Skin Barrier Function as a Self-Organizing System

Mitsuhiro DENDA

Shiseido Research Center, 2-12-1 Fukuura, Kanazawa-ku, Yokohama, Kanagawa 236-8643, Japan
E-mail: mitsuhiro.denda@to.shiseido.co.jp

Abstract. Skin Barrier function which protects internal organs from the environment resides in the uppermost thin heterogeneous layer, called stratum corneum. The stratum corneum is composed of dead protein-rich cells and intercellular lipid domains. This two-compartment structure is renewed continuously and when the barrier function is damaged, it is repaired immediately. Under low humidity, the stratum corneum becomes thick, the lipid content in the stratum corneum increases and water impermeability is enhanced. The heterogeneous field in the epidermis induced by ions, such as calcium and potassium regulates the self-referential, self-organizing system to protect the living organism.

1. Introduction: Heterogeneous Structure of Skin Barrier

The most important role of the skin for terrestrial animals is to protect the water-rich internal organs from the dry environment. This cutaneous barrier function resides in the upper most thin layer (approximately 10–20 μm in humans) called stratum corneum. The water impermeability of this layer is 1000 times-higher than that of other membranes of living organisms (POTTS and FRANCOEUR, 1991). This is the same level as that of a plastic membrane with the same thickness (TAGAMI, 1998).

The stratum corneum is composed of two components, i.e., protein-rich nonviable cells and intercellular lipid domains (ELIAS *et al.*, 1993). The lipid molecules in the intercellular domain form a bilayer structure (Fig. 1). The water impermeability is due to the conformation of the lipid molecules and also the order of the dead cells (DENDA *et al.*, 1994). Because of this specific "brick and mortar" structure, the stratum corneum shows high water impermeability.

The uppermost layer of the skin, called epidermis, is mainly constructed of keratinocytes (Fig. 2). The epidermis is in a constant state of self-replacement. At the bottom layer, keratinocyte stem cells divide into daughter cells, which are displaced outward, and which differentiate through successive overlying layers to enter the stratum corneum (Fig. 2B). Then, the keratinocytes die, (apoptosis) and their cellular organelles and cytoplasm disappear during the final process of differentiation. Intercellular lipids are primarily generated from exocytosis of lipid-containing granules called lamellar bodies, during the terminal differentiation. The secreted lipids spread over the intercellular domains and form
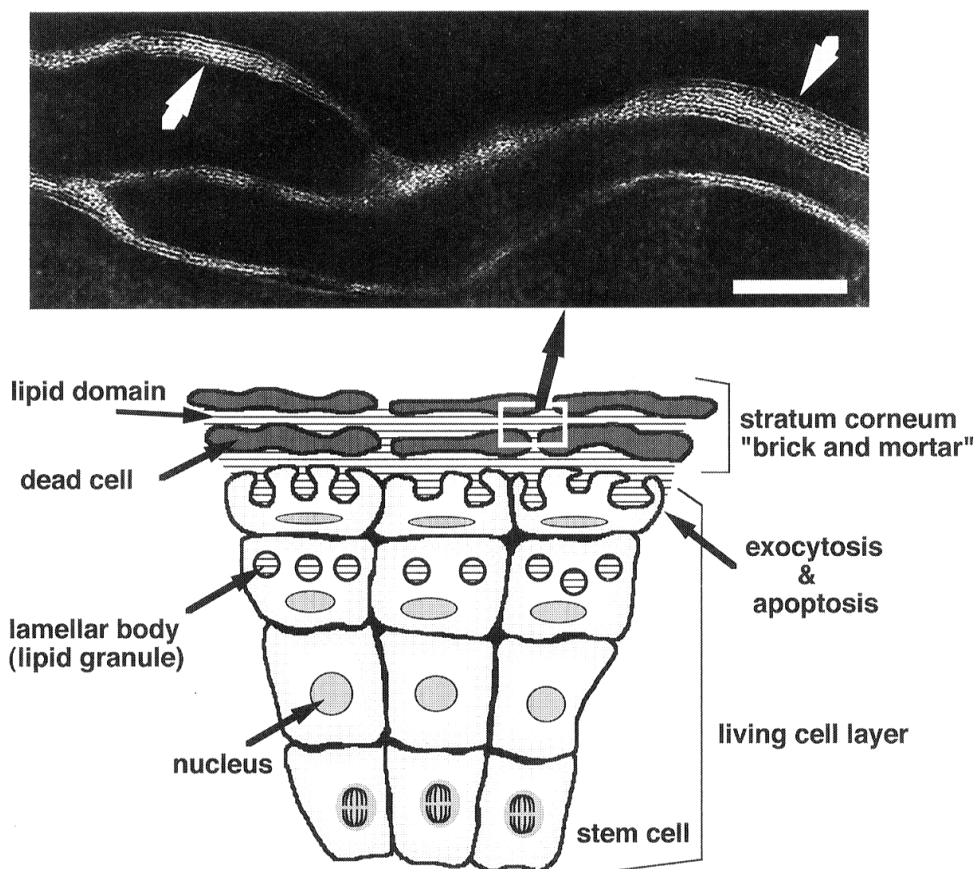
Fig. 1. Electron microscopic observation of the lipid bilayer structure in the intercellular domain of the stratum corneum. White arrows indicate the structure. Bar: 0.2 μm.

