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Review

Fibroblasts: Origins, definitions, and functions in health and disease

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SUMMARY

Fibroblasts are diverse mesenchymal cells that participate in tissue homeostasis and disease by producing complex extracellular matrix and creating signaling niches through biophysical and biochemical cues. Transcriptionally and functionally heterogeneous across and within organs, fibroblasts encode regional positional information and maintain distinct cellular progeny. We summarize their development, lineages, functions, and contributions to fibrosis in four fibroblast-rich organs: skin, lung, skeletal muscle, and heart. We propose that fibroblasts are uniquely poised for tissue repair by easily reentering the cell cycle and exhibiting a reversible plasticity in phenotype and cell fate. These properties, when activated aberrantly, drive fibrotic disorders in humans.

INTRODUCTION

Fibroblasts are referred to canonically as cells that create and maintain an anatomically diverse array of extracellular matrix (ECM)-rich connective tissues to support a broad range of essential organ functions, like resistance to blunt and sharp injuries in the skin or organ-wide stretching and elastic recoiling in the intact breathing lung. In doing so, fibroblasts provide essential niches and positional information for neighboring cells via microarchitectural, biomechanical, and biochemical cues in the ECM and regulated secretion of soluble mediators such as cytokines, growth factors, and metabolites (Figure 1). Beyond producing connective tissue, fibroblasts serve as progenitors for specialized mesenchymal cell types, such as bone-forming osteoblasts or lipid-filled adipocytes, during embryonic development, adult homeostasis, and injury, repair, and remodeling. In this review, we use the term "fibroblasts" to refer to cells that (1) secrete many of the same structural and signaling macromolecules that contribute to tissue's extracellular space, (2) adopt a transient and contractile myofibroblast phenotype in response to tissue damage, (3) act as signaling niche cells for tissue-resident stem cells, and/or (4) serve as progenitors, sometimes called mesenchymal stem cells, for specialized differentiated mesenchymal cells (Lemos and Duffield, 2018; Pittenger et al., 1999, 2019).

Fibroblasts were first described as a distinct cell type in 1858 by German pathologist Rudolf Virchow, who called them "Spindelzellen des Bindegewebes"—"spindle-shaped cells of the connective tissue" (Virchow, 1858; Figure 2A). The term "fibroblast" was first proposed by Ernst Ziegler to describe cells that produce new connective tissue upon healing (Ziegler, 1895; Figure 2B), and this observation was replicated by Santiago Ramón y Cajal, who observed "célula fusiforme" or "fibro-células" as essential producers of granulation tissue in healing skin wounds and scars (Cajal, 1896; Figure 2C).

Fibroblast research was facilitated by the advent of *in vitro* techniques developed in the 1900s. These methods allowed

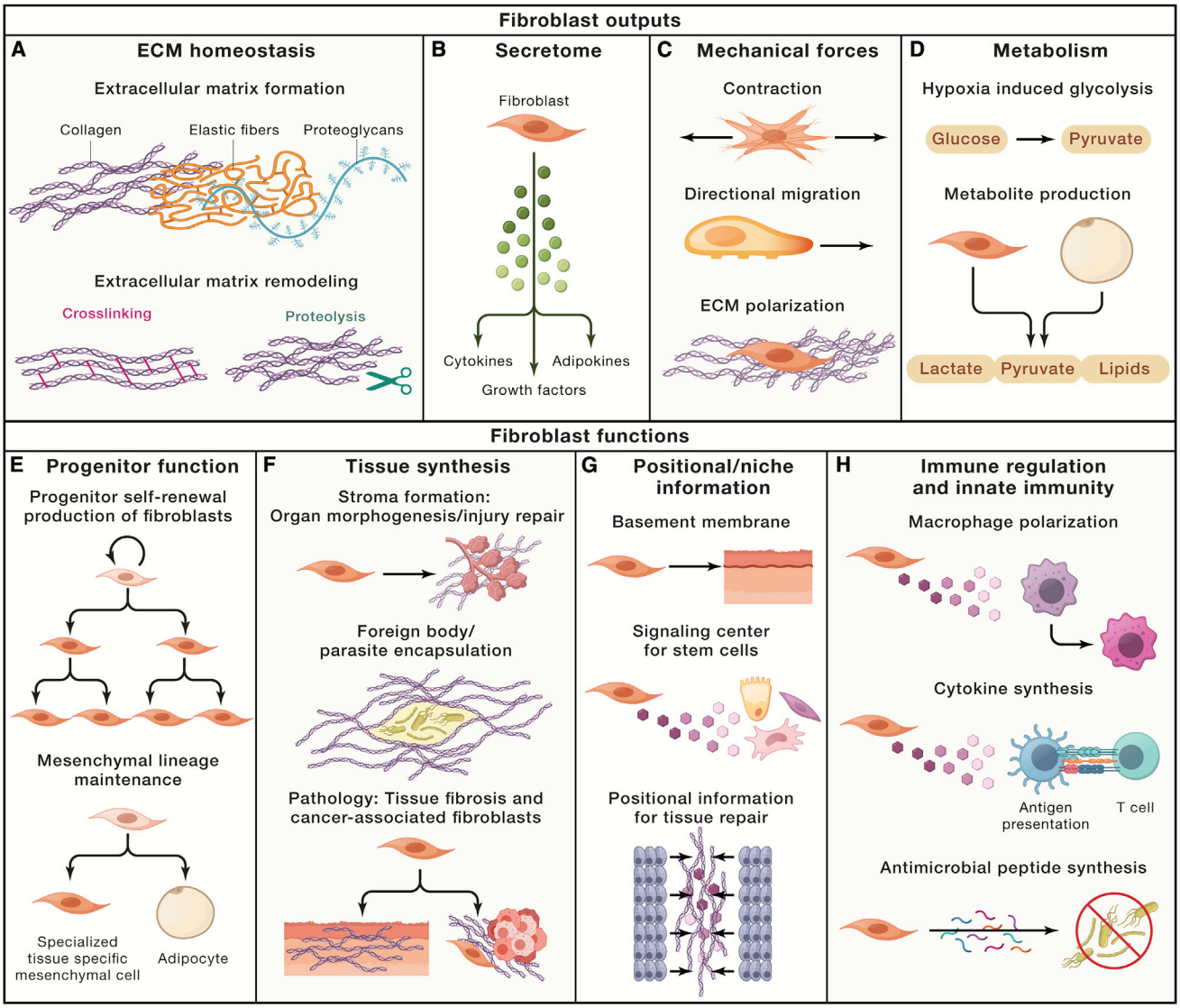

Figure 1. Summary of fibroblast outputs and functions

(A–D) Key outputs of fibroblasts and their mesenchymal lineages include extracellular matrix (ECM) secretion and remodeling (A), secretion of signaling factors for surrounding cells (B), mechanical force generation (C), and regulation of tissue metabolism and metabolite secretion (D).

(E–H) Fibroblasts also function as progenitor cells for mesenchymal lineages (E), as "makers" of new tissue during organ morphogenesis and tissue repair and upon various pathological conditions (F), as sources of positional information across distinct anatomical regions of the same organ and as key signal contributors toward stem cell niches (G), as well as target cells and reciprocal modulators of diverse innate and adaptive immune functions (H).

culture of primary fibroblasts derived from embryonic chick heart explants, which could be propagated easily upon passaging before other cell types (Burrows and Neymann, 1917; Carrel, 1912; Ebeling, 1913; Hogue, 1919; Figure 2D). The establishment of the 3T3 fibroblast cell line, derived from mouse embryos, more than 50 years later (Todaro and Green, 1963; Todaro et al., 1964) further advanced our understanding of the biology and lineage potential of fibroblasts. These discoveries include, among others, identification of fibroblast growth factors (FGFs) (Gospodarowicz, 1974); the phenomenon of multi-lineage differentiation of cultured fibroblasts into bone, cartilage, and adipose cells (Junker et al., 2010); and the key role of fibroblasts in production, remodeling, and contraction of ECM.

Despite the large number of *in vitro* fibroblast studies, the *in vivo* relevance of these cell culture observations remains unclear, and the true spectrum of fibroblasts' properties and their lineage potential in their native *in vivo* environment is only recently being explored in depth. This is largely enabled by the advent of new genetic model organisms that permit specific labeling, tracing, and mutation of fibroblasts in tissues and by application of single-cell genomic technologies. Emerging evidence implicates fibroblasts in driving significant changes in the tumor-associated macroenvironment, as

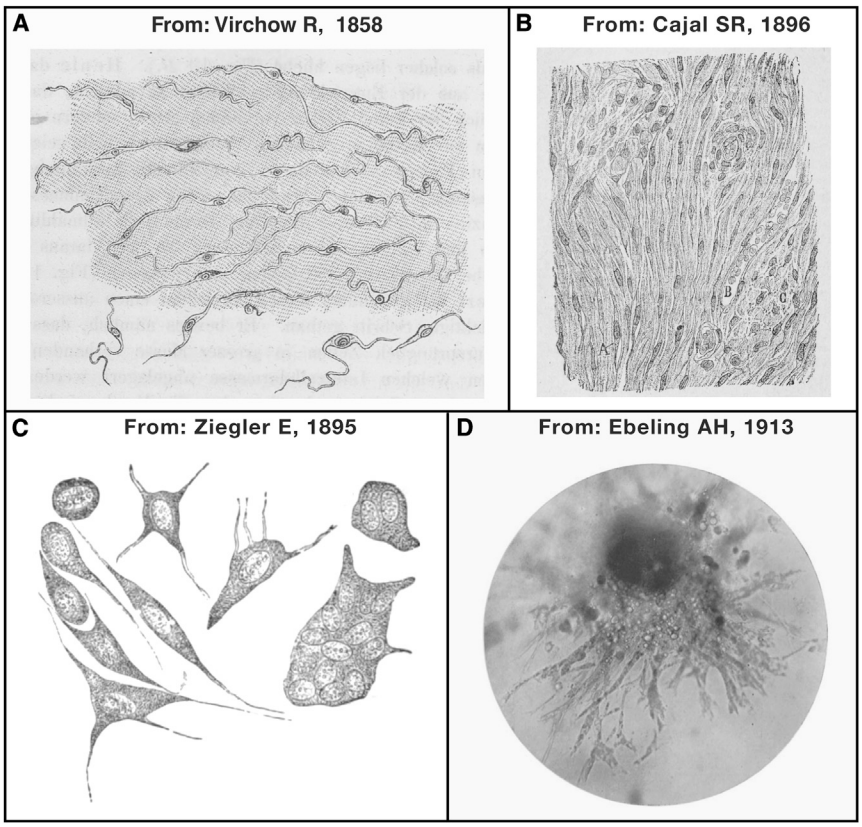

Figure 2. History of fibroblast discovery

(A) First drawing of fibroblasts by Rudolf Virchow as "spindle-shaped" cells embedded within the connective tissue of pig embryos. Modified from Virchow (1858).

