Therapy of Skin Diseases
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A Worldwide Perspective on Therapeutic Approaches and Their Molecular Basis
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Treatment of skin diseases has changed remarkably during the last decade. This is largely the result of a better understanding of the molecular and cellular basis of many skin diseases. Thus, novel targets have been identified and specific drugs developed which directly interfere with or alter the disease processes. This change is readily apparent when considering the novel agents available for psoriasis and atopic dermatitis, and also for viral and other infectious skin diseases. Interestingly, many of these new agents are administered systemically either orally or by subcutaneous injection. And yet, as with all forms of drug therapy, these highly efficacious agents can also be associated with severe side effects and drug-induced toxicity. Accordingly, the dermatologist must be aware of the medical status of the patient as well as all other medications that are being prescribed concomitantly. Careful monitoring of the risk:benefit ratio is always critical.

Simultaneously, with the rapid development of novel therapeutics, there has been a major evolution in the clinical practice of dermatology with considerable variations across different areas of the world. In European countries, the discipline is relatively broad, in some countries including allergy and phlebology, as well as dermatologic surgery and dermatologic oncology. In European countries, patients with skin disease are often treated as in-patients by dermatologists, whereas in the United States, this occurs only rarely and the patients are admitted to beds assigned to Internal Medicine and dermatologists consult on their management. Asian dermatology has been profoundly affected by both European and American dermatology and the selection of therapeutic agents often reflects those influences.

The result of these developments is that regional differences are commonplace in the treatment of skin diseases, some correlating with the dermatologic features of patients from diverse ethnic backgrounds, others relating to variations in the different health care systems and/or the medical education and the awareness of dermatologists regarding particular treatment options. In the age of Internet, novel therapies are instantly available and potentially applicable to patients globally.

This book was conceived to address these changes and it has two major aims. First, it summarizes novel therapeutic procedures that are based on understanding the pathophysiology of skin diseases. Second, it aims to bring together in one place the variability of treatment modalities employed in the practice of dermatology around the world in Asia, Europe, and the USA. Every effort has been made to assure that all chapters indicate global variations either in the occurrence or the expression of skin
diseases and their treatment. All manuscripts have been reviewed carefully by experts familiar with the practice of dermatology in Asia, Europe, and the USA. It is our hope that this book will prove to be a valuable reference tool for dermatologists everywhere.

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Part

Introduction
The skin is the largest organ of the body and crucial for terrestrial life by providing a sturdy barrier toward the outside world. This barrier protects the organism from dehydration and prevents microbes and damaging agents from entering. The skin is challenged on a daily basis by a range of external insults, such as changes in temperature, UV light, and bacteria to thermal and mechanical injuries. Since in most cases, the skin is able to handle challenges without the occurrence of overt disease, this organ, by nature, must be an extremely versatile and dynamic tissue.

During evolution, the skin has gained a number of structural and functional features that allow it to react in an adequate manner to those external signals and injuries. Most importantly, the skin has developed ultra-structurally defined subcompartments that topically restrict external and internal damage.

The skin is composed of an epithelial and a mesenchymal compartment, the epidermis and the dermis, which are connected by a highly specialized extracellular matrix structure, and the basement membrane (Fig. 1.1.1). The dermis is resting on the subcutis, a fat layer that connects it to the fascia and the underlying muscles. These two compartments communicate extensively in various ways and at different levels, and this is crucial to establish, maintain, and restore homeostasis. During skin morphogenesis, this reciprocal interaction also determines the formation of the epidermal appendages, such as hair follicles, sweat glands, sebaceous glands, and nails, all structures that are required for normal skin function. Strong regional differences exist in the thickness and differentiation status of dermis and/or epidermis and the distribution of skin appendages. These variations are ontogenetically determined and form the basis for differential skin function required in various anatomical areas.

This chapter provides a general overview of, and introduction to, the cellular composition of the skin, the most important functions of the different cell types, and their particular contribution to the multifunctional skin barrier. Although it emphasizes several aspects more than others, this chapter does not aim at going extensively into details, and for the most part, uses citations of excellent and comprehensive reviews to refer to the reader who is interested to learn more on particular subjects. In addition, many chapters of this book will discuss the different aspects discussed here in light of skin disease.