a bilayer structure (ELIAS *et al.*, 1993).

In this article, I describe the skin barrier homeostasis as a self-organizing system and also suggest an important role of heterogeneous ionic field in the epidermis on the homeostasis of the barrier function.

2. Homeostasis of Skin Barrier: Self-Referential System

When the stratum corneum barrier function is damaged by stripping with adhesive tape or treatment with an organic solvent or detergent, a series of homeostatic processes in the barrier function is immediately accelerated, and the barrier recovers to its original level (ELIAS *et al.*, 1993). This process includes lipid synthesis, lipid processing and the acceleration of exocitosis of lamellar bodies.

This homeostatic repair process is blocked by occlusion with a water impermeable membrane such as plastic membrane or latex membrane. The occlusion with a water-
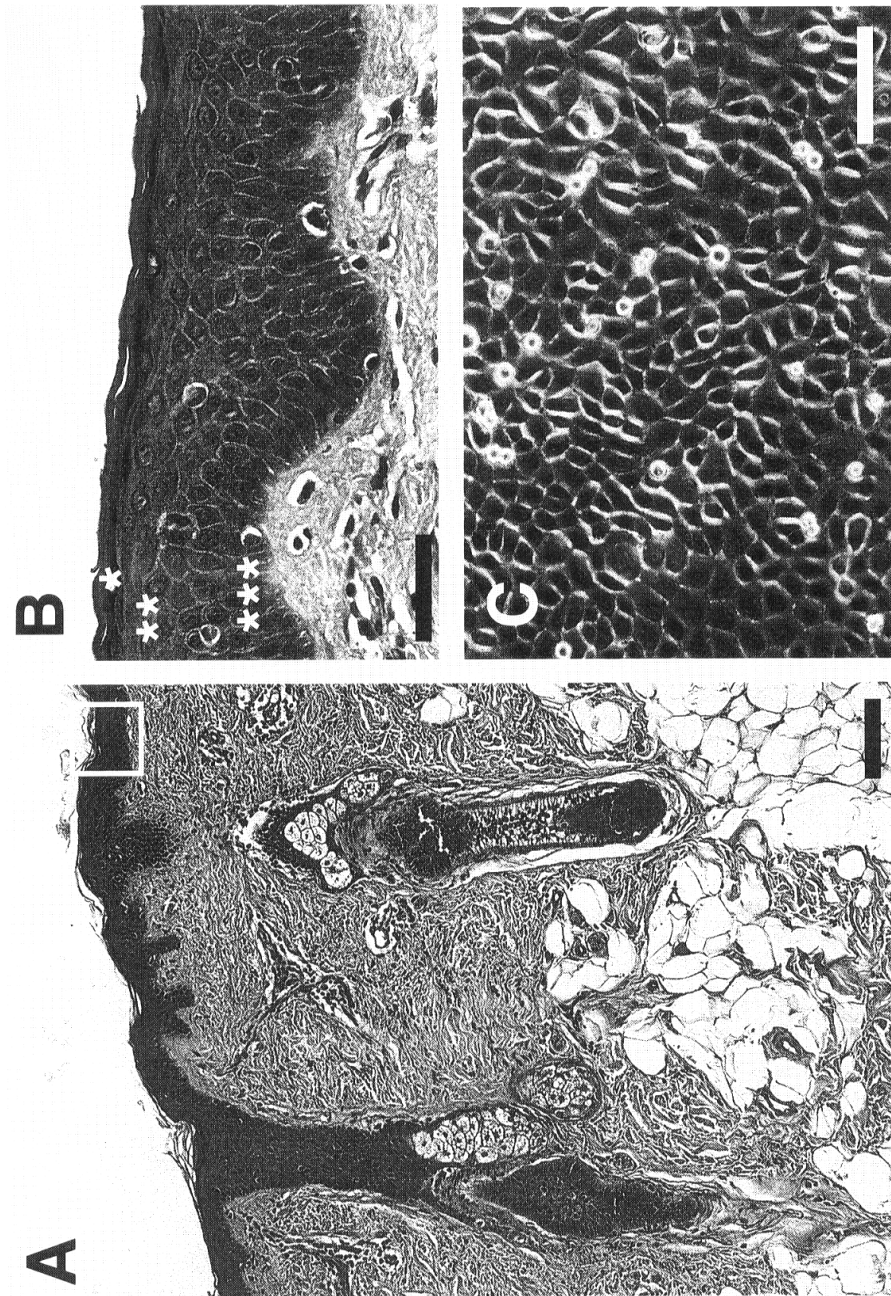
Fig. 2. Heterogeneous structure of the epidermis is constructed of one type of cell, keratinocyte. A: Light microscopic observation of the whole human skin. White box, top right, is the epidermis. Bar: 100 μm. B: Human epidermis at a high magnification. ***: germinating keratinocyte, **: flattened keratinocyte, *: stratum corneum, i.e., dead keratinocyte. Bar: 50 μm. C: Cultured keratinocyte. Bar:20 μm.

permeable membrane such as Gortex does not perturb the repair process (GRUBAUER *et al.*, 1989). Thus, the skin barrier homeostatic function is a self-referential system which is always monitoring its original function, i.e., water impermeability. The skin barrier homeostatic process is regulated by the peripheral function (GRUBAUER *et al.*, 1987).

On the other hand, the skin barrier homeostatic system is under the influence of the central nervous system. Exposure to psychological stress delays the skin barrier repair and sedative drugs can prevent the delay (DENDA *et al.*, 1998a, 2000a). Our recent study demonstrated that odorants which have a sedative effect could improve the barrier homeostasis (DENDA *et al.*, 2000b). Various environmental factors which affect our emotion also influence the peripheral homeostasis. And also the barrier recovery rate shows a circadian rhythm (DENDA *et al.*, 2000c). This suggests that the skin barrier homeostasis is related to the physiological stage of the whole body.

The skin barrier function also has an ability to adapt to the environment. Under a low humidity environment, the barrier function is enhanced (DENDA *et al.*, 1998b). The thickness of the stratum corneum increases in a dry environment. The content of the intercellular lipid in the stratum corneum increases and consequently, the transepidermal water loss decreases, i.e., the water impermeability increases. In the nucleated layer of the epidermis, the number of lipid-containing lamellar bodies increases and the recovery rate after barrier disruption increases (DENDA *et al.*, 1998b). These results suggest that the skin barrier function senses the environmental change and reorganizes its function to adapt the new environment. Another aspect of skin barrier homeostasis as this self-referential, self-organizing system.

