BP3+	- positioning in T zone - maintain T cell homeostasis via IL-7 - express extracellular matrix for conduit network - lymphocyte migration - express CXCL12, BAFF, and IL-6 - express iNOS to regulate T cell responses	- increased PDPN and Thy1 expression with immunization - proliferative expansion - CXCL9+ subset may be interferon-exposed state	[4,11,12,14,15,16,28,38]	**HLA-DRA^{hi}**	PDPN+ Thy1+ CD34- FAPα+	- sublining fibroblasts	- mass IL-6 producers. - interferon signature - express extracellular matrix - activated state enriched in rheumatoid arthritis	[24••,26••]	**CD34−**	PDPN + Thy1+ SMA−	- perivascular adventitial fibroblasts	- expanded in systemic sclerosis and murine wounds - increased VCAM1 expression when activated (e.g. in DLE)	[42,48]
Follicular dendritic cells (FDCs)	PDPN$^{+/-}$ BP3+ CXCL13^{+} CD21/35^{+} CDH11+ Thy1$^{-/lo}$	- positioning in B follicles - present antigen to B cells - maintain germinal centers	- increased BP3, PDPN, CD21/35, ICAM and VCAM1 with formation of secondary follicles - in light zone of germinal centers	[16••,46]	**DKK3+**	PDPN+ Thy1+ CD34− HLA−DR^{lo} FAPα+	- sublining fibroblasts	- activated state enriched in rheumatoid arthritis	[24••,26••]	**Adipose-derived stromal cells (ADSCs)**	PDPN + Thy1+ EpCAM− CD34+ Sca1+	- in dermal white adipose tissue - can differentiate into multiple mesenchymal lineages - reparative with anti-inflammatory and angiogenic properties	- increased PDPN expression with fibrosis - decreased survival and reduced numbers in fibrosis	[49,50]

Table 1 (*Continued*)

Lymph Node					Synovium					Skin				
Fibroblast Subtype	Phenotype	Function	Inflammatory State	Ref.	Fibroblast Subtype	Phenotype	Function	Inflammatory state	Ref.	Fibroblast Subtype	Phenotype	Function	Inflammatory state	Ref.
Marginal reticular cells (MRCs)	PDPN + CXCL13+ MAdCAM + Tnfsf11+ CDH11+ $Thy1^{-/lo}$ BP3+	- back of the B cell follicle near subcapsular sinus - express CXCL13 and BAFF - express RANKL to support macrophages - can give rise to FDCs	- increased PDPN expression with immunization	[11,12]	**CD55+**	PDPN + Thy1- CD34+/− $HLA\text{-}DR^{hi}$ CDH11 +/− FAPα+	- lining fibroblasts	- express RANKL - can promote cartilage destruction. - increased PDPN and αSMA expression in rheumatoid arthritis	[18,22••,25••, 26••,51]					
CXCL12-expressing reticular cells (CRCs)	PDPN+ CXCL12+ CDH11+ $Thy1^{-/lo}$	- regulate B cell trafficking and germinal center responses	- pre-existing follicular CRCs later form germinal center dark zone CRCs during immune responses	[15,16••,52]						Salivary Gland				
Medullary reticular cells (MedRCs)	PDPN+ CXCL12+ CXCL13− CCL21− CDH11+ $Thy1^{-/lo}$ BP3− (mouse) BP3+ (human)	- express BAFF and IL-6 to support plasma cell survival - regulate plasma cell positioning	- increased PDPN expression with immunization - proliferative expansion - increased collagen expression	[12••]						**PDPN+ CD34+**	FAPα+ $ICAM^{hi}$ $VCAM^{hi}$	- support tertiary lymphoid structure formation with inflammation	- enriched for IL7 and BAFF in Sjogren's syndrome - increased ICAM/VCAM/ chemokine expression from $ICAM/VCAM^{lo}$ state and proliferative expansion in murine model of Sjogren's	[43•]
										PDPN+ CD34−	FAPα-	- support tertiary lymphoid structure formation with inflammation	- enriched for CXCL13, CCL19, and CCL21 in Sjogren's syndrome.	[43•]

Abbreviations: FRC: fibroblastic reticular cell, RC: reticular cell, FDC: follicular dendritic cell, TRC: T-zone reticular cell, DLE: discoid lupus erythematosus, SC: stromal cell, CRC: CXCL12-expressing reticular cells, PDPN: podoplanin, PDGFRβ: platelet-derived growth factor receptor-β.

Figure 1



Fibroblast and immune cell organization in lymph nodes and synovial tissue.
Upper left: In the lymph node, anatomically distinct structures are defined by the presence of unique immune cell types; including B cell follicles, T cell zones and medullary cords with plasma cells. Lower left: Each of these regions contains fibroblasts with distinct phenotypes, such as the follicular dendritic cells (FDC) in B cell follicles and fibroblastic reticular cells in T zone (TRC) and the vascular-rich medulla (medullary RC). Upper right: In the inflamed synovial tissue from patients with rheumatoid arthritis (RA), aggregates of CD4 T and B cells typically arise near the vasculature, whereas other immune cells are found in less organized patterns throughout the sublining. Lower right: Synovial fibroblasts are thought to be of two major subclasses, the lining fibroblasts are organized in a layer that interfaces with the synovial fluid while sublining fibroblasts are scattered throughout the extracellular matrix below the lining. In RA, at least two unique activated fibroblast phenotypes are induced and will likely prove to localize in independent niches containing-specific immune cell types. The matching of colors of fibroblast subtypes across synovium and lymph node are theoretical and based on the discussion in the text. Left panels adapted from Ref. [16••].

expression [32•], and it will be interesting to understand the extent to which parallel mechanisms are used by these three lining cell systems.