(B) Drawing of fibroblasts as fusiform cells within newly formed connective tissue of a "painful" keloid. Modified from (Cajal, 1896).

(C) Drawing by Ernst Ziegler, who first proposed the term "fibroblast" to describe cells that produce new connective tissue upon healing. Various forms of cells in the new granulation tissue are shown. Mononuclear fibroblast-shaped cells are in the bottom left corner. Modified from Ziegler (1895).

(D) Microphotograph of fibroblasts established from embryonic chick heart explant. Cells after 75 passages are shown. Modified from Ebeling (1913).

reviewed extensively elsewhere (Sahai et al., 2020). Here we focus on fibroblast development and their role in adult tissue homeostasis and repair, including recent evidence that highlights the function and heterogeneity of fibroblasts across and within organs and how they are regulated at the molecular level to contribute to tissue development, homeostasis, and repair, and fibrotic disease pathologenesis.

CROSS-ORGAN COMMONALITIES IN FIBROBLAST BIOLOGY

Single-cell RNA sequencing (scRNA-seq) data from several organs has revealed an unappreciated degree of heterogeneity in fibroblasts within and across tissues. Comparing fibroblasts from mouse heart, skeletal muscle, intestine, and bladder revealed that less than 20% of fibroblast-enriched genes overlapped between these four organs (Muhl et al., 2020). Most recently, an even broader cross-tissue comparison of mouse scRNA-seq data identified two universal fibroblast populations expressing the peptidase inhibitor *Pi16* or collagen *Col15a1*, each with shared enrichment for the ECM factor *dermatopontin* (*Dpt*). The latter gene marks the majority of platelet-derived growth factor receptor α (PDGFRα^+) cells in the surveyed tissues by genetic lineage tracing in mice (Buechler et al., 2021). Murine fibroblast populations expressing these universal markers persisted throughout injury, tumorigenesis, or inflammation, with additional specialized subpopulations emerging in these perturbed states. Notably, a population similar to *Pi16*$^+$ mouse fibroblasts was also found in unperturbed human tissues (Buechler et al., 2021), suggesting a cross-species contribution to homeostasis. Further analysis will be required to determine the convergence and divergence of fibroblast populations across murine organs, especially because not all fibroblasts express *Pdgfra*, such as lipofibroblasts in the lungs (Xie et al., 2018) or skin fibroblasts after wounding (Guerrero-Juarez et al., 2019), which also show largely nonoverlapping patterns of *Dpt* and *Col15a1* and nearly absent *Pi16* expression. Beyond gene markers, functional properties are the ultimate discriminator of shared versus unique themes in fibroblast biology. In this section, we outline the shared functions of fibroblasts across multiple tissues and, in a separate section, highlight numerous tissue-specific differences.

Scaffold and signaling: Common fibroblast functions

A major shared function of fibroblasts is ECM synthesis to create connective tissue by depositing fiber- and sheet-forming collagens, proteoglycans, elastin, fibronectin, microfibrillar proteins, and laminins, which collectively comprise the "matrisome." Fibroblasts also actively remodel ECM microstructure through covalent crosslinking, protein glycosylation, and controlled proteolysis via balanced secretion of modifying enzymes such as lysyl oxidase, matrix metalloproteinases (MMPs), and MMP inhibitors (Lu et al., 2011). The ratio of specific ECM molecules and nuanced remodeling activity by fibroblasts can produce an array of compositionally, microanatomically, biomechanically, and functionally distinct ECM across organs that can support a range of specialized cells, such as keratinocytes in the resilient and soft skin, epithelial cells in the malleable and elastic lungs, striated muscle fibers in the contractile skeletal muscle, as well as endothelial cells of blood vessels (Figure 1A; Hynes and Naba, 2012). Fibroblasts also "tug and pull" on their ECM, resulting in tissue-level mechanical forces and matrix polarization (Huang et al., 2012; Figure 1C), and contribute to tissue-specific matrisomes and tissue mechanics.

Beyond the matrisome, fibroblasts secrete numerous cytokines, adipokines, and growth factors (Figures 1B and 1H) whose properties, including diffusion dynamics, are modulated by the ECM and converge to create signaling niches and positional cues for diverse other cells, including, but not limited to, tissue-resident stem cells and immune cells (McGee et al., 2013; Figure 1G). In this light, fibroblasts' role in encoding positional information for other cells is particularly important for proper embryonic development, as revealed in classic tissue recombination studies. For example, when embryonic chick skin epithelium and mesenchyme from scale- or feather-producing body regions were exchanged, the type of skin appendage that formed was instructed by fibroblast-containing dermis (Dhouailly and Sengel, 1975).

Signaling between tissue-resident cells and fibroblasts can establish regional differences and lineage trajectories of fibroblasts in tissues. For instance, synovial fibroblasts exhibit a positional identity that is induced by endothelium-derived Notch signaling (Wei et al., 2020). Another mechanism by which instructive differences in fibroblast biology are established is through expression of specific Homeobox (HOX) transcription factors, which specify body plans along major axes—cranio-caudal, dorsal-ventral, and proximal-distal directions—including in humans (Chang et al., 2002). For example, HOXA13 regulates distal identity and is expressed specifically by finger and foreskin human fibroblasts (Rinn et al., 2006). Regional expression differences exist in other genes that are likely downstream of HOX factors, such as Agouti in mice (Candille et al., 2004), the Wingless-related integration site (WNT) pathway antagonist DKK1 in humans (Yamaguchi et al., 2004), and fibronectin in rodents and humans (Yasuda et al., 2006). Therefore, distinct "HOX codes" of skin fibroblasts drive regional differences in matrisome and signaling factors that, in turn, serve as "information" for adjacent cell types. Reestablishing this positional information may also be an important step during tissue regeneration after injury. For example, restoration of fibroblast HOX codes may function as a pioneering event to drive skin regeneration in adult mice (Abbasi et al., 2020). Beyond skin, positionally distinct fibroblasts with unique HOX codes have been identified recently in synovial joints in mice and humans (Frank-Bertoncelj et al., 2017).

Myofibroblasts: Contraction and coordination of tissue repair

In adult organs, fibroblasts are relatively quiescent unless tissue repair mechanisms or dynamic structural changes are initiated. Recent single-cell analyses indicate that, during tissue development and repair, fibroblasts display transcriptional changes similar to cellular differentiation trajectories, suggesting adherence to lineage hierarchy (Abbasi et al., 2020; Guerrero-Juarez et al., 2019; Phan et al., 2020, 2021). Quiescent fibroblasts have also been shown to function as progenitors that can be induced to divide rapidly to produce many more ECM-secreting fibroblasts and additional distinct mesenchymal lineages, such as adipocytes, in response to injury and hair cycling in the skin (Figures 3 and 4; Junker et al., 2010; Rivera-Gonzalez et al., 2016).

To facilitate tissue repair, signaling and physical factors induce quiescent fibroblasts to form myofibroblasts, which, through their expression of contractile proteins such as αSMA, orchestrate biomechanical remodeling and contraction via traction force (Pakshir et al., 2019) onto the voluminous amounts of new ECM they themselves secrete (Hinz, 2010; Tschumperlin, 2013; Figure 3). Compared with quiescent fibroblasts, mature myofibroblasts adhere to ECM longer (Hinz, 2007), even in the presence of the same signals, suggesting that disengagement of focal adhesions may be essential for myofibroblast state termination (Thannickal, 2013). External adhesion "information" is transduced in myofibroblasts via the cytoskeleton and involves activation of tension-sensitive myocardin-related transcription factor A (MRTF-A) and serum response factor (SRF) (Crider et al., 2011), among other mechanisms.

Beyond contraction, myofibroblasts also function to transform the surrounding tissue environment by modulating resident immune cell functions (Ferrer et al., 2017; Van Linthout et al., 2014) and phagocytosing dead cells (Nakaya et al., 2017). Although myofibroblast functions are vital during acute injury repair, their aberrant activation upon chronic injury or sustained inflammation can lead to disorganized and excessive ECM production, promoting localized scarring, diffuse fibrosis, and, in some instances, aiding tumorigenesis (Desmoulière et al., 2005; Shi-wen et al., 2009). This excessively stiff and compositionally abnormal ECM disrupts the microarchitecture and results in loss of other tissue-resident cells, causing organ dysfunction that can range from mild derangement to catastrophic failure. Fibrosis is estimated to contribute to almost 50% of all deaths in the developed world (Friedman et al., 2013), and despite the existence of drugs that can delay its progression, to date there is no truly curative treatment (Dempsey et al., 2019). Thus, illuminating the fibrogenic functions of tissue fibroblasts holds remarkable therapeutic potential, which we discuss below.

Myofibroblasts arise in response to several signaling pathways, including transforming growth factor β (TGF-β), WNT, and platelet-derived growth factor (PDGF) signaling and, to some extent, by inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), or IL-6 (Figure 3). These factors act on the quiescent, tissue-resident fibroblasts, which are viewed as the dominant source of myofibroblasts after injury. Other specialized mesenchymal cells can also alter their lineage specificity and generate myofibroblasts (Figure 4). For example, pericytes, mesenchymal cells that surround blood vessels and are transcriptionally distinct from fibroblast populations (Armulik et al., 2011), can migrate out of their perivascular location, develop myofibroblast properties, and contribute to excessive ECM deposition in mouse models (Hung et al., 2013; Kuppe et al., 2021; Sava et al., 2017). A relatively small portion of myofibroblasts under certain wounding conditions in the skin and other organs has also been shown to derive from circulating hematopoietic progenitors, commonly myeloid cells (Guerrero-Juarez et al., 2019; Opalenik and Davidson, 2005; Sinha et al., 2018). Studies in mice have also revealed that mature adipocytes in the skin can deplete their lipid stores and convert into contractile myofibroblasts (Kruglikov and Scherer, 2017; Marangoni et al., 2015; Shook et al., 2020). Myoblasts in murine skeletal muscles can also form myofibroblasts as part of the persistent injury-repair cycle upon muscle dystrophy (Biressi et al., 2014). Finally, lipofibroblasts in the mouse lung can adopt functions of

