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Review

A short field guide to fibroblast function in immunity

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ABSTRACT

Fibroblasts in secondary lymphoid organs, or fibroblastic reticular cells (FRC), are gate-keepers of immune responses. Here, we frame how these cells regulate immune responses via a three-part scheme in which FRC can setup, support or suppress immune responses. We also review how fibroblasts from non-lymphoid tissues influence immunity and highlight how they resemble and differ from FRC. Overall, we aim to focus attention on the emerging roles of lymphoid tissue and non-lymphoid tissue fibroblasts in control of innate and adaptive immunity.

1. Introduction

Fibroblasts have been fundamental in furthering our understanding of the immune system. Seminal experiments performed by Zinkernagel and Doherty to uncover major histocompatibility restriction utilized infected fibroblasts as targets for cytotoxic T cells [1]. The potent antiviral cytokine, interferon-β, was originally identified as "fibroblast interferon" [2]. A vaccine exclusively targeting antigenic peptides to fibroblasts may represent a viable preventative treatment for HIV/AIDS [3,4]. Fibroblasts are essential instruments in the immunologist's toolbox, historically used to study other components of an immune response and overlooked for their own contributions to immunity and tolerance. However, new studies are uncovering important functions for these cells in setting up, supporting and/or suppressing immune responses in infection, autoimmunity and cancer. Here we propose a framework based on existing and emerging knowledge to bring into focus how fibroblasts impact immune responses in different tissue microenvironments.

1.1. Fibroblasts and lymphoid fibroblasts, defined

Fibroblasts are non-hematopoietic, non-endothelial, non-parenchymal, non-epithelial, non-mesothelial cells. They are typically of mesenchymal origin but can originate from mesothelial- [5], epithelial- [6], endothelial-to-mesenchymal transition [7], and possibly from hematopoietic cells (fibrocytes) [8]. These cells define the architecture of tissue microenvironments by depositing and remodeling extracellular matrix components [9]. Fibroblasts are primary actors in wound healing and fibrosis [10], though these functions will not be addressed in depth here. Like tissue-resident immune cells, fibroblasts exhibit topographic diversity, tissue-specific functions and heritable positional memory [11–14]. Yet, our understanding of stromal-immune interactions in non-lymphoid tissues has been somewhat limited due to a paucity of robust methodologies for selectively identifying and manipulating fibroblasts *in situ*. Despite these hurdles, the pace of definitive research in this field will undoubtedly accelerate with the emergence of innovative genetic and pharmacologic tools that enable faithful elucidation and modulation of fibroblast function in their natural tissue settings.

Due to the advent of novel tools, such as the *Ccl19*Cre mouse [15], recent work has illuminated definitive roles for lymphoid fibroblasts in immune responses (reviewed in Ref. [16]). Secondary lymphoid organs (SLO), which include lymph nodes (LN), spleen and Peyer's Patches, are tissues where adaptive immune responses are initiated. SLO-resident fibroblasts, also known as fibroblastic reticular cells (FRC), are generally defined by expression of the surface molecules podoplanin (PDPN; also known as gp38 or Aggrus) and platelet derived growth factor receptor-α (PDGFRα, CD140α) and lack of endothelial marker platelet endothelial cell adhesion molecule (PECAM-1, CD31) and hematopoietic marker CD45 [17]. FRC derive from mesenchymal lymphoid tissue organizer cells in the LN anlage during embryogenesis and mature into immunologically competent fibroblasts upon lymphotoxin-β-receptor ligation [15]. Similar to activated fibroblasts in non-lymphoid tissues (often referred to as "myofibroblasts", See Box 1), FRC are highly contractile, which restricts the size of LN [18,19]. To date the field has identified 5 subsets of FRC based on surface phenotype, function and location (reviewed in Ref. [20]); however, emerging technologies are likely to reveal further heterogeneity within the stromal compartment of lymphoid organs and beyond.

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Box 1
Fibroblast nomenclature

The fibroblast field is wide in scope and has a unique cache of esoteric terms. Here, we define some common terminology used.

