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### Review Regionalisation of the skin



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#### ABSTRACT

The skin displays marked anatomical variation in thickness, colour and in the appendages that it carries. These regional distinctions arise in the embryo, likely founded on a combinatorial positional code of transcription factor expression. Throughout adult life, the skin's distinct anatomy is maintained through both cell autonomous epigenetic processes and by mesenchymal–epithelial induction. Despite the readily apparent anatomical differences in skin characteristics across the body, several fundamental questions regarding how such regional differences first arise and then persist are unresolved. However, it is clear that the skin's positional code is at the molecular level far more detailed than that discernible at the phenotypic level. This provides a latent reservoir of anatomical complexity ready to surface if perturbed by mutation, hormonal changes, ageing or experiment.

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#### 1. Introduction

The fundamental structure of the skin is that of a stratified water-tight epidermis lying atop a dermal connective tissue. In addition, most of the skin is studded with cutaneous appendages such as hair or feather follicles, scales and a range of glands. On a single body, this basic structure is modified such that the skin's local thickness, its type and degree of pigmentation and the density, size and types of appendages carried vary in distinctive ways. While all of the skin carries out the fundamental barrier role to prevent desiccation and infection, these local modifications achieve specialised roles in secretion, insulation, cooling, camouflage, display and resistance to abrasion.

The mature skin arises from interactions between the surface epithelium of the embryo, called the ectoderm, and its underlying mesodermally derived mesenchyme. The ectoderm stratifies to produce the multi-layered epidermis prior to birth, while the mesenchyme produces extensive extracellular matrix to become the dermis. During this process, clusters of ectodermal cells are designated to become skin appendages, these cells condensing to form placodes and then growing down into or out from the dermis to undergo the morphogenesis that will generate the mature

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appendage. These growths are predominantly ectodermal and may be associated with a mesenchymal condensation, as seen in the hair follicle primordia, or not, as in the eccrine sweat glands [1–3].

Appendages vary in form and function by skin region. In birds much of the body is feathered, though bare areas called apteria separate the distinct feather tracts. The foot carries two types of scale; on the dorsal surface are large and overlapping scutate scales, while on the ventral surface are the smaller, circular reticulate scales of the sole [4]. Mammals generally have a continuous hair covering on the body, with eccrine sweat glands typically restricted to the palmoplantar (sole) skin of the ventral foot, and other gland types form at distinct sites [3,5]. In rodents, the tail also develops thick keratinised scales with hair follicles lying between them [6].

Once formed, the dermis is composed of a connective tissue matrix in which resident fibroblasts predominate, and which also carries nerves and blood vessels. The epidermis is composed mainly of keratinocytes, with smaller populations of pigment producing melanocytes and Langerhans cells acting as immune sentinels. The dermis has relatively little cell turnover through proliferation, though it is infiltrated by immune cells which swarm and depart upon infection or irritation. The epidermis undergoes very high cellular turnover, driven by rapid keratinocyte proliferation on its basal layer and loss of cells at its surface, several layers above [1]. At different body sites the epidermis varies in thickness, pigmentation, and in the types of keratin produced. The friction-resistant palmoplantar epidermis is particularly distinct from that of the haired skin, being very thick and unpigmented. At other body sites epidermal thickness and pigmentation vary more subtly. Regional variations in keratinisation mode and appendage characters are dermatologically important as they influence the anatomical locations affected by conditions such as acne, alopecia, eczema and keratoderma.

Diverse approaches have been taken to understand the basis of skin regionalisation, initially focussing on identifying specific cell types that possess positional information and then on how this information is sustained and shared among all the cells of the skin. Some principles arising from these studies connect the skin's regionalisation mechanisms and its molecules to positional determination events elsewhere in the body, but major questions regarding the origin and transmission of skin positional information remain to be answered.

