Proliferative Responses of the Skin to External Stimuli

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The skin, in particular the epidermis, offers unique opportunities to investigate the induction and control of cellular proliferation and tissue homeostasis both under in vivo and in vitro conditions. Moreover, it represents one of the most feasible model systems for experimental cancer research. As the primary border of the body, the skin has important protective and defensive functions. A general response to external injury consists of a thickening of the epithelial layer (epidermal hyperplasia) combined with an inflammatory reaction. This hyperplastic transformation of the skin is a critical condition of skin tumor development (i.e., conversion and promotion) and of the wound response. It is believed to be due to a transformation of keratinocytes into an activated state characterized by an increased rate of proliferation and the ability to release a series of growth factors and other cytokines that coordinate the defense reaction (e.g., hyperproliferation, recruitment of leukocytes, activation of the immune system) along autocrine and paracrine feedback loops. The initial and probably later phases of this response depend critically on a local release of eicosanoids such as prostaglandins and lipoxygenase-generated factors. A unique reaction seen upon phorbol ester treatment of mouse skin is a strong induction of the enzyme 8-lipoxygenase, which might be involved in skin tumor development by catalyzing the generation of clastogenic metabolites thought to play a role in the conversion stage. Hyperplasia may be considered to be the result of an imbalance between the rates of cell gain and cell loss. Therefore, hyperplastic transformation has to be distinguished from another response of skin to external stimuli where the homeostatic equilibrium is maintained (i.e., no hyperplasia develops in spite of strong hyperproliferation). This balanced hyperproliferation as induced by mild stimuli (pressure, phorbol ester 4-O-methyl-TPA) is neither accompanied by inflammatory reactions nor by the symptoms of keratinocyte activation. It may simply be due to an increased rate of cell-cycle traverse in the proliferative tissue compartment. In contrast, the prostaglandin-dependent activation of keratinocytes leading to hyperplastic transformation resembles in many aspects (such as, for instance, the activation of cell-cycle-related genes) the G0-S transition of cells in vitro. The control of proliferative homeostasis in normal epidermis is an unresolved problem. It is not known whether the rate of cell proliferation adapts automatically to the rate of terminal differentiation or whether this adaption is regulated by local factors such as the elusive chalone or other inhibitory signals like transforming growth factor β. The same is true for stimulatory growth factors such as epidermal growth factor and transforming growth factor-α whose function may be that of wound hormones rather than of homeostatic regulators of normal tissue regeneration.

Introduction

The beautiful smooth surface of human skin suggests simplicity, but it covers one of the most complex and most reactive organs, which as an outer shield of the body, is destined to interact and cope with the environment. The skin performs its functions by means of a highly sophisticated communication network between different compartments and cell types (e.g., epidermis, dermis, blood vessels, sweat and sebaceous glands, nerves, immunocompetent cells, invading leukocytes. At the same time, these interactions provide the very conditions for skin tumor development.

Skin Tumorigenesis and Cell Proliferation

The skin offers one of the most suitable and best characterized models for investigating the mechanisms of carcinogenesis, in particular the relationship between cell proliferation and tumor development. It has been known for a long time that under certain
experimental conditions, initiation (the initial mutagenic event of tumorigenesis) may result in a life-long state of latency that is lifted only by a massive induction of cellular proliferation, for instance by wounding, UV irradiation, or application of irritating chemicals. This phenomenon is called tumor promotion. In skin, the induction of cellular hyperproliferation cannot only overcome the latency of cancer but also the latency of other genetically determined diseases such as eczema, psoriasis (Köbner phenomenon), and common warts. Vice versa, tumor promotion by wounding has also been reported for many other tissues, even including plants where crown gall tumorigenesis due to bacterial infection is promoted by wounding. Thus, the induction of cellular proliferation, in particular in the course of a wound response, may provide a general mechanism by which genetically determined but latent hyperproliferative states can be expressed (1).