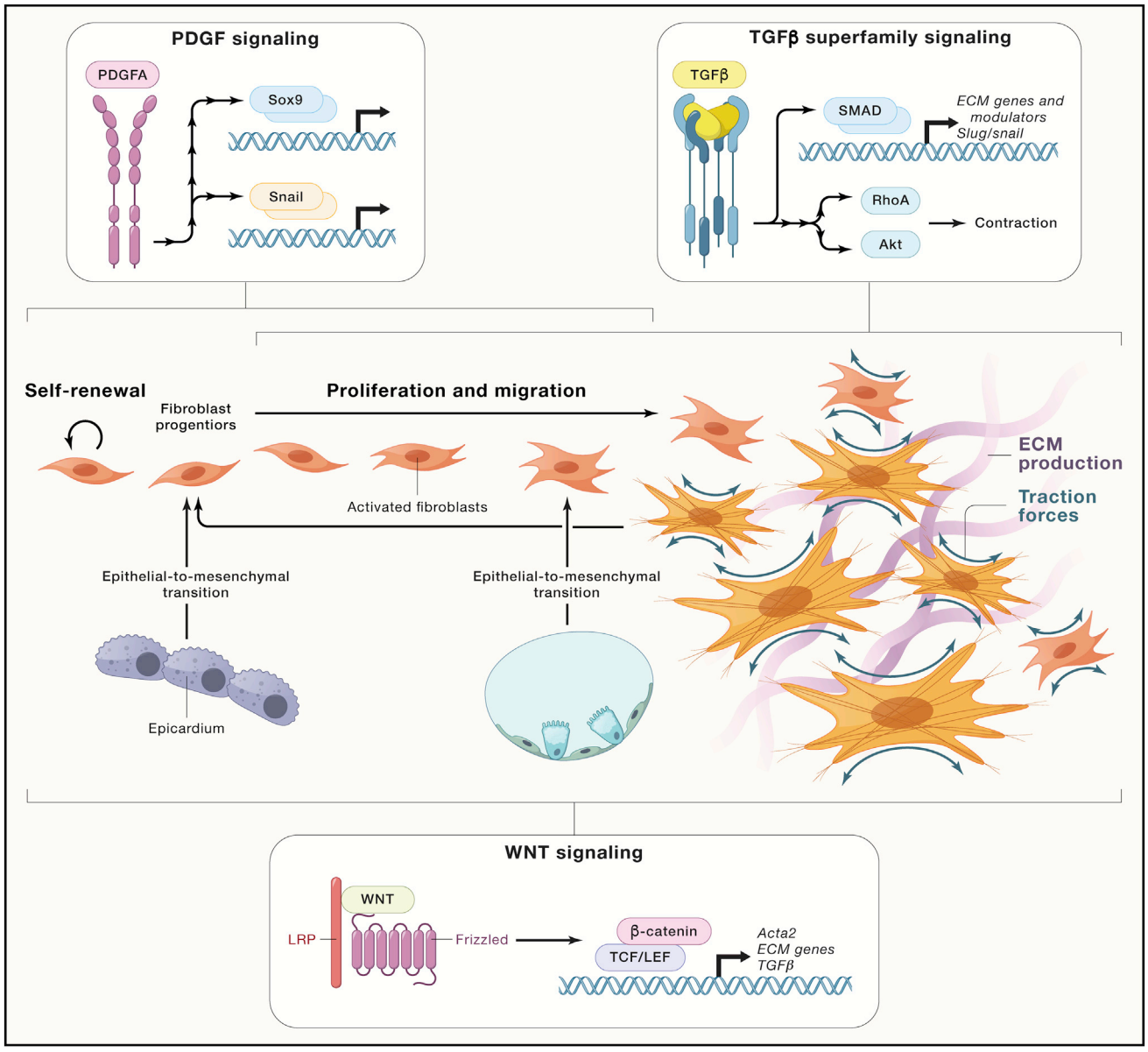

Figure 3. Key roles of PDGF, TGF-β, and WNT signaling pathways in regulating fibroblast functions

Platelet-derived growth factor (PDGF) signaling (blue) regulates diverse aspects of fibroblast development and homeostasis, including epithelial-to-mesenchymal transition (EMT) in the embryonic heart, long-term self-renewal, and proliferation in adult tissues. Signaling via the transforming growth factor β (TGF-β) superfamily of ligands promotes myofibroblast state activation, including contractile protein and ECM gene expression. Among other effects, TGF-β superfamily signaling can induce fibroblast proliferation and lineage transitions by other cells toward a fibroblast state, including via EMT in the lung. WNT signaling regulates fibroblast proliferation, migration, myofibroblast state activation, and ECM deposition. All three pathways can activate transcription of genes to control fibroblast biology, and TGF-β activates Akt and RhoA to induce cellular contraction.

myofibroblasts, including αSMA expression and ECM overproduction (El Agha et al., 2017; Rock et al., 2011).

Although, traditionally, myofibroblasts were thought to be terminally differentiated, accumulating evidence indicates that they are, in fact, temporary and reversible (Hinz et al., 2012). Despite the prominent transcriptional and epigenetic changes that accompany myofibroblast formation, contractile gene expression and function by myofibroblasts decrease and eventually cease when tension reduces in late-stage skin wounds (Hinz et al., 2001). Moreover, myofibroblasts can display broader lineage plasticity and convert into other specialized mesenchymal lineages upon injury resolution. For example, myofibroblasts in large murine skin wounds terminate their contractile behavior and reprogram into new lipid-filled adipocytes in response to bone morphogenetic protein (BMP) ligands secreted by hair follicles (Plikus et al., 2017). During trauma-induced heterotopic ossification, fibroblasts can assume chondrogenic and osteogenic mesenchymal fates in extraskeletal

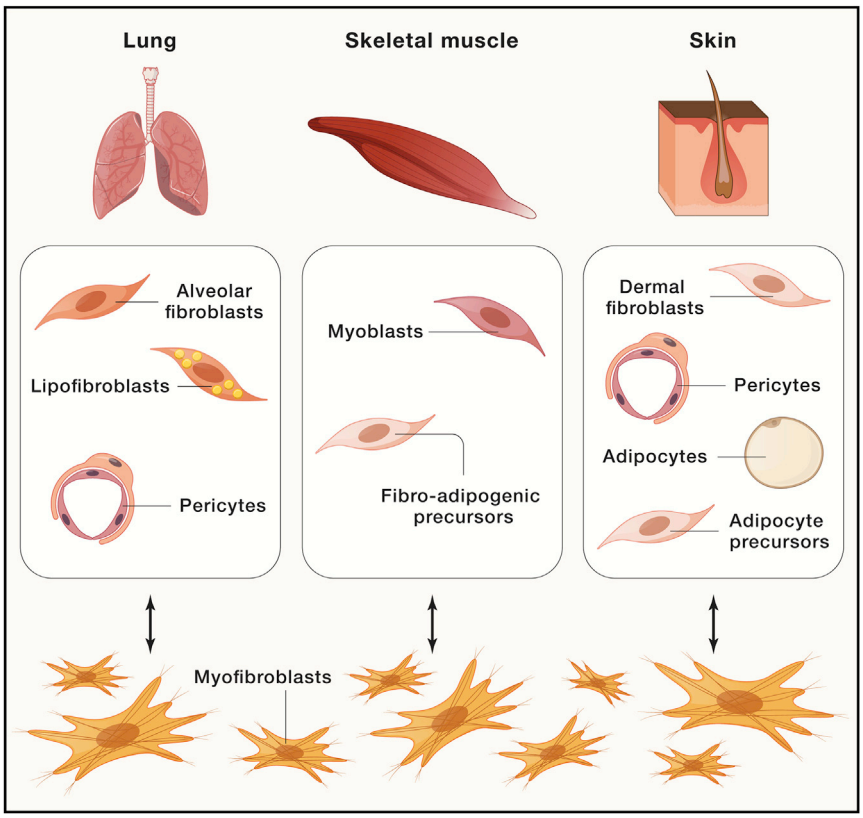

Figure 4. Diverse cellular sources of myofibroblasts

Diverse tissue resident mesenchymal cells, including specialized fibroblast progenitors, pericytes, and adipocytes, can become activated and undergo reversible conversion toward a myofibroblast state. Examples of lung, skeletal muscle, and skin are provided.

locations, such as in the skin, in mice and humans (Cappato et al., 2020). Whether such heterogeneity in origin and function occurs in humans remains an active area of investigation.

Fibroblast plasticity

It is emerging that fibroblast lineages are plastic and do not follow the canonical stem cell lineage model, in which undifferentiated and long-term self-renewing progenitors unidirectionally produce differentiated and, typically, postmitotic progeny (Morrison and Spradling, 2008). Lineage plasticity displayed by fibroblasts during tissue repair resonates with that by other cell types, such as epithelial hair follicle stem cells. The latter normally produce hair-fated progeny but respond to wounding by temporarily switching to making short-lived epidermal keratinocytes to close the breached skin barrier (Ge et al., 2017; Ito et al., 2005). The crucial need to repair damaged tissue induces normally quiescent and, in some instances, postmitotic mesenchymal cells, such as adipocytes, to reenter the cell cycle and produce new ECM-making and contracting myofibroblasts. When the damage is healed, myofibroblasts revert to quiescence and, in some instances, prune via apoptosis or senescence (Demaria et al., 2014; Wilkinson et al., 2019). Fibroblast plasticity may be possible because they deposit most of their differentiated product (i.e., ECM proteins) outside of the cell (Hynes and Naba, 2012) as opposed to, for example, keratin filament-laden suprabasal epidermal cells or sarcomere protein-filled myofibers, which may permit fibroblasts to remain relatively unspecialized and exit cellular quiescence upon stimulation.

Epigenetic regulation of fibroblast identity and dynamic state transitions, including the myofibroblast state, is a subject of intense research. For example, several microRNAs can activate, sustain, and terminate the myofibroblastic state across different reparative contexts (Wei et al., 2019; Yang et al., 2013), and more durable epigenetic modifications have also been implicated (Duong and Hagood, 2018). For example, during non-scarring kidney repair, wound-responsive fibroblasts suppress *RASAL1*, a promoter that encodes an inhibitor of Ras oncoproteins, and this enables transient activation. *RASAL1* suppression is reversible, and its eventual restoration is necessary for proper myofibroblast state resolution. Extended exposure to profibrotic signals, such as TGF-β, results in initial suppression and subsequent hypermethylation of the *RASAL1* promoter, which causes irreversible transcriptional suppression, lasting myofibroblast activation, and chronic fibrogenesis (Bechtel et al., 2010). It remains less clear which epigenome modifications in fibroblasts enable recapitulation of developmental programs during regenerative healing. Future work is needed to determine whether different fibroblast pools harbor distinct levels of latent plasticity and whether fibroblasts retain an epigenetic memory of earlier reparative events that heightens their responsiveness to subsequent insults, as seen in epithelial cells (Naik et al., 2017). Answers to these questions will inform future therapeutic efforts to suppress the dual nature of fibroblast plasticity in tissue repair by restricting fibrogenic capacity in favor of readoption of native tissue functions.

SIGNALING REGULATION OF FIBROBLAST LINEAGES AND FUNCTION

Key aspects of fibroblast biology, from proliferation and self-renewal to myofibroblast formation and differentiation to other mesenchymal lineages, are regulated by a diverse array of signaling pathways that act in autocrine, paracrine, and endocrine manners. Although many signaling factors can affect fibroblasts and contribute to fibrosis, such as FGFs (Xie et al., 2020), in this section, we review major roles of the PDGF pathway in fibroblast proliferation and self-renewal, TGF-β superfamily

pathways in fibroblast function, the canonical WNT pathway in fibroblast lineage specification and fibrosis, as well as mechanotransduction and danger-associated molecular pattern (DAMP) stimulation (Figure 3).