3. The Role of Ions in Barrier Homeostasis

The mechanism of the regulation of skin barrier homeostasis described above, is not clear. Studies suggest that ionic signals such as calcium and potassium play an important role in the homeostatic mechanism of the epidermal barrier function (LEE *et al.*, 1992; MENON *et al.*, 1992; DENDA *et al.*, 1999). In normal skin, calcium is localized with high concentration in the epidermal granular layer, i.e., uppermost layer of the epidermis, just below the stratum corneum (Fig. 3). On the contrary, the concentration of potassium is the highest in the spinous layer, i.e., middle of the epidermis, and the lowest in the granular layer (Fig. 3). These results suggest that both calcium and potassium play an important role in the skin barrier homeostasis. Ionized calcium is the most common signal transaction element (CLANPHAM, 1995). Calcium might play various roles in the formation of the stratum corneum barrier. For example, it induces terminal differentiation (WATT, 1989), formation of the cornified envelope which is important as the basement of the barrier (NEMES *et al.*, 1999b), and also epidermal lipid synthesis (WATANABE *et al.*, 1998). MENON *et al.* (1994) demonstrated that alteration of the calcium gradient affects the exocytosis of the lamellar body at the interface between the stratum corneum and epidermal granular layer.

The ion profile has been reported to be altered in various skin diseases (FORSLIND *et al.*, 1999). Abnormal calcium distribution is observed in psoriatic epidermis and atopic dermatitis which shows abnormal barrier function. Ions might also play an important role in the pathology of the skin.
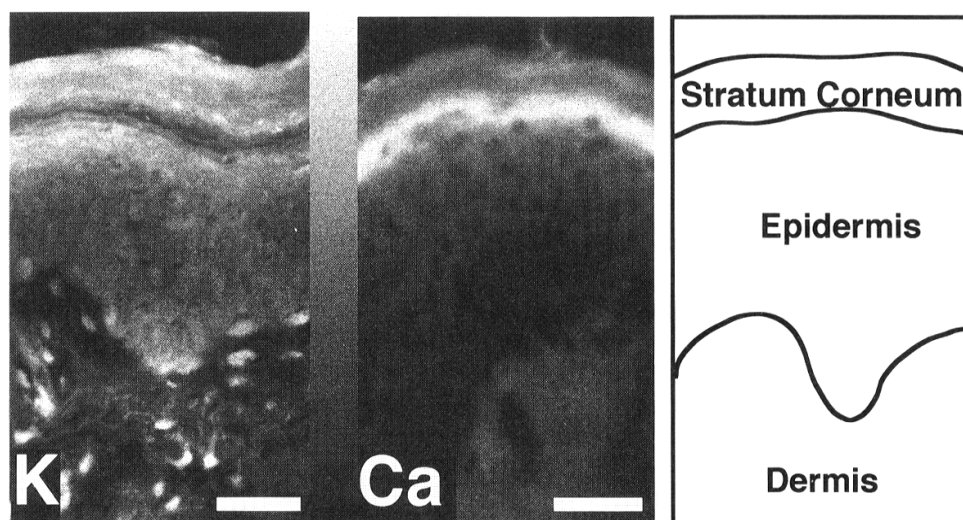
Fig. 3. Distribution of potassium and calcium in human epidermis. Calcium was stained with Calcium Green 1 and potassium with PBFI. The potassium concentration was low at the bottom of the stratum corneum, where the calcium concentration was the highest. Bars: 20 μm.

As described above, a low environmental humidity accelerates epidermal differentiation, barrier homeostasis (DENDA *et al.*, 1998b), epidermal proliferation and inflammatory responses (DENDA *et al.*, 1998c). Water flux through the epidermis might be the first signal of these epidermal responses because some of them are prevented by occlusion with water impermeable membrane (DENDA *et al.*, 1998c). The mechanical stress may cause calcium flux in epithelial cells (FURUYA *et al.*, 1993). The distribution of calcium and other ions we demonstrated here might play an important role as a second messenger or a sensor system in the epidermis.

4. Conclusion: Self-Organizing Boundary Structure for Sustaining Life

Skin is an interface of the living system. Especially, the stratum corneum forms a tough barrier against the environment. It must always respond to environmental changes. Whenever it is damaged, it must be repaired immediately. Thus, this system has a sensor for the environmental changes and also a self-repairing device. These functions might be regulated by ion fluxes. Ions such as calcium, form a heterogeneous field in the epidermal tissue, which may respond to the alteration of the out side world. With this smart system, animals can survive away from the ocean while still having an ocean-like internal environment.

