Review

CellPress

Understanding fibroblast heterogeneity in the skin

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Fibroblasts are found in most tissues, yet they remain poorly characterised. Different fibroblast subpopulations with distinct functions have been identified in the skin. This functional heterogeneity reflects the varied fibroblast lineages that arise from a common embryonic precursor. In addition to autocrine signals, fibroblasts are highly responsive to Wnt-regulated signals from the overlying epidermis, which can act both locally, via extracellular matrix (ECM) deposition, and via secreted factors that impact the behaviour of fibroblasts in different dermal locations. These findings may explain some of the changes that occur in connective tissue during wound healing and cancer progression.

Varied origins and functions of fibroblasts

Fibroblasts are mesenchymal cells that deposit collagen and elastic fibres of the ECM in connective tissue [1–4]. This simple operational definition, however, masks the considerable heterogeneity of fibroblasts found in different tissues (healthy or diseased) and at different stages of development. Indeed, fibroblasts in different body sites arise from different embryonic origins [5]. For example, fibroblasts in face skin arise from the neural crest; those in ventral body skin derive from the lateral plate mesoderm; and those in back skin originate from the dermomyotome [6–10] (Figure 1).

While genetic tools for lineage tracing have led to considerable progress in elucidating stem cells and lineage relationships in most cell types and tissues [11], characterisation of fibroblasts has lagged. This is, in part, because of the challenge of defining clonal relationships when the progeny of an individual cell do not remain attached to one another, and in part because of a lack of defined markers to distinguish different fibroblast subsets. It is important to consider the lineage relationships of fibroblasts because this may influence their differentiation potential [7]. For example, mesenchymal stem cells from the bone marrow share similar properties with tissue resident fibroblasts; however, just because different cell populations express common markers does not mean they have a common origin [12]. Nevertheless, recent advances in marker identification, functional assays, and lineage tracing have led to new insights into fibroblasts in the skin. These findings reveal that functional heterogeneity reflects, at least in part, the existence of different fibroblast lineages, and that fibroblasts respond readily to signals from the overlying epidermis and thereby exhibit surprising plasticity. These observations provide new ways of interpreting the dynamic changes in fibroblast behaviour – such as proliferation and migration – observed in tissue repair and disease.

Mesenchymal cells of skin connective tissue

The dermis, the connective tissue underlying the epidermis, provides a good example of how even within one tissue, in a single body site, and at a single developmental stage, fibroblasts are remarkably diverse [13–15] (Figure 2; Tables 1 and 2). In neonatal (P2) mouse back skin, the upper (papillary) dermis is distinguished from the lower (reticular) dermis by differences in fibroblast density and by the maturity of the collagenous ECM [16]. Signals from epidermal stem cells in the hair follicle bulge induce adjacent fibroblasts to form the smooth muscle known as the arrector pili muscle (APM), which controls piloerection [17].

A cluster of fibroblasts at the base of the hair follicle, known as the dermal papilla (DP), has specialized signalling properties required for hair follicle morphogenesis and coordination of the hair cycle [18,19]. The dermal papillae that are associated with different types of hair follicles are distinct [20] and there is evidence that some dermal papilla cells have the ability to differentiate into a wide range of cell types, including nerve and cartilage [21,22]. Further heterogeneity is evident in the region underlying the reticular dermis, known as the hypodermis or dermal white adipose tissue, since this contains a mixture of pre-adipocytes and mature adipocytes [23].

Two other skin mesenchymal cell types that warrant consideration are perivascular smooth muscle cells (pericytes) and mesenchymal stem cells (MSCs), both of which express some markers in common with fibroblasts (Table 1). MSCs form part of the perivascular stromal compartment of the bone marrow and can be isolated from bone marrow cell preparations as the cells that adhere to tissue culture plastic, in contrast to the non-adherent haemopoietic cells [12]. Although there have been some reports that MSCs contribute to the dermis [24–26], more recent studies, involving lineage tracing and bone marrow transplantation, suggest that this is not the case [27–29].

