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# Epidermal kinetic alterations required to generate the psoriatic phenotype: a reappraisal

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## Abstract

*Objectives*: Although there have been major advances in understanding immunopathogenesis of psoriasis, the basic processes causing psoriatic morphology remain to be identified.

*Materials and methods*: Our group has designed a systematic review of studies (1962–2009) on keratinocyte kinetics in psoriasis. We obtained data from MEDLINE, PubMed, Current Contents, reference lists and specialist textbooks. A general equation for evolution of the differentiated epidermis has been analysed. Necessary conditions for observed qualitative change in homeostasis between normal skin and established psoriatic lesions were determined.

*Results and discussion*: Increase in the number of cell divisions (or imbalance in symmetric division rates of committed progenitor cells) and/or decrease in physiological apoptosis in the germinative compartment, together with feedback loops that limit thickening of the skin, are required to generate psoriatic morphology, that is, to increase the absolute size but decrease relative size of the differentiated cell compartment with respect to the germinative compartment.

## Introduction

Psoriasis is a relapsing skin disease resulting from key genetic underpinnings as well as from complex, aberrant relationships between skin and the immune system (1–6). It is characterized by increased cell turnover in the epidermis and aberrant differentiation of keratinocytes, with elongation of rete ridges and parakeratosis, resulting in lesional areas of thick and scaly skin. Besides these morphological alterations, normal epidermis and established psoriatic epidermis have basically a similar pattern: (i) they are composed of two interconnected compartments, the germinative compartment and the differentiated compartment; (ii) they are in a steady state: number of cells produced by division is identical to number of cells lost by desquamation (1,7,8). Difference between the two tissues is quantitative: psoriatic epidermis contains three to four times more cells than the normal epidermis. Proportionally, increase in cell population (more than doubling) is more pronounced in the germinative compartment than in the differentiated compartment so that the psoriatic differentiated compartment is characterized by an increase in its absolute size and decrease in its relative size (7,9). Although there have been recent major advances in understanding the complex interplay between keratinocytes and immunocytes in development of psoriasis (1–4), the basic cell kinetic defects needed to generate psoriatic morphology remain largely unknown.

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## Materials and methods

References for this article have been identified from the authors' personal knowledge of psoriasis, reference lists in previously published studies, and detailed searching of PubMed and MEDLINE with search terms, 'differentiated', 'epidermis', 'germinative', 'keratinocytes', 'kinetic', 'mathematical', 'psoriasis', 'stem cell' and 'transit-amplifying'. Only articles published in English, German and French have been included. On the mathematical side, evolution of the differentiated compartment is described by a continuous differential equation expressing balance between differentiation of proliferating cells ($P$) and elimination (essentially by desquamation) of differentiated cells ($D$). Normal skin and established psoriatic lesions are considered to be in steady states of cell dynamics, with cell production and cell loss balancing each other (Fig. 1). Necessary conditions for absolute

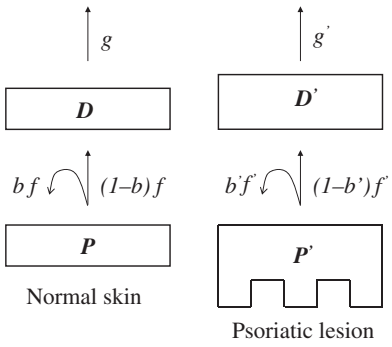


**Figure 1. The epidermis consists of a proliferative compartment (*P*) and a differentiated compartment (*D*)**. Proliferative cells undergo division at rate *f*. A fraction of the daughter cells is proliferative and the rest is differentiated. Their contribution to variation of the proliferative and differentiated compartments is b and 1 − b respectively. Differentiated cells are lost at the surface by desquamation at a rate *g*. In psoriatic epidermis, there is increase in size of the proliferative compartment with elongation of rete ridges and increase in absolute size and decrease in relative size of the differentiated compartment. Normal skin and established psoriatic lesions are considered to be steady states of cell dynamics, with cell production and cell loss balancing each other.

expansion of the differentiated compartment but decrease in its relative size with respect to the germinative compartment, are derived and physiologically interpreted.