Role of PDGF signaling

Developmental expansion and long-term maintenance of fibroblast lineages requires their self-renewal via proliferation. This key property of fibroblasts critically relies on PDGF signaling. PDGF ligands act locally within tissues and can be produced by fibroblasts themselves or by other cell types to function as homo- and heterodimers of four different polypeptide chains, from A through D. Although PDGF-AA, PDGF-AB, and PDGF-BB are processed and secreted as dimers, PDGF-CC and PDGF-DD are secreted as inactive forms (Kazlauskas, 2017). PDGF ligands engage with PDGFRα and PDGFRβ tyrosine kinase receptors, which activate multiple downstream signaling cascades, including the RAS/mitogen-activated protein kinase (MAPK) and AKT/phosphatidylinositol 3-kinase (PI3K) cascades, which, in turn, propagate signaling to their downstream effectors.

PDGFRα is commonly expressed by the progenitor cells of multiple mesenchymal lineages, including fibroblasts and adipocytes (Uezumi et al., 2014), and *Pdgfra*-null mice die prior to birth, showing prominent deficiencies in cardiac mesoderm, somitic mesoderm, and neural crest-derived mesenchyme (Soriano, 1997). In the developing mouse heart, PDGF signaling induces expression of the transcriptional regulators Sox9, Snail, and Slug, which induce epicardial cells to undergo EMT to form the majority of cardiac fibroblasts (Figure 3). Conditional gain- and loss-of-function studies in mice have illustrated the importance of PDGF signaling in maturation of postnatal fibroblast lineages, long-term maintenance of their progenitor function, and ECM homeostasis. For example, mice with the constitutively active receptor *Pdgfra* display connective tissue hyperplasia and develop systemic fibrosis in multiple organs, including the skin and heart (Gallini et al., 2016; Olson and Soriano, 2009). On the other hand, mice with *Pdgfra* deficiency display tissue hypoplasia. Likewise, tissue- and cell-type-specific losses of *Pdgfa* ligand in mice lead to prominently reduced proliferation and self-renewing potential of dermal adipocyte precursors in the skin (Rivera-Gonzalez et al., 2016), αSMA^{+} dermal progenitors in the hair follicle (González et al., 2017), and fibroblasts in the lungs (Gouveia et al., 2018). Temporal regulation of PDGF activation during myocardial infarction induces cardiac fibroblast self-renewal and proliferation without triggering fibrosis (Asli et al., 2018), and pharmacological inhibition of PDGF signaling reduces ECM production during skeletal muscle repair (Smith et al., 2011). Thus, the PDGF signaling pathway serves as the major signaling regulator of fibroblast development and long-term homeostasis by supporting fibroblast stem cell self-renewal, proliferation, and migration.

Role of TGF-β superfamily signaling

During tissue repair, fibroblasts secrete and mechanically rearrange large quantities of new ECM. To perform these functions, fibroblasts must transition from a resting state, when ECM production is minimal, to a contractile myofibroblast state, when they upregulate matrisome synthesis and activate the contractile apparatus. Although transition to the myofibroblast state is essential for tissue repair after injury, its aberrant and sustained switch critically drives fibrosis and contributes to cancer progression. Activation of the myofibroblast state is dominantly controlled by the TGF-β pathway (Massagué, 2012), and human fibrotic tissue displays elevated expression of TGF-β ligands in the lungs, skin, and skeletal muscle (reviewed in Lodyga and Hinz, 2020).

Upon homeostasis, TGF-β ligands, together with latency-associated peptides (LAPs) and latent TGF-β-binding proteins (LTBPs), form large latent complexes (LLCs) (Shi et al., 2011) that are tethered in the ECM. Upon injury or fibrotic stimuli, TGF-βs are rapidly released from the LLCs upon proteolytic cleavage of LAPs or via mechanical forces generated onto ECM. TGF-β ligands bind hetero-tetrameric receptor complexes and activate the canonical SMAD pathway, including receptor-phosphorylated SMAD2/3, co-activator SMAD4, and inhibitory SMAD7 (Hata and Chen, 2016). Phosphorylated SMAD2/3 complexes translocate to the nucleus, where they interact with other context-dependent transcription factors to regulate downstream genes (Verrecchia et al., 2001). TGF-β can also activate non-canonical signaling pathways implicated in fibrosis, such as MAPKs, Rho-like GTPase signaling, and PI3K/AKT (Zhang, 2017). Because SMAD-driven mechanisms are the most well studied, they will be discussed in detail below.

Multiple studies reinforce the essential role of TGF-β signaling in ECM homeostasis, myofibroblast formation, and fibrosis development (Lodyga and Hinz, 2020). For instance, deletion of TGF-β receptor II in mouse fibroblasts abrogates contraction and ECM production in skin wounds (Denton et al., 2009). Postnatal activation of TGF-β receptor I in mouse fibroblasts recapitulates fibrotic phenotypes in the skin (Sonnylal et al., 2007) and heart even in the absence of injury (Nakajima et al., 2000). TGF-β-regulated SMAD2/3 complexes activate transcription of matrisome genes; contractile factors, such as αSMA; and connective tissue growth factor (CTCF), which also cooperates with TGF-β to sustain a myofibroblast state (Tsai et al., 2018). *Smad3* deletion in mice protects against bleomycin-induced lung fibrosis (Zhao et al., 2002), skin fibrosis (Lakos et al., 2004), and cardiac fibrosis (Dobaczewski et al., 2010). TGF-β signaling also affects myofibroblast formation via metabolic reprogramming of fibroblasts through mitochondrial biogenesis or glycolysis (Bernard et al., 2015).

Other members of the TGF-β superfamily of ligands also affect fibroblast biology. BMP signaling, which activates SMAD1/5/8 proteins to alter gene expression with co-activator SMAD4 (von Bubnoff and Cho, 2001), affects differentiation of several fibroblast-derived lineages (Wang et al., 2014). During regeneration of skeletal muscle, BMP signaling converts fibroblasts to myoblasts (de Lima et al., 2020), and during wound healing in the skin, it reprograms myofibroblasts to adipocytes (Plikus et al., 2017). BMP is also required to maintain the specialized identity of the so-called dermal papilla (DP) fibroblasts that constitute an essential signaling niche for epithelial stem cells in the hair follicle (Rendl et al., 2008).

Another TGF-β superfamily member, Activin A, which, like TGF-β ligands, activates SMAD2/3 (Pangas and Woodruff,

2000), is upregulated in human scars and other fibrotic diseases. When overexpressed from keratinocytes in mouse skin, Activin A upregulates gene expression within matrisome, secretome, and modulating enzyme categories by skin fibroblasts and reduces ECM deformability after injury (Wietecha et al., 2020 and references therein). Furthermore, Activin A inhibition can attenuate liver and lung fibrosis in mouse and rat models, respectively, and may affect fibroblast biology in fibrosis more broadly (reviewed in Werner and Alzheimer, 2006). Thus, the TGF-β superfamily can activate distinct fibroblast mechanisms to drive tissue repair and contribute to fibrosis.

Role of WNT signaling

The canonical WNT pathway regulates fate specification of fibroblasts in development and can modulate the continuum of fibrosis and regeneration in adult tissues. Canonical WNT ligands bind to complexes of low-density lipoprotein receptors (LRPs) and Frizzled receptors on their target cells. In the absence of a WNT signal, cytoplasmic β-catenin is phosphorylated by a multiprotein destruction complex consisting of Axin, the adenomatous polyposis coli (APC) protein, and several kinases, leading to its ubiquitin-mediated degradation. Upon ligand binding, the destruction complex is dissembled, leading to cytoplasmic β-catenin stabilization and translocation to the nucleus, where it forms complexes with transcription factors of the TCF/LEF family to regulate downstream gene expression (MacDonald et al., 2009).

During morphogenesis, the canonical WNT pathway has been shown to regulate fate specification of fibroblast progenitors into various lineages, notably in the skin. WNT signaling is activated in the papillary fibroblast progenitors of the upper skin layer and then becomes progressively restricted to the so-called dermal condensate cells of developing hair follicles (DasGupta and Fuchs, 1999; Zhang et al., 2009). Dermal condensate cells eventually mature into adult DP fibroblasts, and this process fails in mice with loss of function in WNT signaling (Millar, 2002). On the other hand, consistent with the inhibitory effect of WNT signaling on adipocyte differentiation of mesenchymal cell *in vitro*, its activation in the so-called reticular fibroblasts of the lower skin layer inhibits formation of cutaneous adipocytes in development (Mastrogiannaki et al., 2016) and during regeneration in adult skin wounds (Plikus et al., 2017). Moreover, in skin wounds, transient WNT activity in myofibroblasts promotes regenerative healing with new hair follicles (Lim et al., 2018), whereas its chronic activity drives fibrotic response and failure to regenerate hairs (Gay et al., 2020). The effect of WNT signaling on fibroblast development and injury response in other tissues remains poorly understood.

Mechanotransduction signaling

Along with soluble growth factors, fibroblast behavior is prominently influenced by biochemical and biomechanical properties of the surrounding ECM, which vary between and even within the same organs. The biomechanical differences in ECM are sensed by fibroblasts through integrin-associated focal adhesions (Balaban et al., 2001) and are interpreted analogous to biochemical signals. Biomechanical cues from the ECM induce activation of MRTFs (Huang et al., 2012) and the transcriptional cofactors Yes-associated protein (YAP) and TAZ (Jorgenson et al., 2017) as well as chromatin state changes (Le et al., 2016). Sensing of biomechanical inputs promotes fibroblast proliferation and can induce a myofibroblast state (Huang et al., 2012) and acquisition of pro-fibrotic lineage identity (Mascharak et al., 2021), which, in turn, can contract ECM to release ECM-bound TGF-β (Wipff et al., 2007), further amplifying the response. Restoration of biomechanical tissue properties using biomaterials as well as direct pharmacological targeting of mechanosensitive pathways that can override this form of fibroblast activation are viewed as promising future antifibrotic strategies (Mascharak et al., 2021; Meli et al., 2020).

