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ESSENTIALS Skin provides a mechanical and immunological barrier against the external environment, but has further roles in thermoregulation, me- tabolism, and the regulation of fluid balance, as well as being so- cially important in contributing to physical and chemical attraction between individuals. There are more than 1000 different skin diseases, although rela- tively few are commonly encountered in general medical prac- tice. However, several skin conditions can reflect a general medical problem such as a systemic infection, or a cutaneous manifestation of internal disease (e.g. patients with underlying malignancy, endo- crine disorders, or chronic inflammatory diseases). An understanding of skin structure and function is also important in dealing with the common clinical scenario of ‘skin failure’ resulting from adverse drug reactions, burns, or extensive trauma. Introduction The skin is the body’s largest organ. In a 70 kg individual, the skin weighs over 5 kg and covers a surface area approaching 2 m2. Structurally, skin consists of a stratified cellular epidermis (made of keratinocytes) and an underlying dermis of connective tissue (fibroblasts, collagens, elastic tissue, and ground substance) (Fig. 23.1.1). Below the dermis is a layer of subcutaneous fat, which is separated from the rest of the body by a vestigial layer of striated muscle. The skin also contains hair follicles, sweat glands, blood vessels, autonomic and sensory nerves, as well as pigment cells (melanocytes), antigen-presenting cells (e.g. Langerhans’ cells), neuroendocrine (Merkel) cells, and some resident inflammatory cells (lymphocytes and mast cells). Origin of the skin The skin arises by the juxtaposition of two major embryological elements: the prospective epidermis, which originates from a sur- face area of the early gastrula, and the prospective mesoderm, which comes into contact with the inner surface of the epidermis during gastrulation. The mesoderm not only provides the dermis, but is essential for inducing differentiation of the epidermal structures, such as the hair follicle. The melanocytes are derived from the neural crest. While the skin develops in utero it is covered by a special layer, the periderm, which is unique to mammals. The periderm provides some protection to the newly forming skin, as well as having a role in the uptake of carbohydrate from the amniotic fluid. As skin matures in utero, physiological detachment of the periderm (into the amni- otic fluid) occurs by 24 weeks’ gestation. The embryonic dermis is at first very cellular, and at 6–14 weeks three types of cell are present: stellate cells, phagocytic macro- phages, and cells with secretory granules (either

melanoblasts or mast cells). From weeks 14 to 21 fibroblasts are numerous and ac- tive, and perineural cells, pericytes, melanoblasts, Merkel cells, and mast cells can be individually identified. The various components of the skin that can be recognized postnatally start to appear at dif- ferent embryonic time-points, for example, hair follicles and nails (9 weeks), sweat glands (9 weeks for the palms and soles, 15 weeks for other sites), and sebaceous glands (15 weeks). Touch pads become recognizable on the hands and fingers, and on the feet and toes, by 6 weeks, and reach their greatest development at 15 weeks. After this, they flatten and become indistinct. It is these areas that determine the pattern of the dermatoglyphs (fingerprints) that take their place. Structure of the skin Epidermis The normal epidermis is a terminally differentiated, stratified squa- mous epithelium composed of keratinocytes, which progressively move from attachment to the epidermal basement membrane to- wards the skin surface. This process normally takes about 40 days, but is accelerated in diseases such as psoriasis. The brick-like shape of keratinocytes is provided by a cytoskeleton made of keratin inter- mediate filaments. As the epidermis differentiates, the keratinocytes become flattened as a result of the action of filaggrin, a protein com- ponent of keratohyalin granules, on the keratin filaments. Indeed, keratin and filaggrin comprise 80–90% of the mass of the epidermis. The outermost layer of the epidermis is the stratum corneum, where the cells (now called corneocytes) have lost their nuclei and cytoplasmic organelles. The corneocyte has a highly insoluble 23.1 Structure and function of skin John A. McGrath