## Results and discussion

There are relatively few published mathematical models specifically dedicated to kinetics of keratinocytes in psoriatic epidermis. From a kinetic point of view, extension of epidermis can be obtained in two non-exclusive ways: (i) increase in cell production, which can be realized either *via* a decrease in cell cycle time or by increase in the growth fraction (number of cells actively proliferating); (ii) decrease in cell loss by desquamation or cell destruction (necrosis or apoptosis). Despite dramatically reduced turnover times in the germinative as oppose to the differentiated compartment, epidermis in an installed psoriatic lesion retains constant size (steady state) with cell production and cell loss remaining equal.

## Alteration 1

### *Shortened cell cycle time in psoriasis*

This hypothesis was proposed many years ago following results of cell cycle measurement in normal human epidermis and in psoriatic lesions by Weinstein *et al.* (10). The main problem in their measurement is that cell cycle time in human epidermis is quite long and the technique of labelled mitosis curve that they used is inapplicable in good conditions: the curve of labelled mitosis never reached plateau level of 100% and measurement of true S phase was impossible. A second curve of labelled mitosis necessary to measure cell cycle time was not observed in normal epidermis, probably because of large variations in individual cell cycle times of the proliferating cells. More recent data obtained from calculating number of S phase cells in psoriasis by *in situ* hybridization using a histone probe, and number of cycling epidermal cells by immunohistochemistry, using the MIB-1 antibody, show that cell cycle time is not altered in psoriasis (11). Moreover, mathematical models of cell renewal in psoriatic epidermis on the basis of epidermal compartment sizes demonstrated that shortened cell cycle time cannot lead to extension of the proliferative compartment, which is one of the main features of a psoriatic lesion (7). Additional perturbation during installation of a psoriatic lesion is necessary (see below). As we have underlined in the introduction, a psoriatic lesion is in steady state and maintenance of this steady state is a prerequisite to keep psoriatic morphology.

### *Increased growth fraction*

This hypothesis in the past was supported by Gelfant *et al.* (12) and van Erp *et al.* (13). It is based on the assumption that a fraction of the germinative cell population is in a resting phase ($G_0$). These non-proliferating cells can be injected into the cell cycle following appropriate triggering (that is, increase in cell loss by differentiation). Existence of a $G_0$ phase in human epidermis is the subject of controversy. Most studies on the subject were made by analysis of cell flow parameters on dissociated cell populations. The problem is to know whether true $G_0$ cells exist in human epidermis and in which part of the germinative cell population they are situated, stem cell compartment or transit amplifying compartment. Indeed, according to the current model of adult epidermal homeostasis, stem cells have an unlimited capacity for cell renewal and continuously generate a short-lived population of transit amplifying cells (TAC) at a slow rate (with long cell cycle time). TACs differentiate into post-mitotic keratinocytes after several rounds of cell division (14), however, existence of TACs has recently been contested. Lineage tracing experiments in mouse tail epidermis provided evidence for a simple model of homeostasis involving only one type of progenitor cell, referred to as the committed progenitor (CP) cell (15). These cells are found to undergo both symmetric and asymmetric division, at rates that ensure epidermal homeostasis. In homeostatic epidermis, the model depends on just two parameters, average cell division rate and proportion of divisions that result in asymmetric fate (16). In this model, two non-exclusive hypotheses could explain extension of the

germinative compartment. One possibility is that there is a drastic change in behaviour of the CP population requiring imbalance in symmetric division rates to favour production of cycling CP cells. An alternative explanation is that a population of quiescent stem cells is mobilized to generate additional CP cells. The role of intrinsic abnormalities of the germinative cell population in psoriasis has been recently supported by findings of altered expression of various molecules involved in control of epidermal keratinocyte proliferation, such as Jun B, Stat3, Wnt5a or LRIG (17–19) in lesional psoriatic skin. Demonstration of altered levels of several markers of differentiation and proliferation in psoriatic keratinocytes points to inherent malformation of these cell populations in psoriasis (14). This possibility was recently supported by a computational model of tissue homeostasis showing that prolonging fractional period during which keratinocytes proliferate results in the main pathological characteristics of psoriasis (20). Either increased recruitment of quiescent (resting in $G_0$) keratinocytes that would proliferate rapidly for a limited number of cell divisions (short cell cycle time) or increase in the number of cell divisions, that could lead to a larger germinative compartment, although both hypotheses are difficult to distinguish on experimental grounds.