DAMP signaling

As key factors in tissue repair, fibroblasts are sensitive to an array of DAMP signals, like intracellular macromolecules, including RNA, DNA, histones, and heat shock proteins, released from damaged cells as well as to ECM molecule fragments (Turner, 2016). Sensing of DAMPs is mediated through activation of pattern recognition receptors (PRRs), such as transmembrane Toll-like receptors (TLRs) and cytoplasmic nod-like receptors (NLRs) (Schaefer, 2014). Although PRRs are expressed predominantly by innate immune cells, there is emerging evidence that the DAMP system is also active in fibroblasts (Bautista-Hernández et al., 2017). For instance, the ECM component tenascin-C can activate TLR4 signaling in synovial fibroblasts and induce pro-inflammatory cytokine production in the mouse model of rheumatoid arthritis (Midwood et al., 2009), whereas in the heart, DAMP signaling activates an inflammatory and profibrotic response by cardiac fibroblasts (Turner, 2016; Zhang et al., 2015b). Fibroblasts also contribute to DAMP response by the surrounding innate immune cells and other tissue-resident cell types by promoting ECM degradation and fragmentation via secretion of ECM remodeling enzymes. Indeed, following proteolytic cleavage, many ECM fragments can bind to PRRs (McQuitty et al., 2020). For example, cleaved low-molecular-weight hyaluronan (LMW-HA), an abundant extracellular polysaccharide, can bind to TLR2/4 and promote nuclear factor κB (NF-κB)-mediated proinflammatory cytokine production (Lee-Sayer et al., 2015). Interestingly, ECM-derived DAMPs can also mediate the immunosuppressive and pro-repair functions of immune cells that are linked to fibrotic remodeling (Frevert et al., 2018). For example, although LMW-HA promotes inflammation by agonizing TLR2 signaling, high-molecular-weight HA (HMW-HA) inhibits TLR2 signaling and can promote immunosuppressive regulatory T cell action (Bollyky et al., 2007). Thus, fibroblasts contribute to inflammation and tissue repair by activation and responding to DAMP signals.

ORGAN-SPECIFIC FIBROBLASTS

Despite sharing similar properties and responding to many of the same signal transduction pathways, tissue-specific fibroblast functions and lineages exist to support the developmental, homeostatic, and repair needs of specific organs. These tissue-specific fibroblasts emerge during embryonic development as multiple cell lineages converge to form fibroblasts that populate organs arising from all three somatic germ layers, such as

ectodermally derived skin and mammary gland, mesodermally derived skeletal or heart muscle, and endodermally derived lung. The majority of fibroblasts in the body derive from the precursors of paraxial mesoderm and lateral plate mesoderm, whereas fibroblasts in the craniofacial structures originate from the neural crest mesenchyme (Herriges and Morrisey, 2014; Soriano, 1997; Figure 5). In the heart, epicardial and endocardial epithelial cells generate fibroblasts through epithelial-to-mesenchymal transition (EMT) and endothelial-to-mesenchymal transition (EndMT), respectively (Gittenberger-de Groot et al., 1998; Figure 5D).

When fibroblasts populate specific organs, they generate distinct microarchitecture, biophysical and biochemical components of connective tissue. Here, we focus on four well-characterized organs with diverse architectural designs and physiology: two epithelium-rich organs (skin and lung) and two mesenchymal organs (skeletal muscle and heart). We will introduce the organization of these organs into their functional units, delineate fibroblast heterogeneity, and briefly discuss where fibroblasts are located within each unit and the molecular mechanisms that contribute to their development, function, and fibrosis.

Fibroblasts of the skin

Fibroblasts in the skin produce a mechanically resilient, adhesive, but elastic structural foundation that supports epithelial keratinocytes of the outward-facing stratified epidermis and its numerous appendages, primarily hair follicles and sweat glands. Fibroblasts and other mesenchymal lineages in the skin establish three anatomically distinct layers: papillary and reticular dermis and dermal white adipose tissue (dWAT) (Figure 5A). The epidermis is separated from the upper papillary dermis by a sheet of collagen and laminin-rich basement membrane produced jointly by interfacing epidermal keratinocytes and papillary fibroblasts. Although in mice the papillary dermis in most body sites is very thin, in humans it forms complex undulating interdigitations with the epidermis, especially in the digit tips. Fibroblasts within the often very thick reticular dermis produce densely packed ECM that endows skin with its mechanical strength. Fibroblast progenitors also produce and maintain dWAT, which contains a fine, web-like ECM that encases clusters of lipid-filled adipocytes. All three dermal layers also contain immune cells, epidermal appendages, sensory neurons, and blood and lymphatic vessels, creating a complex network of cell communities that jointly support skin's protective functions.

During embryonic development in mice, early mesenchymal precursors give rise to a common skin fibroblast progenitor marked by expression of the transcriptional regulators Engrailed 1 (En1) and hypermethylated in cancer 1 (Hic1) and the transmembrane protein delta homolog 1 (Dlk1) (Abbasi et al., 2020; Driskell et al., 2013; Rinkevich et al., 2015). After establishing a nascent connective tissue, skin fibroblast progenitors undergo progressive specification into distinct fibroblast lineages that assume discrete anatomical niches and express distinct molecular markers. Specifically, papillary fibroblasts in neonatal mouse skin express the transmembrane factors CD26 (also known as Dpp4), Lrig1, and integrin Itga8 as well as the transcriptional repressor Prdm1 (also known as Blimp1). At the same time, precursors of reticular fibroblasts and dermal adipocytes express the transcriptional factors Pparγ and Ebf2 as well as the transmembrane protein Pdpn and the multifunctional signaling factor Sca1 (also known as Atxn1) (Driskell et al., 2013). As skin morphogenesis completes in early postnatal time and adult homeostasis ensues, fibroblasts undergo maturation and change their marker expression patterns (Driskell et al., 2013; Rognoni et al., 2016). For example, unlike in fetal skin, the transcriptional regulator Lef1 becomes a gene marker of adult mouse papillary fibroblasts (Phan et al., 2020).

Despite papillary and reticular dermis being clearly demarcated from one another, mouse studies reveal the distribution of transcriptionally overlapping fibroblasts across skin layers (Shook et al., 2018). This observation suggests that distinct features and functions of dermal layers are the composite result of many cell types and several fibroblast types working together. Recent scRNA-seq studies also rapidly increase our appreciation for fibroblast heterogeneity in the human skin. When compared carefully across several independent human skin scRNA-seq datasets, more than 90% of all dermal fibroblasts can be assigned to one of three shared groups marked by expression of the WNT pathway members *SFRP1* and *SFRP2* as well as the fat-binding *Apolipoprotein E* (*APOE*), respectively (Ascensión et al., 2020). Each of these fibroblast groups can then be subdivided, collectively resulting in as many as 10 subgroups with distinct marker gene combinations. Future work is needed to define the functional role of these heterogenous fibroblast populations.

Skin appendages, especially hair follicles, are populated by highly specialized fibroblasts whose major function is to regulate epithelial lineage activities, including stem cell quiescence, proliferation, and differentiation. In the hair follicle, these include DP fibroblasts, which form a tight cell cluster at its base, and the fibroblasts of the dermal sheath (DS), which encases hair follicle from the outside (Figure 5A). Both types of fibroblasts develop during hair follicle morphogenesis from embryonic papillary precursors via an intermediary dermal condensate progenitor (Mok et al., 2019; Sennett et al., 2015), and when fully formed, they express several specific marker genes (Driskell et al., 2011; Rezza et al., 2016; Shin et al., 2020; Tables 1 and 2). Compared with other skin fibroblasts, DP fibroblasts have several distinctive features. First, they are highly aggregative, including *in vitro*, where they form mound-like colonies before reaching confluence (Jahoda and Oliver, 1984). Second, they specifically associate with and function as the signaling niche for epithelial hair stem cells. Third, their gene expression changes prominently and periodically in synchrony with the hair growth cycle, a repetitive process of growing hairs that consists of dormant, active, and regression phases. The resulting changes in the DP fibroblast secretome critically drive transitions between cycle phases (Sennett and Rendl, 2012). Fourth, unlike other adult skin fibroblasts, DP fibroblasts can induce formation of new hair follicles when recombined with appropriately competent skin epithelium (Guerrero-Juarez et al., 2018; Reynolds and Jahoda, 1992). Last, just like hair follicles themselves, DP fibroblasts are highly heterogeneous across body regions and within the same region. For example, mouse DP fibroblasts that associate with different hair shapes (e.g., straight versus zigzag) exhibit unique gene expression patterns (Driskell et al., 2009; Rezza et al., 2016). Analogous to mice, DP fibroblasts in humans play critical roles

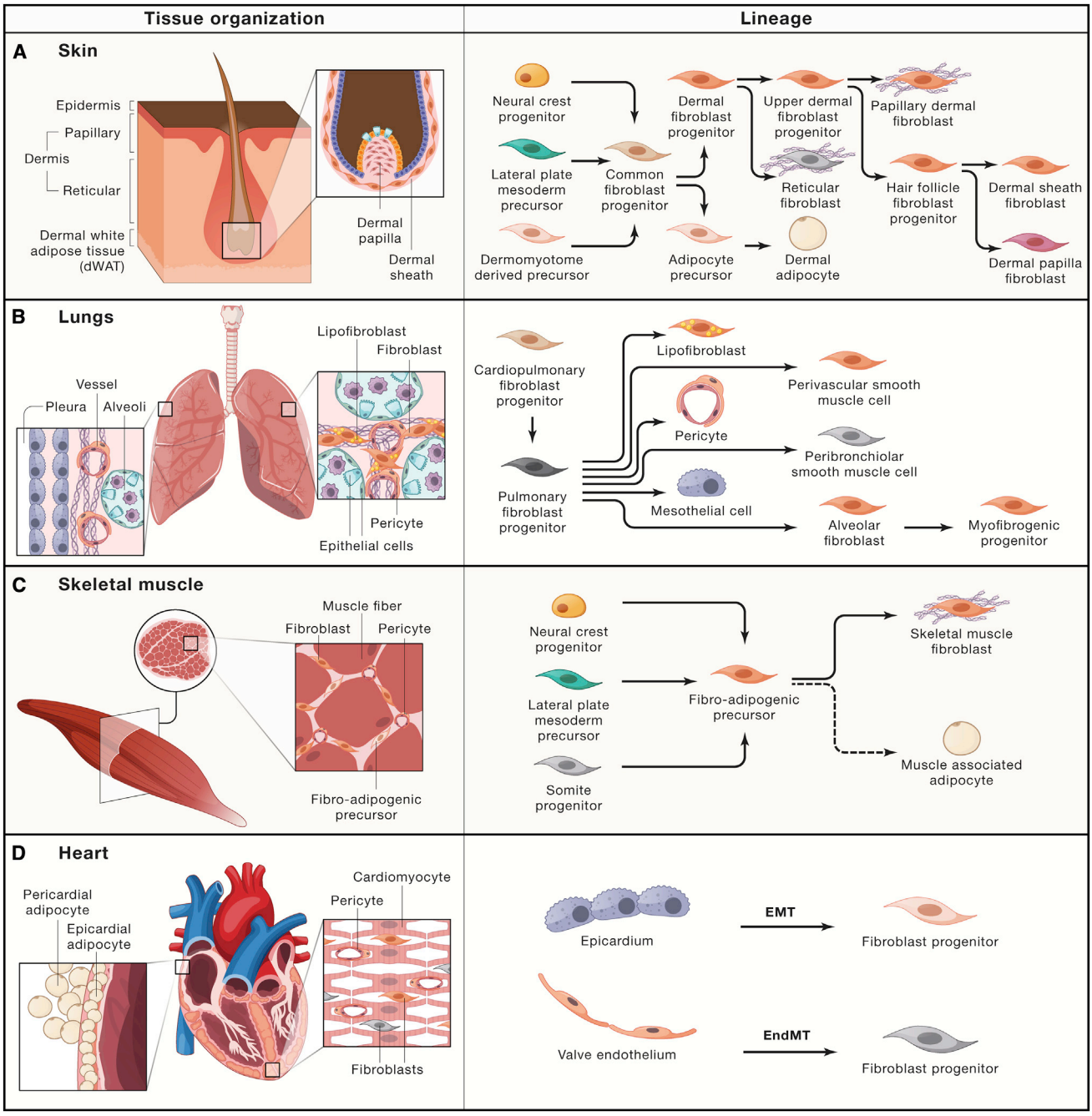

Figure 5. Organ-specific fibroblast organization and lineage relationships

(A) In the skin, diverse fibroblast types reside within its dermal layers, in dWAT, and in association with hair follicles. During skin development, a common mesenchymal progenitor gives rise to dermal fibroblast progenitors that further specify toward fibroblasts of papillary and reticular dermis and hair follicle-associated fibroblasts and to adipocyte precursors of dermal adipose tissue.