#### 2. Embryonic skin regionalisation

## 2.1. Epithelial–mesenchymal interactions determine region-specific appendage identity

The earliest experimental approaches to understanding the basis of skin regionalisation relied on recombination of dermis and epidermis from distinct body sites to produce a composite skin, followed by grafting of this composite to determine its developmental outcome. These experiments aimed to reveal the tissue source of region-specific properties that determine appendage identity. The accessibility of the chick embryo and its strongly marked distinction between the feathered tracts of the body, the non-feathered apteric spaces between the tracts, and the scaled foot, made this species the most intensively studied in determining the tissue in which location is encoded, and the source of most detailed information.

When epidermis from non-feather forming regions was recombined with dermal mesenchyme from foot or body, the ectoderm was found to develop appendages appropriate to the dermal region of origin [7]. Conversely, dermis originating from non-feather bearing skin did not trigger appendage formation in any associated epidermis [8], suggesting that the dermis carries anatomical information, which it conveys to a naïve epidermis. However, the ability of foot dermis to induce scale formation in an adjacent epithelium was found to vary according to developmental stage, and on the origin of the epithelium with which it was joined. Recombinations made at the onset of normal feather patterning between body ectoderm and foot dermis produce feathers [9], while those between foot dermis and unprimed, apteric ectoderm produce scales [10]. At a later stage, by the time of native scale morphogenesis and growth, the foot dermis tends to direct scale formation in adjacent epithelium [8,9]. Thus the prior developmental history of the epidermis was found to play a role in the appendage type that it produces.

The simplest model to explain these stage and site dependent tissue properties posits two types of dermal inductive influence. First, a permissive dermis is required to trigger appendage formation, and this triggering relies on a dermal cell density that is not attained by apteric skin regions [8]. If overlying a suitably dense dermis, the epithelium will undergo its default developmental programme of feather production. Scutate scale formation on the foot, then, is caused by an appendage inducing dermis which also suppresses feather formation. This inhibitory influence is present only at certain developmental stages, explaining the time-restricted phase at which scale formation is triggered by foot dermis [11]. The apparent shifting of the tissue source of regional identity inferred from recombination experiments is thus a result of varying dermal influences coupled with a trend for the epithelium to undergo a progressive commitment to feather formation when exposed to general appendage inductive influences (Fig. 1). This series of experiments suggests that the relative strengths and stabilities of regional identity between dermis and epidermis fluctuate through the embryonic period, with a general dominance of the dermis. Similar experiments using mammalian skin support this view [12].

This idea that avian ectoderm has an inherent tendency to undergo feather formation is supported by the ability of a range of distortions of normal cell–cell signalling pathways to cause feather formation on the dorsal foot. An increase in  $\beta$ -catenin function can achieve the scale to feather transition [13], as can retinoic acid administration [14], stimulation of Delta-Notch signalling [15], or suppression of BMP signals [16]. The existence of multiple mutations capable of producing feathered feet in the chicken [17], and the ability of non-specific treatments such as administration of the nucleoside bromodeoxyuridine [18], also support the concept that feathers have a propensity to form and that a specific foot dermis signalling environment must act to suppress this potential, thereby enabling scutate scale formation. This likely reflects a close developmental, and perhaps evolutionary, link between feathers and scutate scales [11].

In contrast to the active inductive signalling needed to arrange scales and feathers in the appropriate places, avoidance of such epithelial-mesenchymal interaction is essential for corneal development. The location of the cornea is specified by tissue interactions that position the eye, ultimately based on proximity of the optic vesicle and the surface ectoderm [19,20]. Formation of a transparent cornea from this surface ectoderm requires Dkk2 driven suppression of Wnt/β-catenin signalling in order to avoid becoming hair-bearing skin [21]. Thus, the cornea must be blinded to Wnt/ $\beta$ -catenin activity to avoid the skin fate, and expression of Dkk2 is seen to be maintained throughout life in the corneal epithelium. The tissues surrounding the eye also develop a range of glands under the influence of FGF signalling, and the cornea must avoid exposure to these inducers, too, to achieve its transparent state [22]. This suspension of inductive signalling renders the cornea uniquely susceptible to inductive influences into adult life, permitting formation of hair follicles and a keratinised epidermis when mature corneal epithelium is placed under the influence of an embryonic dermis from hair-bearing skin [23].

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