Perivascular smooth muscle cells surround blood vessel endothelial cells and have a contractile function that regulates endothelial cell homeostasis [30]. There are no

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Keywords: dermis; connective tissue; stem cells; lineage; Wnt; adipocytes.

0962-8924/
 http://dx.doi.org/10.1016/j.tcb.2014.10.001

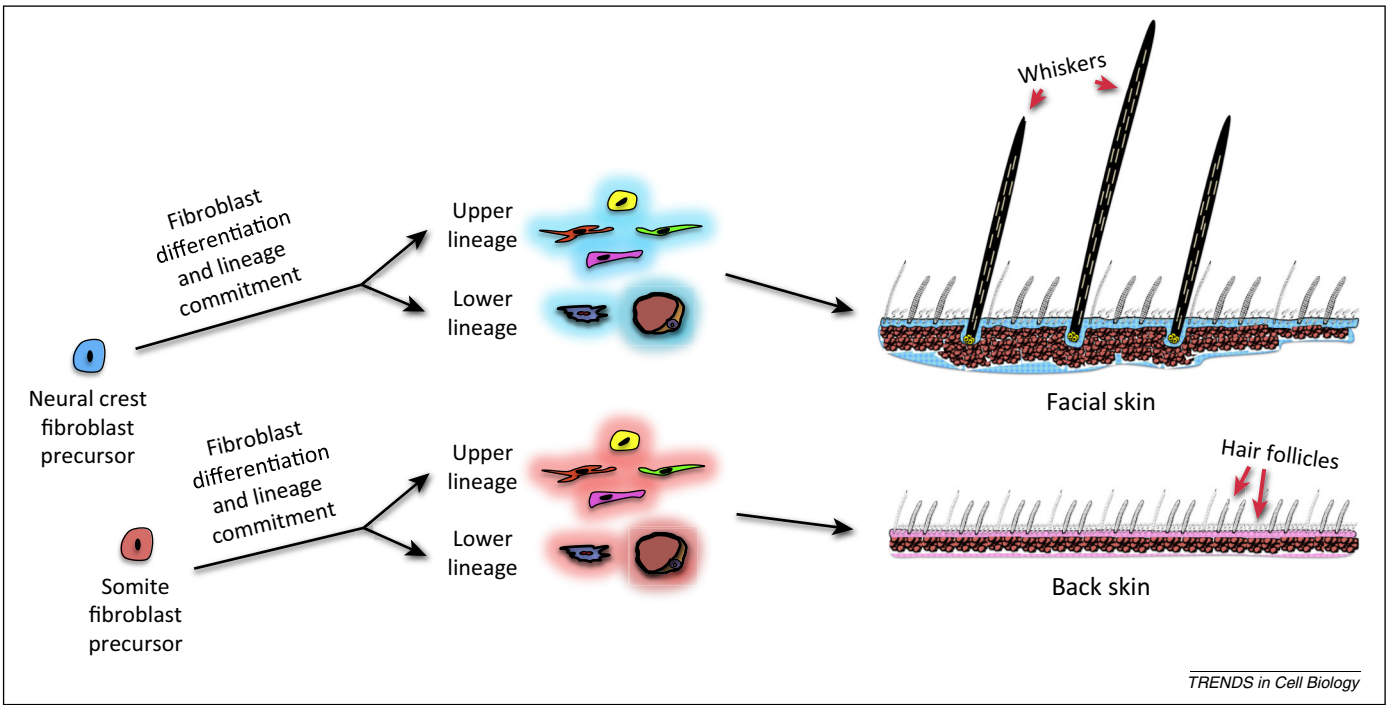

Figure 1. Developmental origins of dermal fibroblasts. Fibroblasts arise from different developmental origins such as the neural crest, dermomyotome, and lateral plate mesoderm. Regardless of the developmental origin of fibroblasts, they undergo differentiation and lineage commitment to give rise to both upper and lower lineages. Redrawn from [5].

definitive markers of pericytes, but the field has utilized α-smooth muscle actin (α-SMA), desmin, and neuron–glial antigen 2 [NG2; also known as chondroitin sulfate proteoglycan 4 (CSPG4)] as markers [31]. In skeletal muscle, pericytes can differentiate into muscle fibres [32]. In skin, pericytes have been identified in the upper dermis and can be isolated with an HD-1 antibody [31]. However, there is currently no evidence that they contribute to the skin fibroblast compartment.