(B) In the lungs, diverse fibroblasts associate with alveoli at the end of the branched epithelium, bronchioles, and vasculature. During lung development, common cardiopulmonary progenitors generate a diverse array of fibroblasts, including mesothelial cells of the pleura, alveolar fibroblasts that support gas-exchanging epithelium, lipid droplet- containing lipofibroblasts, and peribronchiolar and perivascular smooth muscle cells.

(C) Skeletal muscle fibroblasts, fibro-adipogenic precursors, and pericytes lie in the space between muscle fibers. Several developmentally distinct embryonic mesenchymal progenitors give rise to fibro-adipogenic precursors that, in turn, serve as long-lasting sources for muscle-associated fibroblasts as well as adipocytes upon aging and disease states.

(D) Cardiac fibroblasts and pericytes reside between cardiomyocytes. During development, cardiac fibroblasts form from epicardial and endocardial epithelial cells via EMT and EndMT, respectively.

Arrows indicate lineage relationships.

Table 1. Murine fibroblast markers

Skin fibroblast diversity		
Fibroblast subsets	Markers	References
Pan-fibroblast	Pdgfrα$^+$Dpt$^+$Col1a2$^+$Col3a1$^+$ Twist2$^+$Vimentin$^+$	Driskell et al., 2013; Guerrero-Juarez et al., 2019; Abbasi et al., 2020; Phan et al., 2020
Putative common dermal fibro-adipogenic progenitor	En1$^+$Dlk1$^+$Hic1$^+$	Abbasi et al., 2020; Driskell et al., 2013; Rinkevich et al., 2015
Papillary dermal fibroblast	CD26/Dpp4$^+$Dlk1^{neg}Sca1/Ly6a^{neg} Blimp1$^+$EphB2$^+$Lrig1$^+$Trps1$^+$	Driskell et al., 2013; Festa et al., 2011
Reticular dermal fibroblast	CD26/Dpp4^{neg}Dlk1$^+$Sca1/Ly6a^{neg}	
Hypodermal fibroblast	CD26^{neg}Dlk1^{neg} Sca1/Ly6a$^{+/-}$	
DS fibroblast	αSMA$^+$Itgα8$^+$Itgα5$^+$Col11a1$^+$ Acan$^+$CD200$^+$Myh10$^+$Mlck$^+$Myl9$^+$	Heitman et al., 2020; Rahmani et al., 2014; Shin et al., 2020
DP fibroblast	Sox2$^+$Lef1$^+$Crabp1$^+$Rspo3$^+$ Corin$^+$Versican$^+$ Alkaline phosphatase$^+$	Rendl et al., 2008; Sennett et al., 2015; Sennett and Rendl, 2012; Driskell et al., 2013
Hair follicle dermal stem cell (hfDSC)	Sox2$^+$αSMA$^+$Itgα8$^+$ Mgp$^+$Acan$^+$	Rahmani et al., 2014; Shin et al., 2020
Reversible fibroblast states	Marker status	References
Myofibroblast	αSMA$^+$Sm22$^+$ ED-A fibronectin$^+$	Plikus et al., 2017; Hinz et al., 2001
Wound-induced regeneration-competent state	Crabp1$^+$Desmin$^+$Prss35$^+$	Guerrero-Juarez et al., 2019; Abbasi et al., 2020; Phan et al., 2020; Lim et al., 2018
Lung Fibroblast Diversity		
Fibroblast subsets	Markers	References
Cardiopulmonary fibroblast progenitor	Wnt2$^+$Gli1$^+$Isl1$^+$	Peng et al., 2013; Li et al., 2015; Rock et al., 2011
Pulmonary fibroblast progenitor	Tbx4$^+$	Arora et al., 2012; Xie et al., 2016
Alveolar fibroblast	Pdgfrα$^+$ Col1a1$^+$ Npnt$^+$Ces1d$^+$	Rock et al., 2011; Xie et al., 2018
Adventitial fibroblast	Pdgfrα$^+$ Col1a1$^+$ Pi16$^+$Ccl11$^+$	
Peribronchial fibroblast	Pdgfrα$^+$ Col1a1$^+$Hhip$^+$	
Lipofibroblast	Vim$^+$Col4a1$^+$Fabp1$^+$Fabp4$^+$ Lpl$^+$Fabp5$^+$Lipa$^+$Pparg$^+$Plin2$^+$	El Agha et al. 2017; Xie et al., 2018; Al Alam et al., 2015
Myofibrogenic progenitor	Axin2$^+$	Rock et al., 2011
Skeletal Muscle Fibroblast Diversity		
Fibroblast subsets	Markers	References
Fibro-adipogenic precursor (FAP)	Tcf4$^+$Gli1$^+$Sca1/Ly6a$^+$ Pdgfrα$^+$Hic1$^+$	Murphy et al., 2011; Scott et al. 2019; Joe et al., 2010; Uezumi et al., 2010; Chang et al., 2018; Kramann et al., 2015
Heart Fibroblast Diversity		
Fibroblast subsets	Markers	References
Epicardium-derived fibroblast progenitor	Hic1$^+$Gli1$^+$Pdgfrα$^+$Sca1/Ly6a$^+$	Soliman et al., 2020; Forte et al., 2020; Skelly et al., 2018
Valve endothelium-derived fibroblast progenitor	Wif1$^+$Dkk3$^+$	
Pericyte Markers		
Pericyte	Pdgfrβ$^+$Tbx18$^+$Ng2/CSPG4$^+$ Glast1$^+$Rgs5$^+$Desmin$^+$αSMA$^{+/-}$ CD13/Anpep$^+$	Armulik et al., 2011; Hung et al., 2013; Kuppe et al., 2021; Sava et al., 2017

in hair follicle morphogenesis and cyclic growth (Higgins et al., 2013; Oh et al., 2016), and differences in the transcriptional response by DP fibroblasts to androgens across scalp skin regions underlie the pathogenesis of male- and female-pattern baldness (Chew et al., 2016).

Likewise, gene expression by DS fibroblasts is distinct and prominently includes contractile proteins (Table 1; Heitman et al., 2020; Shin et al., 2020). The latter are important during hair growth termination, when smooth muscle-like contraction by the DS helps the shrinking hair follicle to remodel properly

to its dormant shape (Heitman et al., 2020). Near its base, the DS harbors the so-called hair follicle dermal stem/progenitor cells that assure long-term replenishment of the DP and DS with new fibroblasts (Rahmani et al., 2014; Shin et al., 2020). With advanced age, the self-renewal capacity of dermal stem cells diminishes, leading to their exhaustion and permanent hair follicle atrophy. Moreover, DS fibroblasts interface directly with skin-resident immune cells and produce immune-suppressive factors such as the TGF ligands β1 and β2 and immunomodulatory molecules such as programmed death-ligand 1 (PDL1) and CD200, which may contribute to the immune privilege of hair follicles, a property that guards them against autoimmune reactions (Paus et al., 2003).

Underlying the reticular dermis, fibroblast progenitors with adipogenic potential give rise to lipid-laden adipocytes of the dWAT layer, which displays several distinctive properties compared with other white adipose depots in the body (Zwick et al., 2018; Figure 5A). In addition to responding to changes in systemic nutrient availability, dWAT also prominently responds to local signals from cyclically growing hair follicles. During the active hair growth phase, dWAT expands by hypertrophy of pre-existing adipocytes and hyperplasia from dermal adipose stem cells (Festa et al., 2011; Zhang et al., 2016). The growth-promoting effect of hair follicles on dWAT is mediated by signals, including BMP and Hedgehog ligands (Plikus et al., 2008; Zhang et al., 2016). Following hair growth regression, dWAT shrinks in part from loss of lipid and possibly through dedifferentiation of mature adipocytes. dWAT cells also exert several reciprocal effects on hair follicles. During the rest phase, dWAT supports hair stem cell quiescence by secreting BMP ligands (Plikus et al., 2008), whereas at the onset of new hair growth, dWAT stimulates DP fibroblast activity via PDGF ligands (Festa et al., 2011). Beyond hair growth, dWAT progenitors actively sense bacteria and respond by rapidly differentiating and secreting the antimicrobial peptide cathelicidin (Zhang et al., 2015a, 2019), whereas the lipid content of mature dermal adipocytes can modulate skin ECM homeostasis (Zhang et al., 2021).

Skin fibrosis can occur in response to many triggers, including thermal burns, mechanical trauma, infection, radiation, or surgery, or in association with systemic diseases, such as scleroderma and graft versus host disease, and it can result in hypertrophic scarring, keloid scarring, and contractures that can impede mobility and skin reinnervation. Multiple populations of dermal fibroblasts, perivascular cells, as well as dedifferentiated mature dermal adipocytes are sources of activated myofibroblasts and fibrotic ECM in injured or diseased skin (Dulauroy et al., 2012; Marangoni et al., 2015). Proliferative expansion of dermal fibroblasts is a common component of skin fibrosis; however, in certain contexts, such as upon bleomycin-induced fibrosis in mice, dermal fibroblast numbers, in fact, decrease (Shook et al., 2018). This suggests that fibrosis can occur because of exacerbated ECM production of fewer preexisting fibroblasts. Moreover, increasing fibroblast proliferation in permissive wound environments can be associated with enhanced regeneration, suggesting that fibroblast overproduction alone is not a key determinant of fibrosis (Abbasi et al., 2020). Genetic mutations as well as aberrant inflammatory signaling, can drive excessive skin fibrosis. For example, skin in individuals with systemic sclerosis shows upregulated production of IL-13 (Li et al., 2017), whereas in mouse models, skin fibrosis can be driven by IL-21 or MMP12 (Taylor et al., 2018). Multiple types of immune cells have been implicated in skin fibrosis, prominently T cells and macrophages. Studies of immune and non-immune drivers of skin fibrosis, many of which are beyond the scope of this review, are informing the search for new anti-fibrotic therapies. For example, dermal fibrosis can be ameliorated in mouse models upon inhibition of myofibroblast-activating TGF-β and integrin signaling, such as with neutralizing antibodies, or upon stimulation of dermal adipogenesis with the small-molecule PPARγ agonist rosiglitazone (Shi-wen et al., 2010).

