Journal of Theoretical Biology 397 (2016) 52–60

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Mathematical model for calcium-assisted epidermal homeostasis

Yasuaki Kobayashi [a,b,*], Yusuke Sawabu [c], Hiroyuki Kitahata [d], Mitsuhiro Denda [e,b], Masaharu Nagayama [a,b,*]

[a] Research Institute for Electronic Science, Hokkaido University, N12W7, Kita-ku, Sapporo 060-0812, Japan
[b] CREST, Japan Science and Technology Agency, Gobancho, Chiyoda-ku, Tokyo 102-0076, Japan
[c] Department of Mathematics, Graduate School of Science, Hokkaido University, N12W7, Kita-ku, Sapporo 060-0812, Japan
[d] Department of Physics, Graduate School of Science, Chiba University, Yayoi-cho 1-33, Chiba 263-8522, Japan
[e] Shiseido Research Center, Shiseido Co., Ltd., 2-12-1 Fukuura, Kanazawa-ku, Yokohama 236-8643, Japan

HIGHLIGHTS

- A stabilization mechanism of the epidermal structure is proposed.
- The mechanism relies on calcium-induced enhancement of differentiation.
- Key features of epidermal barrier recovery are numerically reproduced.

ARTICLE INFO

Article history:
Received 5 November 2015
Received in revised form
23 February 2016
Accepted 24 February 2016
Available online 4 March 2016

Keywords:
Reaction-diffusion system
Dermatology
Dynamical system

ABSTRACT

Using a mathematical model of the epidermis, we propose a mechanism of epidermal homeostasis mediated by calcium dynamics. We show that calcium dynamics beneath the stratum corneum can reduce spatio-temporal fluctuations of the layered structure of the epidermis. We also demonstrate that our model can reproduce experimental results that the recovery from a barrier disruption is faster when the disrupted site is exposed to air. In particular, simulation results indicate that the recovery speed depends on the size of barrier disruption.

1. Introduction

It is widely recognized that skin is not just a boundary demarcating the body from the environment, but serves as a barrier, particularly against water loss (Elias and Feingold, 2006). Responsible for this barrier function is the *stratum corneum* (SC), the outermost structure of the epidermis, which consists of cornified cells and inter-cellular lipids. In healthy normal skin, its barrier function is fully expressed by ordered arrangement of the cornified cells (Elias and Feingold, 2006), and, therefore, structural disruption caused by skin diseases such as atopic dermatitis and psoriasis can lead to deterioration of the barrier function (Harding, 2004).

Epidermal cells produced in the basal layer start a differentiation process during migration to the upper layers, undergo cornification to become part of the SC, and finally get removed from the surface (desquamation). In this continuous supply and removal of cells, an ordered layer structure of the SC emerges in a self-organized manner as a dissipative structure, in the sense that it can be recovered in a few days when its structure is mechanically disturbed (Elias and Feingold, 2006).

Mathematical modeling is quite often useful to get insights into the underlying mechanism of such self-organized systems, and epidermal models have been proposed so far: Nakaoka and Aihara (2013) proposed a lattice model of stochastic cell dynamics. Also, Schaller and Meyer-Hermann (2007) proposed a particle dynamics model to account for tumor growth. In both models, homeostasis is discussed in terms of the population of cells in individual layers of the epidermis. In order to understand epidermal homeostasis in relation to its barrier function, however, we also need to focus on spatio-temporal structures of the SC. Several particle-based models have been proposed for epidermal structures (Stekel et al.,

* Corresponding authors at: Research Institute for Electronic Science, Hokkaido University, N12W7, Kita-ku, Sapporo 060-0812, Japan.
E-mail addresses: yasuaki.kobayashi@es.hokudai.ac.jp (Y. Kobayashi), nagayama@es.hokudai.ac.jp (M. Nagayama).

http://dx.doi.org/10.1016/j.jtbi.2016.02.032

1995; Rashbass et al., 1996; Maheswaran et al., 2007), although they do not succeed in forming a flat structure of the SC.

Recent studies have revealed that calcium plays important roles on epidermal homeostasis. For instance, genetic skin diseases can be induced by the mutation of the calcium pump and gap junctions (Sakuntabhai et al., 1999; Hu et al., 2000; Mese et al., 2007), and abnormal calcium distribution is observed in diseased skin (Forslind et al., 1999). More precisely, it has been reported that the calcium distribution beneath the SC is closely related to the status of the skin: in normal skin, a localized layer of calcium was observed in the cells just below the SC; and when the SC was impaired, this localization of calcium was lost (Mauro et al., 1998; Denda et al., 2000). Also, calcium wave propagation was found in cultured keratinocytes (grate majority of epidermal cells) when exposed to air (Denda and Denda, 2007), which implies the relationship between calcium signaling and the damage of the skin. These findings seem to make a strong case that calcium localization has an important role in the maintenance and the recovery of the SC.

Although the calcium localization in the epidermis has been mathematically modeled by Cornelissen et al. (2007) and then by Adams et al. (2012), how it affects the structure of the epidermis is still unclear. The effect of calcium ions on proliferation and differentiation has been introduced into a particle-based model (Walker et al., 2006; Sun et al., 2007) to investigate colony formation of keratinocytes, but its effect on the structure of the epidermis has not been addressed. Also, Grabe and Neuber (2005) has simulated the epidermal structure using a particle-based model that takes into account calcium ions, which reproduced a flat epidermal surface. However, the role of calcium ions in the mathematical model is unclear, and hence their model gives little insight into the mechanism for the creation of a flat SC.