section 23 Disorders of the skin 5592 cornified envelope within the plasma membrane, formed by the cross-linking of soluble protein precursors including involucrin and loricrin. The latter contributes 70–85% of the mass of the cornified cell envelope, which also contains several lipids (fatty acids, sterols, and ceramides) released from lamellar bodies within the upper, living epidermis. Keratinocytes also generate hundreds of antimicrobial peptides that have important roles in innate and adaptive immune responses; most are small cationic peptides that can kill bacteria by binding to anionic components in microbe cell membranes. Human skin is also colonized by trillions of commensal micro- organisms, referred to as the skin microbiome, the nature of which is influenced by body site (e.g. dry or moist skin), gender, age, medi- cations, and diet. Host-microbiome interactions are important in protective immune responses and perturbations in the microbiome may contribute to the pathogenesis of many skin diseases including acne vulgaris, psoriasis, and atopic dermatitis (eczema). Melanocytes are located within the basal layer of the epidermis (closest to the dermis). These are dendritic cells that distribute pack- ages of the pigment melanin (melanosomes) to surrounding kera- tinocytes, the process that gives skin its physical colour. The number of melanocytes does not differ much between white and black skin. Rather it is the nature of the melanin and the size of the melanosomes that account for the different appearance. Each melanocyte supplies melanin pigment to c.30–40 surrounding keratinocytes. Another dendritic cell population within the epidermis is the Langerhans' cell, which is of mesenchymal origin, and originates from bone marrow. Langerhans' cells are antigen-presenting cells that process antigens encountered by the skin to local lymph nodes, and thus have a key role in adaptive immune responses in the skin. Dermis Collagen is the major extracellular matrix protein, comprising 80– 85% of the dry weight of the dermis. Twenty-eight different collagens have been identified in vertebrate tissue (distinguished by Roman numerals in the order of their discovery, from I to XXVIII), of which at least 12 are expressed in skin. The main interstitial dermal colla- gens are types I and III, whereas the principal basement membrane collagen (at the junction between the dermis and the epidermis, and around dermal blood vessels, nerves, and

glands) is type IV. Triple-helical collagen monomers polymerize into fibrils and fibres, which then become stabilized by the formation of complex intra and intermolecular cross-links. Collagen fibres are extremely tough and provide skin with its tensile strength. Elastic fibres account for no more than 2–4% of the extracellular matrix in the dermis, and consist of two components, elastin and microfibrils, which together give skin its elasticity and resilience. Elastic microfibrils are composed of several proteins, including fibrillin, that surround the elastin and can extend throughout the dermis in a web-like configuration to the junction between the dermis and the epidermis. Collagen and elastic fibres are deposited by fibroblasts, mesen- chymal cells that show considerable embryonic heterogeneity and body site diversity, with various subpopulations of fibroblasts differentially contributing to skin homeostasis, wound healing, scarring, and formation of hair follicles. The dermis also contains several noncollagenous glycoproteins, including fibronectins, fibulins, and integrins, which are important components of the extracellular matrix, facilitating cell adhesion and cell motility. Between the dermal collagen and elastic tissue is the ground substance, made up of glycosaminoglycan/proteoglycan macromolecules. These contribute only 0.1–0.3% of the total dry weight of the dermis, but play a vital role in providing hydration, mostly via the high water-binding capacity of hyaluronic acid. Indeed, about 60% of the total weight of the dermis is composed of water. Regional variations in skin anatomy The thickness of the living epidermis in normal human skin shows some variation with body site, and usually measures about 0.05– 0.1 mm, although it can be thicker in regions such as the palm and sole, where the stratum corneum can be up to 10 times thicker than in nonacral sites (Fig. 23.1.2). Likewise, the thickness of the dermis can differ considerably, from less than 0.5 mm on the eyelid to more than 5 mm on the back. There are two main types of human skin. Glabrous (nonhairy) skin is found on the palms and soles. It has a grooved surface with alter- nating ridges and sulci, giving rise to the fingerprints. Glabrous skin has a compact stratum corneum, encapsulated sense organs within the dermis, and a lack of hair follicles and sebaceous glands. By con- trast, hair-bearing skin has both hair follicles and sebaceous glands, but lacks encapsulated sense organs. There is also wide variation be- tween body sites. For example, the scalp has large hair follicles that may extend into the subcutaneous fat, whereas the forehead has only small vellus hair-producing follicles, although the sebaceous glands are large. The axilla is notable because it has apocrine glands in add- ition to the eccrine sweat glands that are found throughout the body. Skin renewal The epidermis can regenerate from a heterogeneous collection of keratinocyte stem cells that are located in small clusters in the basal interfollicular epidermis and, in particular, in the bulge region and other parts of hair follicles. Although morphologically similar to other keratinocytes, stem cells are associated with particular mo- lecular profiles. Some keratinocyte stem cells undergo symmetrical cell division to create transient amplifying cells which can proliferate Fig. 23.1.1 Histopathological appearance of normal human skin. This light microscopic image illustrates the structural features of the outer skin layers. BV, blood vessel; D, dermis; E, epidermis; M, melanocyte; SC, stratum corneum. Haematoxylin and eosin; scale bar = 0.1 mm.