While healthy tissue returns to normal after some time, in certain skin diseases the hyperproliferative state, once induced, continues endlessly, probably due to self-perpetuation. Thus, the mechanism of termination rather than induction may be defective. It has been said that a tumor resembles a wound that does not heal or that a would resembles a tumor that heals itself (2,3).

**Hyperproliferation and Hyperplasia**

Starting from a naive point of view, one would expect any hyperproliferation to result in hyperplasia, i.e., in an increase of cell number and tissue mass. In an intact tissue, however, the rate of cell gain is generally closely coupled to the rate of cell decay, thus guaranteeing the stability of tissue mass and function in spite of great fluctuations in the rates of cellular proliferation and cell death. The homeostatic control mechanisms are mysterious. As long as these mechanisms are working properly, any increase of cell gain will be precisely matched by a corresponding increase of cell loss and vice versa; in other words, no hyperplasia will develop even in the case of strong hyperproliferation; the hyperproliferative state will remain balanced (Fig. 1).

A demonstration of balanced hyperproliferation may be taken as proof of the existence of a powerful homeostatic control device in a given tissue. About 15 years ago, we were able to show balanced hyperproliferation in epidermis in vivo, for example, after mild mechanical stimulation (pressure, massage) or application of the phorbol ester 4-0 methyl 12-tetradecanoyl-phorbol 13-acetate [4-0-MeTPA (4)].

The significance of such an observation becomes especially evident when comparing the results obtained with apparently closely related stimuli (such as mechanical removal of the horny layer (versus massage) and application of the phorbol ester tumor promoter TPA (versus 4-O-MeTPA). Both stimuli induce an unbalanced hyperproliferation in the epidermis, which results in pronounced hyperplasia, although the hyperproliferative response (mitotic rate) to these compounds is by no means stronger than the response to massage or 4-O-MeTPA application.

This result clearly shows that hyperplasia is not due to an overshooting of cellular proliferation but that there must be fundamental, qualitative differences between the balanced and unbalanced hyperproliferative response. Indeed, hyperplastic development is accompanied by cellular and molecular events that are not seen upon induction of balanced hyperproliferation (4). These include inflammatory reactions, mediator release from keratinocytes (for instance, eicosanoids), formation of autocrine feedback loops, activation of cell-cycle-related genes such as c-fos, c-myc, ornithine decarboxylase, transforming growth factor-β (TGFβ), and others, and down regulation of growth inhibitory pathways, such as those for glucocorticoids, and β-adrenergic agonists.

Thus, it appears as if balanced hyperproliferation is just due to an acceleration of the cell-cycle traverse in the proliferative tissue compartment, whereas hyper-
plasia results from an entry of spare cells into the cycle, somehow resembling the G_{0}→S transition in **vitro**. These observations prompted us (5) to put forward the concept of "hyperplastic transformation." By using this term, we wanted to distinguish the hyperplastic-inflammatory response from ordinary balanced hyperproliferation.

**Hyperplastic Transformation and Tumor Promotion**

Tumor promotion has been shown to depend critically on repeated hyperplastic transformation, resulting in sustained epidermal hyperplasia (6,7). Hence, it is this kind of hyperproliferative response that is closely related to skin carcinogenesis. It must not be overlooked, however, that sustained hyperplasia may only be a necessary but not a sufficient condition of tumor development in initiated skin, since there are agents and manipulations that act as strong hyperplastic transformants but do not induce tumor development. Stripping the horny layer is such a manipulation (8), whereas deep skin wounding provides, upon initiation, a strong stimulus for tumor development (1). Another example is provided by the phorbol ester of retinoic acid (RPA) (9) or the plant poison mezereine (10), which have been called incomplete tumor promoters because they induce papilloma development in initiated mouse skin only upon short-term pretreatment of the tissue with a complete promoter such as TPA or wounding. Such observations gave rise to the concept of two-stage promotion or conversion–promotion, which means that for the induction of tumor development, in addition to hyperplastic transformation, manipulation is required to convert the initiated skin into a promotable state [i.e., render it susceptible to the promoting effect of continuous hyperplastic stimulation (Fig. 2)]. Thus, the well-established relationship between sustained epidermal hyperplasia and skin tumor promotion seems to be valid only for stage 2 of promotion.