When fibroblasts are isolated from adult skin and placed in culture or transplanted to a new location they exhibit positional memory, which is reflected in *Homeobox* (*Hox*) gene expression [33,34]. Classic tissue recombination experiments have shown differences in the ability of the dermis from hair-bearing and non-hair-bearing regions of mouse skin to induce hair follicle formation [35]. While positional memory likely accounts for the different types of hair follicles in different body sites, fibroblasts arising from the neural crest, lateral plate mesoderm, and dermomyotome are all competent to support hair follicle formation. Indeed, lineage tracing and cell isolation experiments have shown that dermal cells can exhibit characteristics of

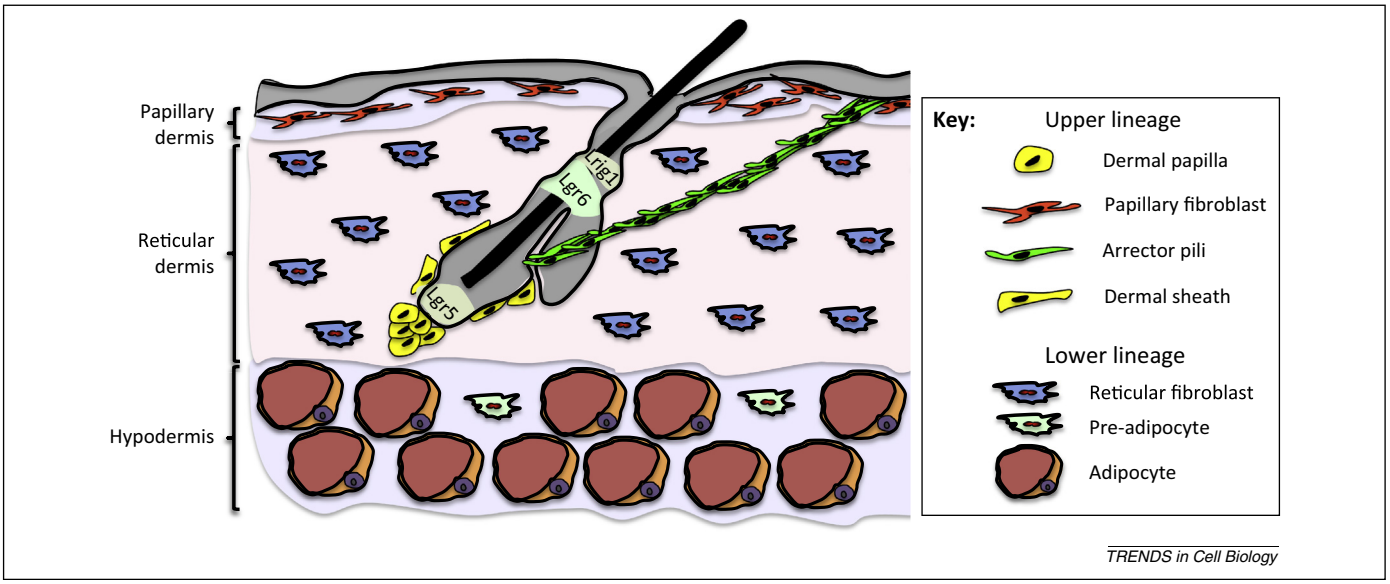

Figure 2. Heterogeneity of epidermal stem cells and mesenchymal cells in skin. The locations of three epidermal stem cell populations (Lrig1+, Lgr6+, and Lgr5+) in the hair follicle are shown. The three dermal layers are also indicated: the papillary dermis, reticular dermis and hypodermis/white adipose layer. The specialised fibroblasts of the dermal papilla (DP) and arrector pili muscle (AP) are derived from the same lineage as the papillary dermis, while reticular fibroblasts, pre-adipocytes and adipocytes share a common origin.