1.1.1 Cellular Composition of the Epidermis

The epidermis and its appendages, hair follicles, sebaceous, and sweat glands form the physical barrier of the organism of the outside world. As a barrier, it
serves several important functions, both physical and immunological, which are reflected in the cell types and differentiation status that make up the epidermis.

Keratinocytes are the most predominant cell type in the epidermis and form the cornerstone of its overall structure and function. Epidermal keratinocytes balance lifelong self-renewal with a spatiotemporally strictly regulated terminal differentiation program, which ultimately leads to the formation of a dead, cornified, and water impermeable cell layer \[1,2\]. This differentiation program generates four functionally different layers, each of which is characterized by a specific expression repertoire of intracellular and cell surface associated proteins (Fig. 1.1.1): (a) the basal layer or stratum basale consists of undifferentiated, proliferating cells. (b) the spinous layer or stratum spinosum contains the cells that have withdrawn from the cell cycle, migrated up from the basal layer while committing to differentiation. These cells also have switched keratins to synthesize a mechanically more stable keratin network. (c) The granular layer or stratum granulosum, dedicated to producing the majority of proteins, lipids, and enzymes for formation of the stratum corneum and (d) the stratum corneum, which is also known as the cornified layer, consists of corneocytes, composed of an insoluble cross-linked protein structure, the cornified envelope that serves as a scaffold for specialized lipids that form the intercellular lamina, thereby providing the epidermis with a water-impermeable barrier. Ultimately, this cornified layer is sloughed off in an only partially understood process called desquamation. The epidermal terminal differentiation program is a form of a programmed cell death that relates to the process of apoptosis, but is fundamentally different in key elements: e.g., cells are not phagocytosed and no activation of classical caspases occurs \[3,4\].

Different populations of stem and progenitor cells located in the basal layer of interfollicular epidermis (IFE) and in specific areas of hair follicles guarantee constant self-renewal under steady state conditions and sufficient plasticity for the fast replacement of lost tissue in case of injury. Morphogenetic signal pathways, such as Wnts, BMPs/TGF-β, Notch and Hedgehogs, control the determination, renewal and maintenance of these stem cells \[5–10\]. The flexible
balance between self-renewal and terminal differentiation is determined by the variable conditions of the extracellular environment.

Over the last decade, it has become clear that keratinocytes also actively contribute to the immunological barrier of the skin [11]. These cells produce antimicrobial peptides, such as defensins, and express Toll-like receptors on their cell surface, important for the control of innate immunity. In addition, upon disturbance of skin homeostasis, these cells secrete a wide range of cytokines and other growth factors that influence the innate and adaptive immune response.

Although over 90% of the epidermis consists of keratinocytes, other cell types, such as Langerhans cells, T-cells, melanocytes and Merkel cells, are present in the different layers (Fig. 1.1.1). These cells serve crucial specialized functions that contribute to epidermal homeostasis and to its restoration upon challenges of the epidermal barrier.

Merkel cells are postmitotic, neuroendocrine cells that produce a large number of cytokines and neuro peptides, form close connections with sensory nerve endings, and are mainly located in the basal layer of the epidermis. Ultrastructurally, these cells are characterized by dense core granules. Although these cells are the least well characterized cells in the epidermis, they are thought to have mechanosensory functions and contribute to the regulation of inflammatory responses [12, 13].

Langerhans cells are immature dendritic cells that form close contacts with keratinocytes and monitor microbial infection. Upon activation, these cells mature and migrate to draining lymph nodes where they present antigens to T-lymphocytes [14, 15]. Recent studies have revealed a novel functional aspect of Langerhans cells, showing that these cells not only contribute to immunostimulation, but also to immunosuppression [16].

