Keratin, a dual role in herpes simplex virus pathogenesis

Harvey M. Friedman∗

Department of Medicine, Division of Infectious Diseases, 502 Johnson Pavilion, University of Pennsylvania School of Medicine, Philadelphia, PA 19104-6073, USA

Received 16 February 2005; received in revised form 13 March 2005; accepted 25 March 2005

Abstract

Keratin is a strong, fibrous protein that coats the skin, male genitalia and some tissues in the mouth and female genitalia. Keratin protects the host by providing a barrier against primary herpes simplex virus infection. We postulate that keratin may also hinder the host by protecting the virus from effective immune responses such as those present on mucosal surfaces, enabling recurrent lesions to preferentially develop within keratinized tissues at mucocutaneous junctions. The natural history of infection supports the importance of preventing infection in keratinized tissues for developing an effective herpes simplex virus vaccine, since potent immunity on mucosal surfaces may be inadequate to protect keratinized tissues.

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Keywords: Herpes simplex virus; Immune evasion; Keratin; Mucosal immunity; Vaccines

Analysis of the natural history of HSV infection reveals interesting differences between the anatomic sites of primary and recurrent orolabial and genital infections. Oral and genital tissues contain two types of epithelial cells, one that produces keratin that coats the cell surface and another that does not. Keratin is a strong, fibrous, helical protein that is found on skin, nail beds, tooth enamel, hair, the hard palate, gingiva and parts of the tongue. Fig. 1 demonstrates keratin covering an HSV lesion within the skin. An under-appreciated aspect of HSV pathogenesis is that most recurrent lesions develop within epithelial tissues that have keratin coats.

Primary HSV infection refers to infection in nonimmune individuals. Primary orolabial infection occurs within the oral cavity mainly on nonkeratin-coated tissues, such as the inner lip and buccal mucosa, but also develops on keratin-coated surfaces, such as the dorsal of the tongue and gingiva (Spruance, 1984). During primary infection virus likely enters nonkeratin-coated epithelial cells from basolateral surfaces (Schelhaas et al., 2003), while infection of keratin-coated tissues, such as the tongue, likely begins in the basal layers of the replicating epithelium when virus enters through minute breaks in the keratin coat (Visalli et al., 1997). Although primary lesions (vesicles and ulcers) develop in both nonkeratin- and keratin-coated tissues, recurrences are almost invariably located within keratinized epithelial tissues. The most common site for recurrent orolabial HSV is at the mucocutaneous junction on the lip. Intraoral lesions are rare; however, when they occur they usually develop within keratinized tissues on the hard palate or gingiva (Eisen, 1998; Spruance, 1984). During recurrent infection, virus reactivates from dorsal root ganglion neurons and enters tissues from sensory nerves rather than through breaks in the skin. These nerves are located within the epidermis and at the epidermal-dermal junction, well below the superficial keratin layer. What then is the function of keratin in recurrent infections?

In the normal host, asymptomatic virus shedding can be detected from nonkeratin and keratin-coated tissues (Corey et al., 1983; Schacker et al., 1998; Spruance, 1984), yet lesions seldom develop within nonkeratin tissues, such as the buccal mucosa in the mouth. In the impaired host, recurrent lesions occur both within keratinized tissues, particularly at mucocutaneous junctions and within the oral cavity, primarily in nonkeratinized tissues, such as the buccal mucosa and inner lip (Greenberg et al., 1987). The observation

∗ Tel.: +1 215 662 3557; fax: +1 215 349 5111.
E-mail address: hfriedma@mail.med.upenn.edu.

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that recurrent lesions in the normal host almost invariably develop within keratinized tissues while in the impaired host lesions occur in both tissue types suggest a role for immunity in the distribution of lesions in the normal host. We postulate that keratinized tissues are the sites of recurrent HSV infections because keratin protects the virus from immune responses, particularly those present on mucosal surfaces.

Similar to oral HSV infection, genital lesions in the non-immune individual develop without keratinized epithelial cells (urethra, medial aspects of the labia minora, vagina and exocervix) and keratinized epithelial cells (penis and lateral aspects of the labia minora and external genitalia). The female genitalia has more nonkeratinized tissues than male genitalia and females are more susceptible to genital HSV infection than males (Smith and Robinson, 2002), suggesting that keratin offers males a protective barrier to infection. Breaks in the epidermis that disrupt the keratin coat are thought to account for primary infection on the penis and at other keratinized sites. In the immune individual, recurrent infection develops as virus reactivates from dorsal root ganglion neurons and enters both keratinized and nonkeratinized tissues. The attack rate for HSV infection was lower in men, since the natural history of HSV suggests that immunity is more effective within keratinized than nonkeratinized tissues. The attack rate for HSV infection was lower in men, since the natural history of HSV suggests that immunity is more effective within keratinized than nonkeratinized tissues. The attack rate for HSV infection was lower in men, since the natural history of HSV suggests that immunity is more effective within keratinized than nonkeratinized tissues. The attack rate for HSV infection was lower in men, since the natural history of HSV suggests that immunity is more effective within keratinized than nonkeratinized tissues. The attack rate for HSV infection was lower in men, since the natural history of HSV suggests that immunity is more effective within keratinized than nonkeratinized tissues. 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