In contrast, the nature of stage 1 (conversion) is still not entirely clear. Conversion has been shown to depend on the induction of epidermal DNA synthesis, to correlate with chromosomal damage, to be effective either before or after initiation, and to result in a rather long-lasting alteration recognizable as promotability. Moreover, conversion depends on the local release of lipoygenase-generated arachidonic acid (AA) metabolites, which may act as clastogenic mediators (11,12). Finally, conversion can be evoked not only by complete promoters such as TPA or by wounding but also by an intracutaneous injection of a mixture of TGFα and TGFβ, two established wound hormones. The latter observation is particularly intriguing because these two cytokines exhibit antagonistic effects of keratinocyte proliferation in **vitro** (i.e., activation by TGFα and inhibition by TGFβ). For more details and an in-depth discussion of mechanistic aspects of conversion, see Marks and Fürstenberger (13).

**The Activated Keratinocyte**

Only recently has experimental dermatology given scope for the theory of hyperplastic transformation by putting forward the concept of the activated keratinocyte (14), which is essentially the cellular counterpart of the more functional concept of hyperplastic transformation. The concept of the activated keratinocyte is the result of the rather dramatic change in our view of this cell type. Until about 1980, the epidermis was considered to provide mainly a resistant, horny layer protecting the body from injury and water loss. In recent years, we have learned, however, that the keratinocyte has many more physiological functions. Together with other skin cells (for instance the antigen-presenting Langerhans cells), the keratinocyte is not only the body’s most advanced outpost, but it occupies a central position as a signaling interface between the surrounding environment and the body (15). The keratinocyte is able to translate a wide variety of harmful environmental stimuli into endogenous signals, which then activate the defense mechanisms of the body. These include attraction and activation of leukocytes and lymphocytes, activation of the immune

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**Figure 2.** The stages of experimental carcinogenesis in mouse skin. Under proper experimental conditions, initiation will not result in tumor development unless additional nonmutagenic manipulations (conversion and promotion) are carried out. The initiation-conversion-promotion approach of skin carcinogenesis results primarily in papillomas, some of which develop into carcinomas. This malignant progression can be enhanced by increasing the dose of the initiator or by treating the papillomas with a mutagenic carcinogen. From Marks and Fürstenberger (99).
system, effects on blood flow, coagulation, and the complement system, as well as on epidermal cell proliferation.

These responses are controlled by a complex cocktail of mediators and cytokines released from epidermal cells and other skin compartments (Fig. 3). Unstimulated epidermis produces such factors only at very low doses or has sequestered them in an inactive state. Upon exogenous stimulation, mediator and cytokine production are strongly induced; in other words, the resting keratinocyte becomes an activated one. The visible result of this activation is hyperplastic transformation.

Thus, the main characteristic of the activated keratinocyte is its ability to express and release, upon stimulation, cytokines and eicosanoids and to express the corresponding receptors together with cell adhesion molecules such as I-CAM-1 (16). Many of these cytokines, such as TGFα, TGFβ, interleukin-1 (IL-1), and others, are subject to autoinduction, thus providing a strong autocrine amplification mechanism (1,14,17). In addition, cytokines may induce each other, for example II-1 and TGFα (18), or stimulate the production of other mediators such as the eicosanoids [II-1, TGFα, bradykinine and others (19,20)].

The effects of cytokines released from the activated keratinocyte are manifold. They may be grouped into the following categories: a) mitogenic activation of the keratinocyte, as has been shown for TGFα, bFGF (basic fibroblast growth factor), IL-1, IL-3 and others, or inhibition, as by tumor necrosis factor (TNFα), INFγ (interferon gamma), catecholamines, and chalones (1,21); b) recruitment of the cells of the inflammatory infiltrate and of T-lymphocytes, as accomplished by IL-1, IL-6, IL-8, PDGF (platelet-derived growth factor), leukotriene B₄ (LTB₄), and 12-HETE (hydroxy eicosatetraenoic acid) (14,18,19,22); c) effects on blood vessels and connective tissue such as fibrosis, angiogenesis, and remodeling of the extracellular matrix, as induced by TGFβ, PDGF, bFGF, TGFα, epidermal growth factor (EGF) (23).