The epidermis also contains a resident population of unique γδT-cells, which are in close contact with Langerhans cells and keratinocytes. These cells regulate skin inflammatory responses and play important roles in graft vs. host reactions in the skin [17]. By secreting different growth factors, they also play important roles in keratinocyte homeostasis and in wound repair [18]. Melanocytes produce melanin in specialized organelles, the melanosomes [19]. These cells are also in close contact with keratinocytes and this interaction determines melanin uptake by keratinocytes and thereby, skin pigmentation patterns [20]. The production and transfer of melanosomes is a complex and incompletely understood process, but plays a crucial role in the defense against the daily assault of UV light.

1.1.2 Cellular and Structural Composition of the Dermis

In contrast to the epidermis, the dermis is rich in extracellular matrix (ECM), and contains relatively fewer cells (Fig. 1.1.1). The upper or papillary dermis is characterized by loose connective tissue and a horizontal plexus of blood vessels, which are connected to a deep plexus located in the subcutis. The lower or reticular dermis makes up the major part of the dermis and mainly contains thick collagen bundles.

Fibroblasts are the predominant resident cells in normal dermis; they are responsible for producing and remodeling ECM. Even though these cells have been studied in depth in vitro with respect to their cellular adhesive, migratory, and differentiation properties, very little is known about their ability to differentiate in vivo. Fibroblasts in the papillary dermis differ from those in the reticular dermis with respect to growth potential and protein production, and both are different from hair follicle-associated fibroblasts [21]. Of interest, the concept of fibroblast heterogeneity applies not only to the skin but also to the entire human body, with fibroblasts in different anatomical sites and microenvironments being distinctly different in their gene expression programs and phenotypes [22]. The origin of dermal fibroblasts is an unresolved issue. They are thought to derive either from resident cells or from circulating mesenchymal progenitor cells that continually replenish the resident population. Modulating the differentiation of circulating or resident precursors is considered a novel approach for interfering with the development of fibrosis [23]. In some organ systems, fibroblasts were shown to originate from epithelial-to-mesenchymal transition (EMT); however, this origin has not yet been proven for the skin. Under the influence of TGF-β and topical mechanical forces, fibroblasts can “differentiate” into contractile myofibroblasts, driving wound contraction and the tissue response to tumors [24]. Fibroblasts as well as myofibroblasts actively participate in dermal homeostasis by contributing a plethora of growth factors.

Mast cells occur in virtually all vascularized tissues and are numerous in anatomical sites that are directly
exposed to the environment and easily identified by the presence of prominent cytoplasmic granules [25]. In the skin, they are frequently associated with blood vessels and appendages. Mast cells constitute an important cell type of the innate immune system and play an important role in inflammation and tissue remodeling. Their activation mainly occurs via the high affinity IgE receptor (FcεRI) or by contact with pathogens. Activated mast cells release an array of mediators e.g., histamine, proteases, and lipid metabolites, thereby causing extensive vasodilation, urticaria, and itching, and are a rich source of growth factors. Although many released substances act as pro-inflammatory mediators, mast cells also seem to have immunosuppressive and anti-inflammatory roles through the release of IL-10 and TGF-β.

Other important constituents of the dermis are blood vessels and a lymphatic system, which are closely interconnected. The cutaneous microcirculation is organized as two horizontal plexuses, the upper one at the level of dermal papillae and the lower one at the dermal-subcutaneous junction. These are joined by paired ascending arterioles and descending venules. Microvascular endothelial cells supply nutrients to the skin and are essential for wound repair and the growth of tumors, and they regulate heat loss and temperature control. Depending on the size of the blood vessel and its location within the dermis, the endothelial tube is surrounded by up to several layers of smooth muscle cells or pericytes and by an outer basement membrane [26]. Endothelial cells and smooth muscle cells/pericytes form tight intercellular junctions with interdigitating processes, which together with the basement membrane control the distribution of biologically active molecules, mediators, or bioactive ECM fragments. Microvascular endothelial cells express a number of adhesion molecules for platelets and leukocytes to safeguard hemostasis and the transmigration of inflammatory and precursor cells from the circulation into the skin.