 and divide a small number of times before undergoing terminal dif- ferentiation. Other keratinocyte stem cells can give rise directly to terminally differentiating cells (asymmetrical division). The key signals that influence symmetrical or asymmetrical division, the distinction between stemness and transient amplification, and the precise start/stop signals for self-renewal are not known, although Wnt and BMP (bone morphogenic protein) signalling are impli- cated. Stem cells in the bulge region have the capacity to migrate (e.g. to the base of the hair follicle in follicular regeneration), as well as to differentiate

into diverse lineages (e.g. hair, sebaceous glands, or interfollicular epidermis). Mesenchymal stem cells can also reside within the dermis and fat, although the precise function of such cells in skin homeostasis or during wound healing has not been well es- tablished. Likewise, the renewal of many skin cells, including kera- tinocytes, might be possible by cellular differentiation from other stem-cell sources such as bone marrow. Functions of the skin Skin provides a barrier against the external environment (Fig. 23.1.3). The cornified cell envelope and the stratum corneum re- strict water loss from the skin, while keratinocyte-derived en- dogenous antibiotics (defensins and cathelicidins) provide an innate immune defence against bacteria, viruses, and fungi. The surface pH of human skin ranges from 4.3 to 5.3; skin pH is lower in people with darker skin because melanin biproducts are acidic. The epi- dermis also contains a network of about 2 × 109 Langerhans' cells, which serve as sentinel cells whose prime function is to survey the epidermal environment and initiate an immune response against microbial threats, although they may also contribute to immune tolerance in the skin. Within the dermis, there are approximately 20 × 109 T-lymphocytes, about twice the total number in periph- eral blood. Melanin in keratinocytes also provides some protection against DNA damage from ultraviolet radiation. An important function of skin is thermoregulation, and there is both a superficial and a deep vascular plexus; vasodilatation and vaso- constriction of these blood vessels helps regulate heat loss. Eccrine sweat glands, present in densities of 100–600/cm2, also play a role in heat control, and may produce approximately 1 litre of sweat per hour during moderate exercise. Secretions from apocrine sweat glands, which are mainly found in the axillae, contribute to body odour (pheromones). Skin lubrication and waterproofing is provided by sebum secreted from sebaceous glands: outpouchings of hair follicles. Subcutaneous fat has an important role in cushioning trauma, as well as in providing insulation and a calorie reserve. Fat also has an endocrine function, generating hormones such as leptin that con- tribute to regulation of appetite and metabolic energy control. Nails provide protection to the ends of the fingers and toes, and are im- portant in pinching and prizing objects. Skin also has a key function in synthesizing various metabolic products, such as vitamin D. Skin also contains motor and sensory nerves. The motor innerv- ation of the skin is autonomic, and includes a cholinergic compo- nent to the eccrine sweat glands, and adrenergic components to both the eccrine and apocrine glands, to the smooth muscle and the ar- terioles, and to the arrector pili muscle (attached to hair follicles). The sensory nerve endings are of several kinds; some are free, some terminate in hair follicles, and others have expanded tips. Failure of the skin Epidermis Loss of a functional epidermis has profound biological and clinical consequences involving the loss of water and electrolytes, cutaneous and systemic infection, and impaired thermoregulation. The clinical importance of an intact skin barrier has recently been highlighted by the discovery that many people with atopic dermatitis (and atopic dermatitis associated with asthma) have loss-of-function mutations in filaggrin (see OMIM 135 940), an important component of the cornified cell envelope. Loss of filaggrin leads to a defective skin barrier with increased transepidermal water loss (leading to skin dryness and itching) and an increased susceptibility to allergic sen- sitization and infection. Loss-of-function mutations in filaggrin, which might occur in up to 10% of the population, are also a major risk factor for systemic allergies and for nut allergy, emphasizing the importance of the skin as a portal for allergen presentation. As far as acquired epidermal failure is concerned, burns, trauma, and adverse drug reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis (TEN, Lyell's syndrome) can all lead to sig- nificant skin detachment and major metabolic imbalances. Stevens– Johnson syndrome can be considered a minor form of TEN, and involves less than 10% of body surface area skin detachment, with Fig. 23.1.2 Regional differences in skin anatomy. The physical differences in the structural

composition of human skin at four different body sites (thigh, scalp, sole, and axilla) are depicted. Compared with thigh skin, the scalp has much larger hair follicles that extend deep into the subcutaneous fat, the sole has a thick stratum corneum, and the axilla has numerous eccrine and apocrine sweat glands.