The cells of the inflammatory infiltrate as well as various nonepidermal cells residing in skin are also producers of cytokines, many of which may act on the keratinocyte. Thus, upon external stimulation, a complex cytokine network rapidly develops between the different compartments of the injured tissue. This network integrates the functions of the various cell types involved in defense and tissue repair. Both induction of an inflammatory infiltrate and the effects on dermis and blood vessels give rise to the formation of granulation tissue or, in the case of carcinogenesis, to the so-

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**Figure 3.** Hyperplastic transformation of skin as the result of keratinocyte activation. Upon irritation or injury of skin, the keratinocytes produce and secrete a complex cocktail of lipid mediators and cytokines. These factors recruit and activate other cell types involved in repair and defense processes, emitting their own chemical signals (right). Many of these factors act on the keratinocytes, where, together with keratinocyte-derived factors they control cell proliferation along para- and autocrine mechanisms: (+) stimulation; (-) inhibition.
called stroma reaction, which is a critical condition of tumor growth (2,13,24).

One important aspect of the network appears to be the interaction between keratinocytes and T-lymphocytes (16,25). This interaction is made possible by the release of T-cell-attracting signals such as IL-8 from keratinocytes and by the expression of I-CAM-1 on keratinocytes and of the corresponding integrin LFA-1 on T-cells.

The interaction is thought to lead to intense cytokine cross-talk between these two cell types. Moreover, it brings T-cells into the vicinity of the antigen-presenting Langerhans cells. As far as chronic hyperproliferation is concerned, it has been suggested that defects in the keratinocyte-T-cell interaction may be causally related to hyperproliferative diseases such as psoriasis and other dermatoses (25) and even cancer. Although cytotoxic T-cells have been shown to be capable of lysing keratinocytes via LFA-1-I-CAM-1 recognition, basal cell carcinoma cells do not express I-CAM-1, thus perhaps escaping immunosurveillance (25).

The Hierarchy of the Epidermal Cytokine Network

An important question is whether some sort of hierarchy exists in the cutaneous cytokine network. As mentioned before, most cytokines are not found in the resting keratinocyte but are induced only upon injury. Such induction processes may take hours or days, so that the corresponding factors cannot be considered as triggering signals.

There are, however, a few exceptions to this rule, and they may be of great importance. They include bFGF, TGFβ, IL-1α, and the eicosanoids, which are all found in unstimulated epidermis but are probably in an inactive form, either as precursors as TGFβ trapped with the extracellular matrix as bFGF, sequestered inside the cell as IL-1 or the eicosanoids (in the form of a protein precursor or as phospholipid-bound arachidonic acid). In each case there is evidence that these inactive mediators are activated and released immediately upon wounding or irritation.

TGFβ has been immunologically demonstrated in the suprabasal cell layers of normal human (26) and mouse epidermis (27). In an elegant study, Kane et al. (26) recently provided immunological evidence that skin expresses an inactive TGFβ-precursor, which is proteolytically activated and released immediately upon injury. Later on, this is followed by de novo synthesis of TGFβ-mRNA. In skin, TGFβ has three major effects (28,29): it inhibits keratinocyte proliferation, it remodels the extracellular matrix, resulting in the induction of keratinocyte migration, and it attracts white blood cells and induces angiogenesis. Thus, TGFβ may play an important role in the wound response (30), in particular in the covering of the wound by migration of epithelial cells and in the stroma reaction by formation of granulation tissue. TGFβ-induced keratinocyte migration may result in an impoverishment of epithelial cells in the vicinity of the wound, resulting in compensatory hyperproliferation, probably enhanced by additional wound hormones such as TGFα, which may overcome the antiproliferative activity of TGFβ at these sites.