MRCs have also been shown to provide FDC precursors upon lymph node expansion during immune responses [35] and are colocalized with ILC3s [36], which potentially reflects a role for MRCs in supporting ILC3s and/or ILC3s in supporting MRCs. It would be interesting to understand if lining fibroblasts, or perhaps a subpopulation of lining fibroblasts, can give rise to sublining fibroblasts and if ILC3s are involved in synovial biology. In this latter scenario, it is interesting to consider that ILC3s are an important source of the LTβR ligand LTα1β2 during the development of secondary lymphoid tissues and stromal recovery after viral infection [37,38] and that the LTβR ligand inhibitor, LTβR-Ig, ameliorated disease development in the collagen-induced arthritis model [39]. While Baminercept, a humanized LTβR-Ig fusion protein, failed to meet primary endpoints in phase IIb trials with RA patients who had failed either DMARD or TNF-targeted therapies, it did reduce the IFN-I signature [40], and it may be possible that LTβR signals may play important roles in modulating the vascular-stromal environment and IFN-I pathways in RA synovium.

$CD34^+$ fibroblasts exist both in the lymph node and synovium (Table 1, Figure 1). In the lymph node, $CD34^+$ fibroblasts are $PDPN^+$ and $CDH11^+$. These fibroblasts are positioned in the lymph node capsule and medulla as perivascular cells and can potentially be progenitors for FRC, MRC, and FDC-like cells as well as pericytes [11,13,16••,]. CD34 also marks adipose-derived stromal cells with progenitor functions [41] and fibroblasts in quiescent skin that can upregulate PDPN and Thy1 in the fibrotic skin of the autoimmune disease scleroderma [42]. $CD34^+$ fibroblasts have also been described in inflamed salivary glands that have FRC characteristics and in intestines, where they help to maintain an epithelial stem cell niche [43•,44]. It will be interesting to understand if synovial $CD34^+$ fibroblasts can have progenitor functions or how they may contribute to niche formation in the synovium.

Distinct FRCs have recently been described in the lymph node medulla where plasma cells accumulate and are

referred to as medullary FRCs (medRCs) (Figure 1). MedRCs have been shown to be in close contact with plasma cells and a key source of plasma cell survival factors such as IL-6, BAFF, and CXCL12 [12••]. The medulla is rich in vessels and plasma cells, and the sublining compartment of the synovium similarly contains a dense network of blood and lymphatic vessels and can be rich in plasma cells, raising the intriguing possibilities that medRCs may share characteristics with some sublining fibroblasts.

Follicular dendritic cells (FDCs) are mesenchymal-derived cells located centrally within B cell follicles that are essential for germinal center (GC) formation and high-affinity antibody production (Table 1, Figure 1). They are characterized by their high expression of CD21/CD35 (complement receptor type 2 and 1, respectively) [45,46]. FDCs have been described in the synovium in the context of tertiary lymphoid structures [17]. Interestingly, FDCs can derive from MRCs or CD34+ perivascular cells [13,35,46,47], and it would be interesting to understand if they could contribute to FDC generation in the ectopic synovial germinal centers found in some RA patients.

Discussion

Classically defined as tissue-resident stromal cells responsible for extracellular matrix generation and structural stability in a tissue, fibroblasts are now understood as critical players in immune responses across tissue types. In lymphoid tissues, fibroblasts have long been understood as central contributors to the development of adaptive immunity by providing both structural and molecular factors essential to T cell and B cell activation and survival. Lymph node studies have laid the groundwork indicating a vast diversity of potential fibroblast phenotypes, which can now be used as comparators to classify fibroblasts from other tissues including, in particular, activated phenotypes elicited by inflammatory triggers akin to a lymph node immunologic response. Single-cell studies on inflamed synovial tissue from RA patients has now shed light on at least 4 distinct fibroblast subsets, but from the experience of lymphoid tissues, there is likely more granularity to be found with additional studies. Understanding unifying themes such as antigen acquisition and support of adaptive immunity will be important in non-lymphoid tissues particularly in the context of autoimmune diseases [31,32•]. Further, whether inherently dysregulated differentiation of these fibroblast subsets underlies pathogenesis in autoimmunity will be an important direction to study in the coming years. Lastly, it will be exciting to understand how fibroblast subsets communicate with and for the greater physiologic state of the body through conduits of the lymph, vasculature, bone marrow and synovial fluid, including how these resident tissue cells types are shaped by perturbations possibly for long periods through stable epigenetic or genetic modifications, thereby leaving lasting imprints of immunologic and inflammatory responses at the local tissue site.

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Declarations of interest

None.

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