- **Cancer associated fibroblast**: fibroblast within tumor microenvironment
- **Fibroblast activating protein alpha (FAP)**: gene encoding a surface protein expressed by some activated fibroblasts and macrophages in some contexts
- **Fibro/adipogenic precursor (FAP)**: fibroblast in adipose tissue or muscle; can develop into adipocytes or secrete ECM
- Fibroblasts-like synovial cell (FLS): fibroblast in joint synovium
- **Fibroblastic reticular cell (FRC)**: fibroblast in the lymph nodes, splenic white pulp and peyer's patches
- **Myofibroblast**: activated fibroblast that expresses alpha-smooth muscle actin
- **Stellate cell**: fibroblast in pancreas or liver; first identified by Kupffer in 1876 in the liver as "sternzellen" (star cells in German) due to their morphology (reviewed in Ref. [121])
- **Stroma**: composite of mesenchymal cells, endothelial cells, nerve bundles enmeshed in extracellular matrix in a given microenvironment. Macrophages are considered stromal components in some cases.
  - **Resting/resident**: fibroblasts naïve to inflammatory stress
  - **Active**: fibroblasts after integrating inflammatory signals
- **Secondary lymphoid organ:** Anatomical site that maintain naïve lymphocytes and location in which adaptive immune responses arise. Lymph node, spleen and peyers patches are considered secondary lymphoid organs.
- **Tertiary lymphoid structure (TLS)**: aggregation of loosely organized B and T cells outside of the lymph node with FRC-like reticular cells, high endothelial venules and follicular dendritic cells.

2. Fibroblasts in lymphoid organs: a paradigm for stromal control of immunity

To contextualize fibroblastic control of immunity, we propose the following framework (Table 1). This model aims to highlight the tripartite manner in which FRC influence immune responses: FRC can Setup, Support and Suppress an immune response in SLO. We describe the supporting evidence below.

2.1. FRC setup a niche for lymphoid cells

Under steady state conditions, FRC create supportive and instructive niches for immune cells and thereby set the stage for adaptive immune responses to unfold in SLO. FRC generate the chemokines *Ccl19* and *Ccl21*, which are ligands for CCR7, a chemokine receptor expressed on naïve T cells and DC. Sensing of CCR7 ligands instigates DC migration to T cell zones and T:DC interactions, thereby facilitating immune responses [15,21]. FRC also express *Cxcl13*, a ligand for CXCR5, which is expressed by B cells [22,23] and follicular helper T cells [24,25] and CXCL12 which can recruit T cells, B cells and DC [26]. Expression of these chemoattractants aids in establishing T and B cell zones of SLO and ensures proper localization of antigen presenting DC for mounting an immune response [27–32]. In addition to coordinating cellular compartmentalization within SLO, FRCs produce the cytokines IL-7 [21] and BAFF [23] which promote the survival of naïve T and B cells, respectively. FRC also maintain marginal zone B cells and ESAM$^+$ DC through expression of the notch ligand Delta-like 1 [33]. Interestingly, depletion of LN FRC, results in a rapid loss of neutrophils, monocytes and dendritic cells from the lymph node [23]. FRC have recently been shown to express *Ccl2* and *Ccl8 in vitro* [34] but the extent to which FRC regulate myeloid cell homeostasis in SLO remains to be determined.

Efficient immune responses require antigens, which can be delivered to LN via migrating DC or lymph. Conduits in SLO rapidly transport afferent lymph containing small antigens, chemokines and cytokines (MW less than ~70–80 kDa) from the subcapsular sinus into the LN parenchyma [35–37]. These conduits are composed of ordered ECM that is generated by FRC and ensheathed by these cells [36–39], reviewed in Ref. [40]. Migratory DC, which express CLEC-2, a ligand for PDPN, can traverse the FRC network via a CLEC2-PDPN cognate interaction in the absence of *Ccl19* or *Ccl21* [41], reviewed in Ref. [42]. Additionally, DC and B cells can acquire lymph-borne antigen from conduits [37], though the immunological consequence(s) of this route of antigen sampling is still under investigation. It should be noted that antigens are not exclusively sampled via conduits and DC that acquire antigen through the lymphatic sinus rapidly induce immune responses [43].

2.2. FRC can support the onset and perpetuation of immune responses

In addition to setting the stage in SLO for immune responses, FRC can support or perpetuate these reactions once they initiate. One means by which FRC may amplify immune responses is by diminished

Table 1
Setup, Support and Suppress framework to understand control of immunity by FRC.

SLO FRC			
Lymph nodes, spleen (white pulp) and Peyer's Patches	- Production of homeostatic cytokines (IL-7, BAFF) - Production of chemoattractant cytokines (Ccl19, Ccl21, Cxcl13) - Production of RA (mLN) - PDPN-based DC migration - Notch ligand expression - Conduit-mediated antigen transport	- Diminished production of chemoattractant cytokines - Production of homeostatic cytokines (IL-7, BAFF) - Release of alarmins (IL-33) - Allow for LN swelling - Increased proliferation	- NOS2-mediated T cell suppression - Limiting IL-15 availability (mLN/PP) - Peripheral tolerance of T cells - PDL1 expression - TGFβ microvesicles polarizing T_{reg} - Excessive ECM deposition (SIV/HIV)
Role in immune response	**Setup** for an immune response	**Support** an immune response	**Suppress** an immune response
Immune response chronology	Before	During	Before or after