Much less is known about the lymphatic system, which drains protein-rich fluid from the extracellular space and transports immune cells from the skin to regional lymph nodes [27]. Lymph capillaries are lined by endothelial cells and are highly permeable due to the lack of a continuous basement membrane. The main difference between vascular and lymphatic endothelial cells in normal adult skin is the presence of VEGF receptor-1 or -2 on vascular endothelial cells, responding to the VEGF-A isoform, and VEGF receptor-3 on lymphatic endothelial cells, responding to VEGF-C. During tissue repair and tumor vascularization, this distinction is less clear and novel markers for the lymphatic system will help in the analysis.

The major part of the dermis is the connective tissue, composed of structural proteins and nonstructural elements produced predominantly by fibroblasts. This ECM provides structural support, organization and orientation to tissues. The structural elements are composed of collagens, elastin, fibrillins, fibronectin and other high molecular weight glycoproteins, which are members of smaller or larger protein families. They are large modular molecules assembled from a limited set of modules or domains, which have biological activity on their own. Most ECM genes have arisen by duplication of genes already present in ancestral organisms. The ECM proteins are embedded in a so-called ground substance of proteoglycans, which supply hydration and elasticity. Interaction between the different macromolecules builds a large macromolecular network [28–30].

One of the less appreciated, but not less important, functions of the ECM is the retention of growth factors such as TGF-β [31, 32]. Adequate stimulation or proteolytic activity can liberate the mediators and topically restrict their activity; this quick adaptive response is critical, for example, in inflammation.

Apart from exerting biological functions such as promoting migration or proliferation as entire ECM proteins, fragments cleaved off from them have gained attention for their own and have distinct properties, which may differ from the parental molecule [33]. One classic example is endostatin with antiangiogenic activity, which is cleaved off from the basement membrane collagen XVIII.

Probably, the largest ECM protein family is that of the collagens (Table 1.1.1), which exist in 28 different

<table>
<thead>
<tr>
<th>Table 1.1.1 Collagen types in the skin</th>
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<tbody>
<tr>
<td><strong>Dermis</strong></td>
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<tr>
<td>Fibril-forming collagens</td>
</tr>
<tr>
<td>FACITS (fibril-associated collagen with interrupted triple helix)</td>
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<tr>
<td>Microfibrillar collagen</td>
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<tr>
<td><strong>Basement membrane collagens</strong></td>
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<tr>
<td>Ubiquitous collagens</td>
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<tr>
<td>Anchoring fibril collagen</td>
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<tr>
<td>Anchoring filament collagen</td>
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<tr>
<td>Endothelial basement membranes</td>
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<td>Epidermal/transmembrane collagens</td>
</tr>
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types [34]. All have a similar structure with a characteristic triple helix, which can vary considerably in length. The fibril-forming collagens I, III and V make up most of the net weight of the dermis and represent the principle tensile element. The interstitial connective tissue also harbors the microfibrillar collagen VI and the fibril-associated collagen XIV. Collagen IV is a network forming molecule that is an essential constituent of the dermo-epidermal basement membrane. Collagen VII is the molecular component of the anchoring fibrils, which connect the basement membrane to the dermis.

Next to secreted collagens, there are unusual, transmembrane, collagens [35]. Interestingly, several of these unusual collagens are subject to ectodomain shedding by metalloproteases, resulting in the release of the extracellular domain. These collagens can thus exist in two functionally potentially very different protein forms. Although the functional significance is unclear currently, this mechanism allows cells to switch rapidly from a cell surface (adhesive) receptor to a secreted form that can serve as an ECM component. One of the best studied examples is collagen XVII, which is an important cellular component of hemidesmosomes in epidermal keratinocytes. It was initially discovered as one of auto-immune antigens in bullous pemphigoid, hence its alternative name BP180. Recently, a novel variant of collagen VI [36] was reported as potential molecular target of atopic dermatitis [37].

