

## Epithelial Stem Cells of the Skin Contribute to the Histopathologic Umbrella-like Appearance in Actinic Keratosis

Motoyuki Mihara

Mihara Dermatology Clinic, Tottori University, 1933-1 Takao, Niimi 718-0003, Japan

### ABSTRACT

Although the histopathologic umbrella-like appearance of the epidermis in actinic keratosis (AK) is well known, its histopathogenesis has remained unknown. The author suggests that the penetration depth of ultraviolet B (UVB) radiation can account for such a histopathologic feature by affecting specific epidermal stem cell pools, as the stem cells in the epidermis and the bulge stem cells and sebocyte stem cells in the mid-dermis reside at different depths.

**Key words** actinic keratosis; bulge stem cell; epidermal stem cell; sebocyte stem cell; ultraviolet B

Hyperplastic/hyperkeratotic actinic keratosis is a frequently encountered subtype of actinic keratosis. Its defining histopathologic feature is the extension of the uninvolved hyperplastic epithelium of the follicular ostia and sweat gland orifices over the dysplastic epithelia of AK in an umbrella-like fashion. This histopathologic feature has been well known as the Freudenthal funnel since it was described by Freudenthal<sup>1</sup> in 1926, but its histopathogenesis has remained unclear to date. The author suggests that this unknown histopathogenesis may be explained by the different resident locations of the epithelial stem cell populations of the skin.

### REPORT

The epithelial component of the epidermis consists of epidermal cells and appendageal cells, including acrotrichial cells and acrosyringial cells. Pinkus and Mehregan<sup>2</sup> proposed a theory termed epidermal symbiosis. According to the theory, the epidermal cells and the appendageal cells maintain homeostasis by mitotic division of their own germinal cells, and they may independently act and react under pathologic conditions. Thus, AK may be considered to be a pathologic condition in which the interrelationship between the epidermal cells and the appendageal cells is disorganised. As described previously,<sup>2</sup> the acrotrichial cells are essentially indistin-



**Fig. 1.** Umbrella-like appearance in actinic keratosis (AK). The border between acrotrichial cells (**at**) and dysplastic epithelial cells of actinic keratosis (**ak**) is sharply defined (hematoxylin and eosin stain). Bar = 50  $\mu$ m.

guishable from the surrounding epidermal cells under normal conditions, while their border is sharply defined in AK (Fig. 1), resulting in the characteristic umbrella-like appearance.

AK is a precancerous lesion usually related to sun exposure. UV exposure is the most harmful agent contributing to sunlight-induced carcinogenesis. In the UV rays from sunlight, approximately 95% of the UV radiation that reaches the Earth's surface is UVA (wavelength of 320–400 nm), and approximately 5% of it is UVB (wavelength of 290–320 nm).<sup>3</sup> However, UVA is poorly absorbed by DNA, while UVB is readily absorbed by DNA.<sup>4</sup> Therefore, UVB more effectively causes DNA damage and photocarcinogenesis. For UVB to perform its biological action, it must penetrate to the appropriate level in the skin. UVB can penetrate the skin to the upper dermis.<sup>3</sup> At this depth, UVB is able to influence epidermal stem cells, but cannot influence the bulge stem cells in the hair follicle bulge and sebocyte stem cells in the base of sebaceous glands, because the resident locations of these stem cells are definitively in the mid-dermis. As a result, they escape UVB-induced DNA damage and maintain normal conditions. Such a pathologic

Corresponding author: Emeritus Professor Motoyuki Mihara, MD

motoyuki@mountain.ocn.ne.jp

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Abbreviation: AK, actinic keratosis

phenomenon may generate an umbrella-like appearance in the epidermis.

Eccrine gland stem cells were recently identified in sweat glands and ducts in the mouse.<sup>5</sup> However, to my knowledge, there has not been a report defining the resident location of eccrine gland stem cells in normal human skin. Thus, there is a possibility that eccrine gland stem cells reside much deeper in the dermis than the hair follicle bulge.

In conclusion, UVB can penetrate the skin to the upper dermis. Therefore, epidermal stem cell DNA is always susceptible to UVB-induced damage from sunlight, while the DNA of bulge stem cells and sebocyte stem cells is protected from UVB damage because these stem cells reside deeper, in the mid-dermis. Histopathogenetically, the umbrella-like appearance of AK epidermis may support such a pathologic phenomenon.

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