section 23 Disorders of the skin 5594 an average reported mortality of 1–5%, whereas toxic epidermal necrolysis is characterized by more than 30% skin detachment, and an average reported mortality of 25–35%. Both conditions are char- acterized histologically by a rapid onset of keratinocyte cell death by apoptosis, a process that results in the separation of the epidermis from the dermis. There may be a pathophysiological role for inflam- matory cytokines and the death receptor Fas (TNF receptor super- family, member 6) and its ligand in the keratinocyte apoptosis during toxic epidermal necrolysis. Fas-mediated keratinocyte apoptosis can be inhibited in vitro by antagonistic monoclonal antibodies to Fas, and by intravenous immunoglobulins, which have been shown to contain natural anti-Fas antibodies. Other explanations of the pathophysi- ology of toxic epidermal necrolysis involve the drug interacting with major histocompatibility complex class I-expressing cells to generate drug-specific CD8 + cytotoxic T cells, which accumulate locally and release granzymes and perforin to kill keratinocytes. CD8 + T cells, natural killer (NK) cells, and NKT cells might also release granulysin, leading to keratinocyte death without the need for direct cell contact. Early recognition of toxic epidermal necrolysis leading to skin failure is, however, vital for optimal patient management. Dermis In normal skin ageing, and in photoageing (skin changes resulting from chronic sun exposure), there is reduced synthesis of inter- stitial collagens (type I and III), and increased synthesis of en- zymes (matrix metalloproteinases) that break down dermal fibres. Paradoxically, there is an increase in elastin synthesis, although this functions poorly and contributes to the wrinkled, sagging appear- ance of aged skin. More specific insight into the consequences of the failure of particular dermal components, however, has been determined from the molecular characterization of genetic disorders such as Ehlers–Danlos syndrome (EDS) and cutis laxa. Ehlers–Danlos syn- drome represents a collection of six major disease groupings as- sociated with varying degrees of hyperextensible fragile skin and loose joints. There are several rarer variants of EDS, with patho- genic mutations reported in at least 18 different genes. Some sub- types may also be associated with catastrophic rupture of arterial blood vessels, the bowel, or the uterus. In some forms of EDS ab- normalities have been detected in type V collagen (OMIM 120 190) and tenascin X (a molecular organizer of connective tissue; OMIM 600 985), and in the vascular type of EDS, in type III collagen (OMIM 120 180). Further pathology has also been demonstrated in type I procollagen (OMIM 120 160) and in two enzymes, lysyl hydroxylase (EC 1.14.11.4; OMIM 153 454) and procollagen N- endopeptidase (EC 3.4.24.14; OMIM 604 539), involved in the for- mation of collagen fibres. Cutis laxa is clinically characterized by loose, sagging skin and, in some subtypes, by extracutaneous ab- normalities such as emphysema, and inguinal or umbilical hernias. Mutations in the gene encoding fibulin 5 (OMIM 604 580), a pro- tein involved in elastin fibrillogenesis, have been shown to underlie some, but not all cases of this disease. In some genetic diseases, such as focal dermal hypoplasia (Goltz syndrome, OMIM 305600), there is a near total failure to develop the dermis, which leads to outpouching of the subcutaneous fat into the overlying epidermis. This disorder results from mutations in an endoplasmic reticulum transmembrane protein, porcupine (see OMIM 300651), which normally activates key Wnt signal cascades needed to generate the dermis. Collectively, these rare genetic diseases highlight the significant clinical consequences of the failure of specific components of the dermis, and provide evidence for their important roles in the maintenance of normal, healthy skin. FURTHER READING

Battie C, et al. (2014). New insights in photoaging, UVA induced damage and skin types. Exp Dermatol, 23 Suppl 1, 7–12. Gonzales KA, Fuchs E (2017). Skin and its regenerative powers: an alliance between stem cells and their niche. Dev Cell, 43, 387–401. Fig. 23.1.3 Function of human normal skin. The skin has several key biological roles, from the formation of a mechanical barrier, the stratum corneum, against the external environment, to providing a calorie reserve in the subcutaneous fat.

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the Ehlers-Danlos syndromes. Am J Med Genet Part C, 175C, 8–26. McGrath JA (2012). The structure and function of skin. In: Calonje E, et al. (eds) McKee’s pathology of the skin, pp. 1–31. Elsevier Saunders, Philadelphia. McGrath JA, Uitto J (2016). Anatomy and organization of human skin.
In: Griffiths CEM, et al. (eds) Rook’s textbook of dermatology, pp. 2.1–2.48. Blackwell Publishing Ltd, Oxford. McLean WH (2016). Filaggrin failure – from ichthyosis vulgaris to atopic eczema and beyond. Br J Dermatol, 175 suppl 2, 4–7. White KD, et al. (2018). SJS/TEN 2017: building multidisciplinary networks to drive science and translation. J Allergy Clin Immunol Prac, 6, 38–69.

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