## Alteration 2

Previous studies have reported that various anti-apoptotic proteins (such as Bcl-$X_L$) are overexpressed in different layers of psoriatic epidermis, and keratinocytes obtained from psoriatic lesions are more resistant to induction of apoptosis than keratinocytes derived from normal epidermis (21). Accordingly, a significant decrease in number of apoptotic cells has been detected in the germinative layer of an established lesion of psoriasis (22). Apoptosis in the normal epidermis is observed in 0.12% of germinative cells. In an established lesion, this proportion decreases to 0.035% of the germinative compartment whose size is larger (13 000 cells/$mm^2$ in normal epidermis and 40 000 cells/$mm^2$ in an established lesion of psoriasis). Decreased apoptosis of cells of the germinative compartment is a plausible explanation for its extension. This is supported by the observation that effective anti-psoriatic therapies such as methotrexate, PUVAtherapy and anti-TNFα strategies could act partly, in addition to their anti-inflammatory properties, through induction of keratinocyte apoptosis (9,23,24). The molecular circuitry of inflammation in psoriasis also favours decreased cell death rather than apoptosis. Many keratinocyte- and immune-derived cytokines involved in psoriasis, such as IL-15, TGF-α, can clearly serve as inhibitors of keratinocyte apoptosis (24). So far, the impact of apoptosis on keratinocyte kinetics cannot be predicted from available experimental data (25).

However, some regulatory mechanisms are needed to generate psoriatic morphology: (i) Psoriatic skin is characterized by decrease in relative size of the differentiated compartment. This decreased relative size is determined by residence time in the differentiated compartment and cell production rate in the germinative compartment [assuming that differentiation and proliferation are two alternative outcomes of a branching process (26)]. (ii) Increase in size of the germinative compartment is limited (psoriasis is not a neoplastic tumour). Impact of increased cell production in the germinative compartment is counteracted notably by increased cell migration from the germinative compartment to the differentiated compartment (decreased transit time of proliferating cells in the germinative compartment).

Those features of psoriatic skin can be qualitatively explained by the effect of potential regulatory feedback loops that impede skin from thickening indefinitely. For that purpose, it is necessary to consider processes that contribute to growth and decay of the differentiated compartment. Mathematically, the equation of evolution of the differentiated compartment is balance between a source term corresponding to the differentiation of proliferating cells ($P$) and a sink term corresponding to elimination (essentially by desquamation) of differentiated cells ($D$)

$$\frac{\mathrm{d}D}{\mathrm{d}t} = m(P,D)P - g(D)D.$$

Source and sink terms are written in such a way that differentiation and elimination explicitly vanish when number of proliferating and differentiated cells, respectively, drop to zero. Influence of interactions between differentiated keratinocytes on desquamation rate is taken into account through the function $g$. For differentiation rate, interactions potentially involve both proliferating and differentiated cells; their effect is expressed by the function $m$. We assume that differentiation results from cell division. This function $m$ is then the product of two factors

$$m(P,D) = [1 - b(P,D)]f(P,D).$$

The first factor depends on the balance between proportions of symmetric divisions producing proliferating ($r_P$) and differentiated ($r_D$) cells

$$b(P,D) = r_P(P,D) - r_D(P,D).$$

The proportion of asymmetric divisions is equal to $1 - r_P - r_D$. The second factor, $f$, expresses effect of cell interactions on mobilization of quiescent cells and/or on average delay between two successive divisions.