Lung fibroblasts

Although analogous to skin in being an epithelium-rich tissue, the lungs are developmentally, architecturally, and functionally distinct, which affects the extent to which their fibroblast populations differ from one another. Skin epithelium is derived ectodermally, and its connective tissue forms distinct layers, with voluminous ECM primed to provide mechanical resilience. In contrast, lung epithelium is of endodermal origin and forms a highly branched tree that terminates in expandable sacs called alveoli. The gas exchange function of the lungs relies critically on the alveolar epithelium forming close physical connections with extensive capillary networks and on the repetitive and rapid ability of the lungs to expand and contract. These functions necessitate the lungs' reticular ECM, which is optimally viscoelastic but sufficiently strong to withstand changes in air pressure and prevent alveolar rupture and potentially lethal barotrauma. Such ECM is produced by a diverse group of pulmonary mesenchymal cells that in development originate from a subset of migrating cardiac mesoderm (Peng et al., 2013; Figure 5B). As the lungs mature, pulmonary mesenchymal progenitors assume distinct spatial positions and functions, including peribronchiolar and perivascular smooth muscle cells, pericytes, numerous populations of interstitial fibroblasts, pneumocyte-supporting lipofibroblasts, and mesothelial cells, which line the visceral pleura (Figure 5B).

The cellular genealogy and disease contributions of these heterogeneous mesenchymal lung populations have been largely defined in mice on the basis of genetic lineage tracing and, more recently, with scRNA-seq. Early mesodermal progenitors that give rise to nearly all mesenchymal cells in an uninjured adult lung and that serve as the source for αSMA$^+$ myofibroblasts following lung injury can be marked on the basis of expression of the transcriptional factor *Tbx4* (Arora et al., 2012). In fetal mice, the Hedgehog pathway member Gli1 labels mesenchymal lung cells except lipofibroblasts (Li et al., 2015). Gli1 expression in these progenitors is functionally important because they depend on Hedgehog signaling for expansion (Kugler et al., 2017). Upon maturation, Gli1$^+$ progenitors increase expression of the shared fibroblast marker PDGFRα (Rock et al., 2011). Additional heterogeneity is recognized within PDGFRα$^+$ lung fibroblasts, and that includes a WNT-responsive subset, identified on the basis of Axin2 expression (Rock et al., 2011). Lipid droplet-containing lipofibroblasts are a distinct mesenchymal lung cell population required for proper development of epithelial alveolar type 2 cells, storage of vitamin A, and production of

Table 2. Transgenic mouse lines used to mark fibroblast lineages in skin, heart, lungs, and skeletal muscle

Skin		
Mouse line	Lineage and Temporal Specificity	Reference
Pdgfra-CreER	Pan Fibroblast	Chung et al., 2018
Blimp1-Cre	Arrector Pili/Papillary Fibroblast/DP/Sheath/ Epidermis/Blood Vessels	Driskell et al., 2013
Dlk1-CreER	Reticular/Hypodermal Fibroblast - Specific if labeled at E16.5-P2	Driskell et al., 2013
En1-Cre	Pan Fibroblast/pericyte	Rinkevich et al., 2015
Twist2/*Dermo1*-Cre	Pan Fibroblast	Phan et al. 2020
Adipoq-Cre	DWAT/Adipose	Rivera-Gonzalez et al. 2016
Hic1-CreER	Pericyte/Sheath/Papillary/Reticular/Hypodermal	Abbasi et al. 2020
Col1a2-CreER	Pan Fibroblast	Florin et al., 2004
αSMA-CreERT2	Sheath/vSMC/Arrector Pili	Rahmani et al. 2014
Tagln/Sm22-CreERT2	Sheath/vSMC/Arrector Pili	Lim et al. 2018
Sox2:GFP	Dermal papilla/Dermal sheath	Driskell et al. 2009
Acan-CreERT2	Dermal sheath	Heitman et al. 2020
Corin-CreER	Dermal papilla/Dermal sheath	Enshell-Seijffers et al., 2010
Heart		
Mouse line	Lineage and Temporal Specificity	Reference
Col1a2-CreER	Pan Fibroblast	Florin et al., 2004
Pdgfra-CreER	Pan Fibroblast	Soliman et al. 2020
Gli1-CreERT2	Cardiopulmonary progenitors/Perivascular mesenchymal progenitors	Peng et al. 2013; Farbehi et al., 2019 Kramann et al., 2015
Wnt2-CreERT2	Cardiopulmonary progenitor	Peng et al. 2013
Wt1-CreER and -CreERT2	Epicardial-derived fibroblasts	Forte et al. 2020; Moore-Morris et al. 2014
Tek/*Tie2*-CreER	Endothelium/endocardium-derived cardiac fibroblasts	Moore-Morris et al. 2014
Lung		
Mouse line	Lineage and Temporal Specificity	Reference
Pdgfra-CreER	Lung interstitial fibroblasts and lipofibroblasts	Rock et al., 2011; Xie et al. 2018
Col1a2-CreER	Pan Fibroblast	Florin et al., 2004
Wt1-CreER and -CreERT2	Injury-activated and interstitial fibroblasts, alveolar/vascular smooth muscle cells	El Agha et al., 2017
Foxd1-CreERT2	Lung interstitial fibroblast and pericyte progenitors	Hung et al., 2013
Skeletal Muscle		
Mouse line	Lineage and Temporal Specificity	Reference
Hic1-CreER	Skeletal muscle mesenchymal progenitors	Scott et al. 2019
Adam12-CreER	Perivascular myofibroblast progenitors	Dulauroy et al. 2012
Tcf4-CreER	Skeletal muscle fibroblasts	Mathew et al., 2011

surfactant (Al Alam et al., 2015). Intriguingly, it remains unclear whether the major population of Gli1$^+$/PDGFRα^+ fibroblasts is the dominant source of lung ECM. It is likely that other lung cell populations partake in ECM synthesis because the latter remains largely intact following Gli1$^+$ cell pruning.

Upon injury, epithelial cells in the adult lung downregulate Hedgehog signaling, which activates proliferation of epithelium and normally quiescent mesenchyme (Peng et al., 2013). Although epithelial stem cells repair airway and alveolar tissue, mesenchymal cells repair and constrict the interstitial stroma. Mouse studies have identified PDGFRα^+/Axin2$^+$ fibroblasts that respond to injury by proliferating within the alveolar niche and PDGFRα^-/Axin2$^+$ fibroblasts that largely contribute to forming an anatomically distinct set of parabronchial myofibroblasts. Among other pathways, WNT signaling is an important driver of injury response by mouse pulmonary fibroblasts, especially by Axin2-expressing cells, and this signaling requirement is conserved in humans; for example, during pathogenesis of pulmonary lymphangioleiomyomatosis, a rare disease in which fibroblasts and other cells form nodules that lead to

progressive decline of pulmonary function (Obraztsova et al., 2020).

Many forms of pulmonary fibrosis involve inexorable, progressive obliteration of parenchymal tissue, which ultimately impairs gas exchange to cause respiratory failure and death. Although no animal model accurately recapitulates all aspects of human lung fibrosis, bleomycin-induced lung injury can transiently increase the abundance of αSMA^+ myofibroblasts and ECM in alveolar regions (Rock et al., 2011). Lineage tracing in this mouse model has implicated numerous mesenchymal cells as the source of fibrotic myofibroblasts, including $PDGFR\alpha^+$ fibroblasts, lipofibroblasts, pericytes, and $WT1^+$ mesothelial cells (El Agha et al., 2017; Hung et al., 2013). Such cooperative contribution of several tissue-resident mesenchymal cell types to fibrosis parallels analogous observations in other organs, including skin responses to wounding. Intriguingly, the bulk of fibrotic tissue-producing lung fibroblasts can be marked with and is regulated by *Tbx4* (Xie et al., 2016), a transcriptional factor that also marks early mesodermal lung progenitors during embryonic morphogenesis (Arora et al., 2012). This suggests cooption of developmental transcriptional regulators by adult fibroblasts for injury response. Targeting of these cells for treatment of human disease remains an active area of investigation.

Skeletal muscle fibroblasts

Distinct from the skin and lungs, voluntary striated muscles lack epithelial structures and instead consist of parallel arrays of large, highly differentiated, and multinucleated muscle fibers whose primary function is force generation via contraction. Although some muscle fibers terminate at the tendon junctions, many of them end within the intramuscular connective tissue and transmit their contractile forces laterally. Intramuscular connective tissue has a complex and hierarchical organization. Its innermost layer, called the endomysium, surrounds individual muscle fibers and contains a specialized laminin- and type IV collagen-rich basement membrane. Acting via its transmembrane receptors, laminin aids mechanical force transduction from the intracellular contractile apparatus to the outer endomysium layer, rich in type I and III collagens (Chapman et al., 2016). Groups of myofibers, called fascicles, are surrounded by perimysium, which forms a continuum with tendons and is rich in so-called perimysium "cables," thick connective tissue bundles composed primarily of tightly packed type I and III collagen III fibrils. Finally, the entire muscle is enveloped by the epimysium connective layer (Chapman et al., 2016). The major role of the perimysium in force transduction and its distinct ECM are supported by specialized perimysial fibroblasts that express high levels of thrombospondins 1 and 4 and type XI collagen. Perimysial fibroblasts express a number of matrisome and non-matrisome genes shared with tendon and cartilage and, on scRNA-seq, display substantial additional heterogeneity, whose functional significance remains to be understood (Muhl et al., 2020). A distinct type of perimysial fibroblasts that express high levels of periostin localize uniquely at the perimysium-endomysium boundary and, on scRNA-seq, share similarities with a constellation of endomysial mesenchymal cells, which include perivascular fibroblasts and fibro-adipogenic progenitors, that have lineage potential to differentiate toward lipid-laden adipocytes (Figure 5C). Similar to skin and heart muscle, which we discuss below, skeletal muscle fibroblasts with progenitor properties express Sca1 (Joe et al., 2010; Uezumi et al., 2010) and, similar to lungs and heart, Gli1 (Kramann et al., 2015). Further, as with the heart, the transcriptional repressor HIC1 has been identified as the regulator of quiescence for skeletal muscle fibroblasts (Scott et al., 2019).