### 1.1.3 Basement Membranes

The epidermis and dermis cooperate in the formation of a highly specialized ECM structure, the basement membrane zone (BM), which physically separates these two compartments. The BM zone consists of a highly complex network of interconnecting ECM proteins, the key components being collagen IV, laminin, nidogen and proteolycans [38–40]. The skin basement membrane zone is characterized by auxiliary structures, the anchoring complexes, which consist of adhesion structures called hemidesmosomes (see below), anchoring filaments and anchoring fibrils. The anchoring filaments are mainly made up of Laminin 5, the major laminin isoform present in basement membranes of the skin and a crucial adhesive substrate for basal keratinocytes. Laminin-5 physically links the epidermis to collagen VII, the molecular constituent of the anchoring fibrils, which form the mechanical connection of the basement membrane to the underlying dermis. The importance of the anchoring complex in the maintenance of skin integrity is underscored by skin blistering diseases that are either caused by genetic mutations in one of these protein constituents of the basement membrane or by the production of auto-antibodies against several components [41–43].

### 1.1.4 Cell–Matrix and Cell–Cell Adhesion in the Skin

Intercellular and cell–matrix adhesion are crucial for cellular communication and play important roles in skin homeostasis and in the response to skin challenges. Cell adhesion is mediated by a large variety of cell adhesion receptors that can be subdivided into several different families. The most prominent of these are the integrin family of cell–matrix and cell–cell receptors, the cadherin superfamily of intercellular adhesion receptors, the IgG family of cell–cell and cell–matrix receptors, the selectins and the proteoglycan receptor family. Upon adhesion, most of these receptors cluster into specialized junctional structures that are associated with the cytoskeleton (Fig. 1.1.2). These structures not only have important adhesive functions but also provide the cell with spatial landmarks important for localized signaling. Indeed, for most adhesion receptors, it is now clear that they not only connect cells to their environment but also, by connecting to signaling molecules, can communicate signals from the cell to its environment (so called inside-out signaling), and from the environment to the cell (outside-in signaling) [44].

Intercellular junctions are most prominent in keratinocytes and endothelial cells (Fig. 1.1.2). However, dermal fibroblasts do form gap junctions and specialized forms of adherens junctions, which can be established over relatively long distances. Intercellular Junction formation is also dynamically regulated upon activation of dermal fibroblasts. In addition, intercellular junctions are crucial for dermal vascular integrity. Dynamic intercellular adhesion also plays a crucial role in the interaction of immune and inflammatory cells with other cell types when skin integrity is perturbed. Four different types of intercellular junctions characterize the epidermis:
1. Desmosomes consist of desmosomal cadherins that are linked to the keratin filament system through specialized cytoskeletal adapter proteins, such as plakoglobin, plakophilins and the plakin desmoplakin. In the skin, desmosomes are not only found in the epidermis but also in vascular endothelia, where they form an intermixed structure with adherens junctions, called syndesmosomes. Although desmosomes show an ultrastructurally similar appearance throughout the epidermis, they have distinct molecular compositions that depend on the differentiation status of the keratinocytes, and most likely contribute specific functions [45]. For example, corneocytes are connected by a specialized variant, the corneodesmosome. Their importance for epidermal integrity is underscored by the existence of genetic and auto-immune skin blistering diseases, which are characterized by mutations in, or antibodies against, desmosomal components [46]. Next to their importance in providing mechanical strength to epidermal intercellular cohesion, novel functions have emerged for desmosomal components in the regulation of differentiation, survival, and growth.

2. Tight junctions form size and ion specific barriers in epithelia and vascular endothelial cells. In the epidermis, functional tight junctions are present in the granular layer. Tight junctions consist of two different four transmembrane spanning protein families, the occludins and claudins that link to actin via several different linker molecules e.g., the scaffolding proteins ZO-1/2. Differential expression of claudins provides tight junctions found at different sites with their size and ion speciﬁcity and, thereby, determine the tightness of the epithelial and vascular barrier [47,48]. For keratinizing epiderelia, it was originally thought that the secretion and deposition of a cross-linked protein–lipid barrier obviated the need for a tight junction barrier in such tissues, even though tight junctional proteins were identified in the epidermis. The first functional evidence that a tight junction component is required for barrier function in epidermis came from claudin-1 knockout mice, which showed severe water
1.1 Biology of the Skin

1.1.1 Epidermal Tight Junctions

Tight junctions are crucial structures for intercellular communication by forming pores that allow the passage and exchange of small molecules between adjacent cells [55]. Connexin proteins constitute the molecular basis of the pores. Their importance for skin function is demonstrated by connexin mutations that underlie a number of inherited skin related diseases, including Vohwinkel syndrome and ichthyosis, and palmoplantar keratoderma related entities [46, 56].