Like TGFβ, IL-1 is also a multifunctional cytokine, although with a different spectrum of functions (31). IL-1α is trapped inside the keratinocyte in unusually large amounts (14). Because it does not possess anything like a signal peptide sequence, there is no way of ascertaining as yet how it can be released except for cell destruction. This is the central point in the concept of keratinocyte activation where IL-1α is actually proposed to play the key role (14).

Our group has put forward the idea of eicosanoids playing a central role in keratinocyte activation (19,20). This concept is based on the observation that the formation of prostaglandin E2 (PGE2) transiently occurring in mouse epidermis immediately after stimulation by a hyperplastic transformant (irritant, wounding, etc.) is critical for the development of epidermal hyperplasia in vivo, whereas the accompanying inflammatory reaction is controlled by lipoygenase-generated arachidonic acid metabolites.

Indeed, 12-HETE and LTβ have both been shown to have strong leukotactic activity and to induce hyperplastic transformation of skin when injected intracutanously (19,20). The most abundant arachidonic acid metabolite found in hyperplastically transformed mouse skin (at least upon treatment with the phorbol ester TPA) is 8-HETE (19,20). The corresponding enzyme 8-lipoygenase is almost absent in resting epidermis but strongly induced upon treatment with the tumor promoter. The physiological role of 8-HETE and related metabolites is unknown. In the course of skin tumor development, 8-lipoygenase may provide clastogenic arachidonic acid metabolites, inducing chromosomal damage (12), which is thought to be involved in the conversion stage (see above).

The induction of the eicosanoid cascade in skin is a general response to all kinds of irritants, irradiation, and mechanical wounding. Eicosanoid formation in keratinocytes has also been shown to be induced by wound factors such as EGF, TGFα, IL-1, bradykinin, histamine, thrombin, bFGF, and probably many others. Phospholipase A2, the key enzyme of eicosanoid production in keratinocytes, has been found to be activated along multiple pathways of intracellular signal transduction (Fig. 4).

Because IL-1 is an inducer of the eicosanoid cascade in keratinocytes (32), our concept may well fit the idea that IL-1 provides one of the first signals in keratinocyte activation (14). On the other hand, the release of eicosanoids along IL-1-independent routes may explain why hyperplastic transformation is induced by agents that probably do not destroy keratinocytes, which is thought to be prerequisite for IL-1 liberation.
Mechanisms of Keratinocyte Activation

The extremely complex interactions within the cutaneous cytokine network indicate that there are various pathways rather than one master key for keratinocyte activation. Thus, the destruction of epidermal cells may result in the release of preformed mediators such as IL-1, which then trigger the response, whereas primary wound factors such as thrombin, PAF (platelet-activating factor), adenosine nucleotides, kinins, and complement factors may be released from nonepidermal sources and interact with keratinocytes along the physiological pathways of intracellular signal transduction (Fig. 3). Finally, a direct interaction of exogenous stimuli with the cellular elements of signal transduction (for instance, protein kinase C in the case of the phorbol ester tumor promoters) may be envisaged. All these interactions may lead to keratinocyte activation and, as a secondary consequence, to the destruction of keratinocytes, for instance through the release of active oxygen radicals from invading leukocytes. Considering the close relationship between hyperplastic transformation and tumor development, it may be postulated that tumor promotion can be induced either by nonspecific damage such as mechanical wounding or by more specific interactions with intercellular signaling and intracellular signal transduction. Indeed, destructive manipulations such as wounding (1) or application of cytotoxic agents (33,34) exert a tumor-promoting effect just like protein kinase C activators (phorbol esters) or inhibitors of protein phosphatases [okadaic acid (35)]. Moreover, cytokine injection into initiated mouse skin exhibits a substantial tumor-promoting effect, as we have recently shown for TGFα plus TGFβ (35). In any case, the common denominator seems to be that keratinocyte activation results in hyperplastic transformation, and hence, there seems to be a direct relationship in skin between tumor development and the wound response.

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