Skeletal muscles are highly regenerative, a property that is supported by the so-called satellite stem cells, which are myogenic and express PAX7 (Relaix and Zammit, 2012). In response to muscle injury, satellite stem cells and the surrounding interstitial fibroblasts activate and expand concurrently. Normally, satellite cells should expand more to give rise to new myoblasts that, upon fusion, produce new myofibers. However, upon satellite cell deficiency, which can be induced experimentally in mice through genetic means or normal aging, muscle fiber regeneration becomes deficient. In response, fibroblasts, including fibro-adipogenic progenitors, expand and generate excessive fibrotic ECM and excessive intramuscular adipocytes that collectively become detrimental to muscle's contractile property. Conversely, when fibroblasts are depleted, premature myoblast differentiation, smaller myofibers, and rapid depletion of the satellite cell reserve occurs (Murphy et al., 2011). Therefore, fibroblasts do not merely compete for tissue space with satellite cells but form a signaling niche, necessary for long-term maintenance and proper cellular dynamics of the myogenic lineage. The niche function of muscle fibroblasts parallels that played by DP fibroblasts in the context of hair follicle epithelial stem cells.

In response to injury, activated skeletal muscle fibroblasts undergo dynamic gene expression changes that are analogous to those in other organs, such as the skin or heart. First, they express cytokines and other proinflammatory factors, followed by genes involved in the cell cycle and ECM. The latter enable activated myofibroblasts to rapidly deposit a provisional matrix, which then provides a new scaffold for regenerating myofibers. As muscle regenerates, the provisional matrix is remodeled rapidly and then removed almost completely, leaving space for the newly expanding myofibers (Joe et al., 2010; Scott et al., 2019). In this regard, regeneration of myofibers over the provisional ECM that remodels rapidly partially parallels the ability of large skin wounds to regenerate new hair follicles and adipocytes, both of which form within a provisional scar tissue.

Fibroblasts of the heart

The heart muscle is an anatomically and physiologically complex contractile organ whose major cell population, cardiomyocytes, connect with one another to form an electrically coupled tissue via intercalated disks that constitute its middle layer, called myocardium. The heart is also rich in fibroblasts that generate and remodel a robust ECM network essential for electrical conductivity and heartbeat rhythm. In addition to myocardium, fibroblasts populate the outermost epicardium layer, which contains specialized adipose tissue, as well as the innermost endocardium, which is bordered by a layer of endothelial cells. In contrast to fibroblasts in most other organs that originate from mesenchymal progenitors via progressive specification, the majority

of cardiac fibroblasts form via EMT, and those residing in the interventricular septum and right ventricle are the product of EndMT (Gittenberger-de Groot et al., 1998; Figure 5D).

As in other organs, adult cardiac fibroblasts are heterogeneous, and their lineage contributions are distinct. Single-cell transcriptomics studies of adult murine cardiac fibroblasts consistently reveal two main populations (Skelly et al., 2018) A smaller population of endocardial-derived fibroblasts expresses the WNT signaling factors *Wif1* and *Dkk3* and presents a gene signature related to valve leaflets and, intriguingly, endochondral specification toward the bone lineage. A larger population of epicardially derived fibroblasts further dichotomizes into groups characterized by high expression of genes associated with metabolism or genes associated with cell migration. The latter, single-cell fibroblast population is likely identical to a previously isolated fibroblast population that expresses the markers PDGFRα and Sca1 and displays high clonogenic properties (Chong et al., 2011).

Considering that heart muscle is poorly regenerative and that injury typically results in repair with a functionally deficient, noncontractile scar, much effort has focused on understanding cardiac fibroblasts in the context of fibrosis. In response to acute injury, such as myocardial infarction, cardiac fibroblasts rapidly activate expression of chemoattractant, proinflammatory, and profibrotic signals (Forte et al., 2020). Epicardial adipocytes in mice can also promote inflammation, such as via release of fatty acids (Chang et al., 2018). Similar to acute wounds in other organs, such as skin, murine cardiac fibroblasts in the infarction site become contractile (i.e., myofibroblasts) and proliferate transiently (Fu et al., 2018). They acquire an elongated aspect ratio and express distinct ECM proteins, including cartilage oligomeric matrix protein (Comp) and thrombospondin 4, which are normally restricted to skeletal elements, such as bones, tendons, or cartilage. These and other related ECM factors are thought to confer added strength to the mature cardiac scar, which is critical for its longevity within the constantly contracting heart. As the cardiac scar remodels, fibroblast populations distal of the infarcted muscle also display changes consistent with compensatory interstitial fibrosis, including expression of ECM proteins and matrix remodeling factors.

When lineages are considered, injury to the myocardium activates epicardially and endocardially derived fibroblast populations (Moore-Morris et al., 2014), but the exact cellular origin of cardiac fibrosis has yet to be fully resolved. The essential role of PDGFRα^+ fibroblasts in cardiac fibrosis is supported by mouse studies in which deletion of *Hic1* in *Pdgfra*-expressing cells results in epicardium thickening, interstitial fibrosis, and intra-myocardial adipogenesis in the absence of damage (Soliman et al., 2020). Other studies in mice have suggested that heterogeneous populations of PDGFRα^+ fibroblasts are important for cardiac fibrosis development, including epicardially derived Sca1$^+$ *Gli1*$^+$ (Farbehi et al., 2019; Soliman et al., 2020) as well as fibroblast activation protein α-expressing subsets. The clinically relevant marker podoplanin (Pdpn) is highly expressed in individuals with ischemic cardiomyopathy patients, when inhibited in mice, post-infarction repair is promoted (Cimini et al., 2019).

FIBROBLAST-TARGETING THERAPIES

Promoting regenerative healing

Although robust mechanisms exist to repair injuries in mammals, they often culminate in fibrosis, which presents a major clinical challenge. Currently approved antifibrotic therapies target fibroblast activation in established disease and are not able to restore the architecture and function of diseased tissues. Thus, development of strategies aimed at promoting repair of injured tissues would significantly advance the field. In this light, chronic non-healing wounds of the skin offer an opportunity to intervene because they can be diagnosed at an early stage. To date, however, the only US Food and Drug Administration (FDA)-approved growth factor for chronic diabetic foot ulcers is a gel preparation of low doses of recombinant PDGF, which in clinical studies significantly decreases the time to healing (Steed, 2006). However, this treatment has a limited effect on other forms of non-healing skin ulcers, such as pressure ulcers (Yamakawa and Hayashida, 2019). Several other studies have shown promising results with other growth factors in animal models, but clinical trials did not prove effective in humans, which may reveal the difference in tissue repair strategies between human and murine skin (Yamakawa and Hayashida, 2019).

Mechanical tension may also be a therapeutic target to improve tissue repair and promote regeneration. Deletion of the mechanically sensitive focal adhesion kinase (FAK) in fibroblasts can reduce scar formation in mice. Interestingly, mechanical offloading can improve wound repair in pigs (Gurtner et al., 2011), and a study inhibiting the mechanically sensitive transcription factor YAP in mouse skin fibroblasts promotes scarless wound healing and tissue regeneration, including hair follicle regeneration (Mascharak et al., 2021). Yap inhibition has also been shown to abrogate liver, lung, and kidney fibrosis in animal models, suggesting that targeting mechanically sensitive pathways might shift scarring repair to a more regenerative healing process.

Although the plasticity of fibroblasts can be problematic in the context of fibrotic diseases, it also presents an opportunity for regenerative interventions. This realization has driven recent efforts to restore tissue anatomy and function by reprogramming fibroblasts *in vivo in situ* via molecular strategies that include direct reprogramming. In the context of skin wounds, the innate ability of fibroblasts to become supportive of hair follicle regeneration can be induced by transcriptional reprogramming. For example, temporally induced supraphysiological activation of Hedgehog signaling in wound fibroblasts in mice can potently enhance their ability to acquire DP fibroblast identity, which results in regeneration of large numbers of hair follicle-like structures in large and small wounds (Lim et al., 2018). Similar results have also been achieved by deleting the transcriptional repressor *Hic1* in fibroblasts (Abbasi et al., 2020) or following fibroblast-specific overexpression of *Lef1* (Phan et al., 2020). "Deeper" *trans*-lineage reprogramming of fibroblasts into keratinocytes in skin wounds *in situ* is possible upon viral transduction with the keratinocyte lineage-associated transcription factors *Dnp63a*, *Grhl2*, *Tfap2a*, and *Myc*, producing fibroblast-derived epidermis and enhancing wound re-epithelialization in mice (Kurita et al., 2018).

Analogous proof-of-principle examples of therapeutic *in vivo* reprogramming of fibroblasts have been shown in the liver and heart. Viral delivery of transcription factors such as *Foxa3*, *Gata4*, *Hnf1a*, and *Hnf4a* to myofibroblasts in the liver reprograms them into hepatocyte-like cells and reduces signs of liver fibrosis in a mouse model (Rezvani et al., 2016; Song et al., 2016). Likewise, virally delivered *Gata4*, *Mef2c*, and *Tbx5* induce direct reprogramming of heart-resident fibroblasts into cardiomyocytes *in vivo*, resulting in reduced fibrosis and improved cardiac function in a mouse model of myocardial infarction (Miyamoto et al., 2018). The above examples clearly highlight the therapeutic potential of direct reprogramming of tissue-resident fibroblasts into "worker" cells and suggest it as a novel scar replacement strategy. However, several important issues, including efficiency of reprogramming factor delivery using non-integrative vectors and high fibroblast specificity, if not exclusivity, will need to be solved for this attractive approach to be deemed safe for clinical applications.

CONCLUSIONS AND PERSPECTIVES

The last several decades have seen remarkable progress in our understanding of fibroblast biology across organs and conditions. The field has progressed from phenotypic studies of cultured cells performed more than a century ago to complex genetic and functional observations *in vivo* that have been facilitated by new methods and techniques. These advances have revealed unexpected similarities and unique characteristics of fibroblasts across diverse organs such as the skin, lungs, heart, and skeletal muscle that are currently being leveraged for the treatment of human disease.

Despite this progress, many questions and opportunities remain. For example, ongoing efforts employing single-cell multi-omics and spatial genomics technologies will provide key insights into fibroblast heterogeneity within and across tissues as well as their ability to assume multiple functional states in response to physiological or disease triggers. As our appreciation of essential fibroblast functions extends well beyond ECM synthesis, so does the excitement over novel therapeutic possibilities that modulating them *in situ* can bring for a broad spectrum of diseases characterized by aging, pathologic remodeling, and tissue fibrosis. Emerging areas of investigation, including cross-regulation between wound fibroblasts, immune cells, and the peripheral nervous system, will be critical for understanding how to restore tissues to their pre-injury state. Finally, effective clinical translation will require rigorous verification in native human tissues and in human-like models such as organotypic cultures, xenografts, and pluripotent cell-derived organoids. These and other advances will enable new approaches for prevention, treatment, and perhaps reversal of fibrotic conditions by achieving appropriate and controlled repair.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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