1.1.2 Desmosomes

Desmosomes, or half desmosomes, resemble desmosomes at the ultrastructural and functional level, in that they show a similar organization, and by connecting to keratin filaments, are crucial structures for mechanical stability. Nevertheless, their molecular composition is very different, consisting of the integrin α6β4 and the previously mentioned collagen XVII (formerly known as BPAG1) as adhesion receptors and several cytoskeletal linker molecules of the plakin family, such as plectin and BP230 [57]. The β4 subunit is unique among the integrin β subunits because of its long cytoplasmic domain that, unlike the other actin-linked β subunits, links α6β4 to intermediate filaments. Hemidesmosomes are crucial for the integrity of the skin, since mutations have been found in each of its known components, all of which lead to skin blistering diseases [42, 58].

The β1 and αv integrin subfamilies provide the scaffold of focal adhesions, which recruit a variety of cytoskeletal and signaling proteins, the most prominent ones being talin, vinculin, kindlins, the focal adhesion kinase (FAK), and integrin linked kinase (ILK) [59]. These structures are crucial for skin homeostasis, since they contribute to a wide variety of functions on the different skin cells. Many of these are important for skin homeostasis, as underscored by the loss of β1-integrins in the epidermis of mice, resulting not only in the formation of microblisters, but also in proliferative defects and skin inflammation [60]. Other functions become more important when the skin is challenged. For example, α2 integrins regulate vascularity during wound healing [61]. Although focal contacts as a structure have not been identified in the skin in vivo, related structures are most likely important, as emphasized by the mutations in different focal contact components that underlie skin blistering related diseases [46].

A recently emerging theme is that adhesive junctions may not only be crucial for tissue integrity and serve as clustering sites for signaling molecules, but
may also regulate communication with the nucleus at two different levels. First, it is now clear that many of the cytoskeletal linker proteins associated with adhesive junctions can also translocate to the nucleus where they regulate transcription [44, 62]. In addition, several cytoskeletal linker proteins also interact with components of the nuclear matrix, thereby potentially linking cell adhesion to nuclear positioning and shape changes, which can affect general transcriptional activity [63].

1.1.5 Molecular Basis of the Epidermal Barrier

The physical epidermal barrier is built up by two physically separated compartments: the tight junctions present in the uppermost viable layer, the stratum granulosum and the stratum corneum, which consists of a lipid and protein component, often referred to as “brick and mortar” [64, 65]. Tight junctions and the stratum corneum may cooperate in the formation of a functional barrier in stratifying epithelia. For example, overexpression of claudin-6 in the upper layers of the epidermis or epidermal deletion of the membrane anchored serine protease (CAP)1/Prss8 induced barrier defects that involved alterations in both tight junctions and stratum corneum. Although the underlying mechanisms are unknown, they may involve the coordinated regulation of both barriers by signal molecules such as IKK1 and retinoic acid receptor signaling [66]. In simple epithelia, tight junctions form a fence, thereby separating the apical membrane domain from the basolateral membrane domain. Since formation of the stratum corneum depends on the fusion of lamellar bodies and keratohyalin granules with plasma membranes at the transition between stratum granulosum and stratum corneum layers, it is tempting to speculate that the specific occurrence of tight junctions in the stratum granulosum regulates targeting of protein and lipid vesicles directly towards the “apically localized” stratum corneum (reviewed in [47]).

The importance of site specific expression of keratins is best reflected in the identification of mutations in, until now, 19 keratins in skin related diseases, most of which are associated with skin blistering [69]. These keratin related diseases not only emphasize their crucial importance in providing regional and site specific mechanical strength to epithelia, but also provide intriguing hints for other keratin related functions independent of structure. Keratin mutations identified in both mice and human are associated with pigment defects, albeit the underlying mechanisms by which keratins regulate epithelial pigmentation patterns are mostly unclear. Studies in mice have also uncovered roles of keratins in determining the onset of apoptosis crucial for hair follicle cycling and in the regulation of protein synthesis and cell size. Recently, a fascinating link has been established between focal adhesion formation and keratin filament assembly, suggesting that the different adhesion structures and their associated cytoskeletal networks communicate directly to provide mechanical strength to cells (reviewed in Gu et al., 2007). The plakin
family of cytoskeletal binding proteins may perform key functions in these processes, since they can interact with both actin and intermediate filaments [63].