Accordingly, equation of evolution of the germinative compartment is

$$\frac{\mathrm{d}P}{\mathrm{d}t} = b(P,D)f(P,D)P.$$

We assume that normal and psoriatic skins are steady states of the cell dynamics. Hence they satisfy the equations $b(P,D) = 0$ and

$$D = \frac{f(P,D)}{g(D)}P.$$

From the latter steady state equation, we can derive the condition of simultaneous increase of the germinative and differentiated compartments on one hand and condition of relative decrease of the differentiated compartment (with respect to the germinative one) on the other

$$\frac{\mathrm{d}D}{\mathrm{d}P} = \frac{\frac{1}{g}\left(P\frac{\partial f}{\partial P} + f\right)}{1 - \frac{P}{g}\frac{\partial f}{\partial D} + \frac{fP}{g^2}\frac{\mathrm{d}g}{\mathrm{d}D}} = \frac{\frac{1}{g}\frac{\partial (fP)}{\partial P}}{1 - \frac{P}{g}\frac{\partial f}{\partial D} + \frac{fP}{g^2}\frac{\mathrm{d}g}{\mathrm{d}D}} > 0,$$

$$\frac{\mathrm{d}\left(\frac{D}{P}\right)}{\mathrm{d}P} = \frac{1}{g}\left(\frac{\partial f}{\partial P} + \frac{\partial f}{\partial D}\frac{\mathrm{d}D}{\mathrm{d}P}\right) - \frac{f}{g^2}\frac{\mathrm{d}g}{\mathrm{d}D}\frac{\mathrm{d}D}{\mathrm{d}P} < 0.$$

We first note that the inequality

$$\frac{\partial (fP)}{\partial P} > 0$$

simply amounts to require that increase in size of the germinative compartment cannot produce decrease in size of the differentiated compartment. Next, variables are positive defined, $P > 0$ and $D > 0$, as well as interaction functions, $f > 0$ and $g > 0$. Hence the coefficient of $\partial f / \partial D$ is negative in the first inequality and positive in the second, if the first is fulfilled. The coefficient of $\mathrm{d}g / \mathrm{d}D$ is positive in the first inequality and negative in the second as a consequence of the first. The coefficient of $\partial f / \partial P$ is positive in the second inequality. As a result, the first two inequalities reported above can be satisfied only if at least one of the following conditions is fulfilled:

- The relative rate of differentiation is a decreasing function of the size of the germinative compartment

$$\frac{\partial f}{\partial P} < 0.$$

Assuming that proliferation and differentiation are two alternative outcomes of cell division (26), this is equivalent to saturation of relative growth rate of the germinative compartment as a function of its size. This saturation could reflect, for example, depletion of nutriments away from the dermis.

- The relative rate of differentiation is a decreasing function of size of the differentiated compartment

$$\frac{\partial f}{\partial D} < 0.$$

According to the same assumption, proliferation bursts following removal of suprabasal layers by tape stripping or plucking (27,28), or alternatively proliferation inhibition after suppression of cell loss at the surface by skin occlusion (29,30), are strong pieces of evidences of such negative feedback of size of the differentiated compartment on differentiation.

- Increase of the differentiated compartment produces acceleration of elimination rate (desquamation and/or apoptosis)

$$\frac{\mathrm{d}g}{\mathrm{d}D} > 0.$$

Accordingly, several authors have found that, in contrast to the germinative compartment, number of apoptotic cells appears to be increased in the differentiated compartment of established psoriatic lesions (22).

In conclusion, extension of the germinative compartment can be obtained either by increased number of cell divisions, by imbalance in symmetric division rates that favour production of cycling CP cells, by mobilization of quiescent keratinocytes or by decrease in physiological apoptosis in the germinative compartment. Typical morphology of the psoriatic lesion (increase in absolute size but decrease in relative size of the differentiated compartment) can be explained by three distinct mechanisms potentially involved in epidermis homeostasis. They all correspond to feedback that prevents increasing epidermal hyperplasia.

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