In this paper, we propose a particle-based mathematical model of the epidermis where calcium dynamics is incorporated, and demonstrate that epidermal homeostasis can be maintained with the aid of calcium dynamics. In particular, we will show that calcium dynamics can suppress spatio-temporal fluctuation of the boundary of the stratum corneum. Using this model, we will also perform numerical experiments on barrier disruption to investigate a possible role of calcium dynamics on the recovery process.

Epidermal homeostasis is strongly disturbed by various kinds of skin diseases, and the involvement of calcium in such skin disorders is reported (Proksch et al., 2008). Since our calcium model is based on actual responses of the keratinocytes to mechanical stimuli under various conditions (Kobayashi et al., 2014), effects of these factors can in principle be investigated with our model. It is thus expected that our model might be used as a tool for the numerical investigation of skin diseases.

2. The model

We formulate our model of epidermis by taking into account the following properties: reproduction in the basal layer, migration towards the outer layers, differentiation, and calcium dynamics.

Cell i is represented as a sphere with the position $\boldsymbol{x}_i(t)=(x_i(t), y_i(t), z_i(t))$ and the radius $r_i(t)$, defined in a three-dimensional space $\Omega=[0,L_x]\times[0,L_y]\times[0,L_z]$, where the plane $z=0$ defines the boundary of the dermis. On top of the dermis we have the basal layer, defined as $0<z<z^*$, which contains proliferating cells, and on top of it is the suprabasal layer, defined as $z\geq z^*$, where cells are in the process of differentiation or cornified. Proliferation and differentiation are characterized by the phase $\phi_i(t)$ and the state variable $S_i(t)$, respectively. In particular, cornification occurs when the state variable reaches a certain value. Both proliferation and differentiation are affected by the intra-cellular calcium, denoted by $c_i(t)$. Dynamics of each variable is detailed below.

2.1. Cell reproduction in the basal layer

In the basal layer, we assume two types of proliferative cells: stem cells can reproduce infinite number of times, while transit amplifying (TA) cells can reproduce only finite times. A stem cell reproduces one TA cell, and a TA cell reproduces itself.

The phase of the cell division cycle $\phi_i(t)$ evolves in time as

$$\dot{\phi}_i=\omega+\alpha(c_i-c_0)_+, \tag{1}$$

where $(x)_+$ equals x if x is positive and otherwise 0; ω, α, and c_0 are constants; c_0 is the value of calcium at the rest state. It is assumed that the cell cycle accelerates when intra-cellular calcium increases, reflecting an experimental result (Rizk-Rabin and Pavlovitch, 1993; Vandenberghe et al., 2013). When $\phi_i=2\pi$, the cell i enters the cell division period, where the division occurs in a stochastic way, following the Poisson process with the rate γ_{div}. Therefore, in the absence of calcium excitation ($\dot{\phi}_i=\omega$), the average cell division time is given by $T_{\mathrm{div}}=2\pi/\omega+1/\gamma_{\mathrm{div}}$.

When cell i at $\boldsymbol{x}_i$ with the radius r_i exhibits a cell division, two new cells j, k are provided with the radii $r_{j,k}=r_i/2$ and the positions:

$$\boldsymbol{x}_{j,k}=\boldsymbol{x}_i\pm\boldsymbol{t}\frac{r_i}{2}, \tag{2}$$

where the positive and the negative signs correspond to j and k, respectively; the unit vector $\boldsymbol{t}$ is tangent to the dermal surface $z=0$, and its orientation is randomly assigned. After the cell division, the radius grows according to the logistic equation:

$$\dot{r}_j=Cr_j(r_{\max}-r_j). \tag{3}$$

The parameters $\omega, \gamma_{\mathrm{div}}$, and C are chosen in such a way that the cell maximally grows before a next cell division cycle comes. Hence a newly born cell is eventually assigned the initial radius $r_j=r_{\max}/2$. Cells created by a stem cell are assigned the maximum number of cell divisions; cells created by a TA cell with $m>0$ remaining cell divisions are assigned $m-1$ remaining cell divisions; TA cells with $m=0$ do not commit a cell division.

We assume that, while the stem cells are tightly bound to the dermis, TA cells are comparatively loosely bound, so that the TA cells can migrate to the suprabasal layer. Once a TA cell leaves the basal layer, it is considered to start a differentiation process, and the binding force to the dermis is set to zero.

2.2. Differentiation in the suprabasal layer

The differentiation process is determined by the variable $S_i(t)$: $S_i=0$ for cells in the basal layer, and $S_i>0$ for cells in the suprabasal layer. Differentiation process starts when cells leave the basal layer and enter the suprabasal layer, where S_i obeys the following calcium-dependent dynamics:

$$\dot{S}_i=\omega'+\alpha'(c_i-c_0)_+, \tag{4}$$

where ω' and α' are constants: the constant ω' reflects the advance of differentiation in the presence of extra-cellular calcium (Elias et al., 2002). Differentiation is also affected by intra-cellular calcium (Fuchs, 1990; Hennings et al., 1980; Boyce and Ham, 1983). Cells undergo cornification at $S_i=S_{\mathrm{SC}}$, and desquamation at $S_i=S_d$. Thus the cells with $S_{\mathrm{SC}}\leq S_i\leq S_d$ form the SC.

2.3. Kinetic interaction among cells

Cells produced in the basal layer migrate outward by the excluded volume effect: we assume a short-range repulsive