REFERENCES

CLAPHAM, D. E. (1995) *Cell*, **80**, 259–268.

DENDA, M., KOYAMA, J., NAMBA, R. and HORII, I. (1994) *Arch. Dermatol Res.*, **286**, 41–46.

DENDA, M., TSUCHIYA T., HOSOI, J. and KOYAMA, J. (1998a) *British J. Dermatol*, **138**, 780–785.

DENDA, M., SATO, J., MASUDA, Y., TSUCHIYA, T., KOYAMA, J., KURAMOTO, M., ELIAS, P. M. and FEINGOLD, K. R. (1998b) *J. Invest. Dermatol*, **111**, 858–863.

DENDA, M., SATO, J., TSUCHIYA, T., ELIAS, P. M. and FEINGOLD, K. R. (1998c) *J. Invest. Dermatol*, **111**, 873–878.

DENDA, M., KATAGIRI, C., HIRAO, T., MARUYAMA, N. and TAKAHASHI, M. (1999) *Arch. Dermatol. Res.*, **291**, 560–563.

DENDA, M., TSUCHIYA, T., ELIAS, P. M. and FEINGOLD, K. R. (2000a) *Am. J. Physiol.*, **278**, R367–R372.

DENDA, M., TSUCHIYA, T., SHOJI, K. and TANIDA, M. (2000b) *British J. Dermatol*, **142**, 1007–1010.

DENDA, M. and TSUCHIYA, T. (2000c) *British J. Dermatol*, **142**, 881–884.

ELIAS, P. M., HOLLERAN, W. M., MENON, G. K., GHADIALLY, R., WILLIAMS, M. L. and FEINGOLD, K. R. (1993) *Curr. Opin. Dermatol*, 231–237.

FORSLIND, B., WERNER-LINDE, Y., LINDBERG, M. and PALLON, J. (1999*) Acta Derm. Venereol (Stockh)*, **79**, 12–17.

FURUYA, K., ENOMOTO, K. and YAMAGISHI, S. (1993) *Pflugers Arch.*, **422**, 295–304.

GRUBAUER, G., FEINGOLD, K. R. and ELIAS, P. M. (1987) *J. Lipid Res.*, **28**, 746–752.

GRUBAUER , G., ELIAS, P. M. and FEINGOLD, K. R. (1989) *J. Lipid Res.*, **30**, 323–333.

HENNINGS, H., HOLBROOK, K. A. and YUSPA, S. H. (1983) *J. Invest. Dermatol*, **81**, 50s–55s.

LEE, S. H., ELIAS, P. M., PROKSCH, E., MENON, G. K., MAN, M. Q. and FEINGOLD, K. R. (1992) *J. Clin. Invest.,* **89**, 530–538.

MENON, G. K., ELIAS, P. M., LEE, S. H. and FEINGOLD, K. R. (1992) *Cell Tis Res.*, **270**, 503–512.

MENON, G. K., PRICE, L. F., BOMMANNAN, B., ELIAS, P. M. and FEINGOLD, K. R. (1994) *J. Invest. Dermatol*, **102**, 789–795.

NEMES, Z., MAREKOV, L. N. and STEINERT, P. M. (1999) *J. Biol. Chem.*, **274**, 11013–11021.

POTTS, R. O. and FRANCOEUR, M. L. (1991) *J. Invest. Dermatol*, **96**, 495–499.

TAGAMI, H. (1998) *The Japanese J. Dermatol*, **108**, 713–727.

WATANABE, R., WU, K., PAUL, P., MARKS, D. L., KOBAYASHI, T., PITTELKOW, M. R. and PAGANO, R. E. (1998) *J. Biol. Chem.*, **273**, 9651–9655.

WATT, F. M. (1989) *Curr. Opin. Cell Biol.*, **1**, 1107–1115.