Keratins form the core components of the corneocytes, the anucleate cells of the stratum corneum [70]. This requires bundling of the keratin filaments, in which the late differentiation protein filaggrin plays an important role in the bundling of keratins and in the formation of the cornified envelope that forms the outer layer of the corneocytes. At the late steps of cornification, filaggrin is processed into free hygroscopic amino acids that act as the natural moisturizing factors of the skin. Indeed, mutations in filaggrin underlie ichthyosis variants and are also associated with atopic dermatitis, indicating its crucial importance not only in stratum corneum formation, but also in skin hydration [71]. Filaggrin is initially produced in the granular layer as a huge precursor, profilaggrin, which aggregate to form the characteristic keratohyalin granules of this layer. The cornified envelope consists of a dense network of proteins, mostly loricrin, involucrin and cornifin, which are tightly cross-linked to each other by enzymes such as transglutaminases [3]. Specialized desmosomes, so-called cornedesmosomes, connect corneocytes. A crucial step of desquamation is the proteolytic cleavage of these cornedesmosomes. The intercellular space between corneocytes is filled by the lipid lamellae, a specialized structure of lipids crucial for epidermal water barrier function [72, 73].

An important aspect of cornification and the subsequent process of desquamation is the spatiotemporal activation and inhibition of proteases, cross linkers and lipid enzymes [74]. Although not well understood, these complex processes are balanced by inhibitors and activators of these enzymes and are at least partially regulated by gradients in pH and Ca²⁺-concentrations. The importance of proper spatiotemporal activation is stressed by diseases caused either by inappropriate activation or inhibition of these different enzymes due to e.g., lack of inhibitors or activators [75, 76].

1.1.6 Cellular Communication Within the Skin

In recent years, it has become increasingly clear that the different skin cell types have a profound functional influence on each other, and that an extensive cellular cross-talk regulates cell proliferation, differentiation, and coordinates the cellular and immunological responses to environmental challenges. Data generated in the recent past have resulted in a change of paradigm in understanding skin homeostasis and substantial number of skin diseases. It is now clear that keratinocytes and fibroblasts not only represent the scaffold of the epidermis and dermis, but are also actively involved in the regulation of e.g., the innate and adaptive immune system [77]. They do so by secreting a large number of different mediators to communicate with endothelial cells and with inflammatory cells during wounding or disease conditions. These include pro-inflammatory cytokines, such as IL-1, IL10, and IL-6, antibacterial peptides, and growth factors such as VEGF or TGF-β. In turn, the activity of these cells and their extracellular mediators profoundly influence the differentiation status of the keratinocytes and fibroblasts, thereby determining their response when the multifunctional skin barrier is challenged [78, 79]. An important modulatory role in skin communication is provided by the ECM that not only serves as an important structural scaffold but also, by interacting with cells and many of the cytokines and growth factors, alters their functional activity. Together, these new findings and insights have led to the realization that the primary cause of skin diseases associated with barrier dysfunction and inflammation can reside in keratinocytes and fibroblasts with a secondary contribution of classical inflammatory cell types, activated through cellular communication. In addition, such primary defects in the skin can affect homeostasis of other organs, resulting in associated diseases in these organs.

1.1.7 Concluding Remarks

The last decade has brought a tremendous progress in the cell biology of the skin and thereby contributed to a better understanding of human skin diseases, as many of the examples mentioned in the following chapters exemplify. What many of these studies clearly revealed, regardless of whether one is looking from a fibroblast, endothelial cell, a keratinocyte, or immune cell point of view, is the extensive communication that occurs between cells and compartments of the skin. These new insights and findings can now be used to identify the primary and secondary events that are still unknown