Arch Dermatol Res (1992) 284 [Suppl]: S10–S11

Archives of Dermatological Research

Pathophysiology of cutaneous inflammation

B. J. Nickoloff

Departments of Pathology and Dermatology, University of Michigan Medical School, M 4232 Medical Science I, Ann Arbor, Michigan, USA

Summary. For the better part of the past century, dermatologists have regarded the skin primarily as a large protective coat. Epidermal keratinocytes were highlighted for their production of keratins and lipids, which contributed to the structural integrity and barrier formation of skin. This "saran-wrap" perspective of skin mentioned keratinocytes only in cutaneous inflammatory reactions as passive targets for damaging diffusion products of infiltrating leukocytes. However, sufficient compelling in vitro and in vivo evidence is rapidly accumulating to support the novel perspective that epidermal keratinocytes can initiate and actively participate in the perperuation of numerous cutaneous inflammatory reactions that involve a highly diverse array of inciting agents. This presentation emphasizes the keratinocyte and highlights the dynamic immunomodulatory capacity of this overlooked epidermal cell.

Key words: Psoriasis – Cytokines – Adhesion molecules – Chemotaxins – Keratinocytes

While the keratinocyte is the major cellular constituent of the epidermal compartment, it has been overlooked as an active contributor to inflammatory skin diseases for more than a century. This rather benign neglect of its proinflammatory potential has been overshadowed by investigators who focus on the molecular basis for kertain gene expression and lipid biosynthetic pathways, which clearly contribute to the structural integrity and barrier function of skin [1]. Indeed, by following this route of investigation much has been learned regarding the importance of barrier formation and its abrogation as contributing to many disease processes [4]. In the past it was felt that when a sufficiently strong stimulus or injury occurred to the skin surface, the barrier would be broken, the brick and mortar wall of keratinocytes delapidated, and a rather nonspecific acute-phase reaction characterized by classical mediators of inflammation would ensue to repair the damage. Keratinocytes were viewed strictly as innocent bystanders of these events and as passive targets which are the unfortunate recipients of microenvironmentally produced noxious substances such as oxygen free radicals, complement fragments, prostaglandins, and leukotrienes. This view was expanded beyond tissue repair to apply to psoriasis and gave rise to the viewpoint that the psoriatic plaque represents an exaggerated wound healing response [6]. It is clearly established that a psoriatic plaque has an altered barrier function, and numerous report have detailed the abnormal keratinization which is characteristic of the lesions (for review see [13]).

However, when we begin to cause cutaneous inflammation without producing any significant cytopathic effects in the epidermis, it becomes clear that keratinocytes can function and actively participate in this dynamic process by initiating and perpetuating important cytokine networks (for review see [7]). Indeed, one may also disturb barrier function by delipidizing the stratum corneum, and even though there is no further structural damage to the epidermis, keratinocytes can increase their production of mitogens [12]. Thus, as we continue to probe the structure/function properties of epidermal cells by using more sophisticated and less traumatic stimuli, it is apparent that keratinocytes can perform many additional functions besides producing keratins and lipids.

One of the immunohistopathological pathways to understand psoriasis was derived from earlier work carried out by Braun-Falco and Christophers [3], who in 1974 demonstrated that initial psoriatic lesions resembled the changes in allergic contact dermatitis reactions. To determine the possible role of epidermal keratinocytes as initiators of inflammatory and immune-based reactions in the skin, we applied the poison ivy antigen (i.e., urushiol) topically to previously sensitized, normal healthy volunteers [5]. Thus, our use of the allergic contact dermatitis link with psoriasis was based on the work by Braun-Falco and Christophers. After the epicutaneous application of urushiol, we made serial observations beginning at time 0 and including 2, 4, 8, 24 and 48 h up to 3 weeks to document the clinical, light microscopic, and immunological changes. Within the initial 8 h following exposure, before there were any clinical or histological changes, the epidermal keratinocytes were observed to dramatically upregulate their tumor necrosis factor-alpha (TNF-α) levels, and this was associated with

concomitant expression by the same cells of their intercellular adhesion molecule-1 (ICAM-1) and the underlying microvascular endothelial cells expression of endothelial cell leukocyte adhesion molecule-1 (ELAM-1) and vascular cell adhesion molecule-1 (VCAM-1). It should be noted that TNF-α is the only known cytokine which can simultaneously induce keratinocyte ICAM-1 ELAM-1, and VCAM-1. As the allergic contact dermatitis reaction proceeded, there was a progressive increase in the expression of these adhesion molecules which paralleled the influx of mononuclear leukocytes. Moreover, during the resolution of the reaction at weeks 2 and 3 there was a marked diminution in the expression of these molecules, which also correlated with a disappearance of T lymphocytes and monocyte/macrophages in the tissue sections.

When purified urushiol was added to multipassaged human keratinocytes, direct activation of the keratinocytes was observed because TNF-α, ICAM-1, and IL-8 mRNAs and proteins could be detected in vitro, confirming the notion that epidermal keratinocyte in vivo was initiating and actively participating in the genesis and perpetuation of the allergic contact dermatitis reaction [2]. These studies were extended independently by a different group of investigators using a murine system of both allergic contact and irritant contact dermatitis, in which after only 30 min of stimulation keratinocyte TNF-α mRNA induction was significantly increased [11]. In both of these experimental systems there were absolutely no cytopathic changes in the epidermal keratinocytes, and hence this very dramatic and rapid activation of keratinocytes preceded the subsequent influx of mononuclear cells, clearly indicating a direct causal relationship involving intiation of the process by keratinocytes and their release of cytokines, adhesion molecules, and chemotaxins such as TNF-α, ICAM-1, ELAM-1, VLAM-1, and IL-8, respectively. In the murine system the development of the clinical reaction was almost completely inhibited by preinjection of the skin with neutralizing anti-TNF-α antibody, adding a functional dimension to these morphological and immunohistochemical studies. We have recently highlighted the relevance of the epidermal keratinocyte as a key immunocyte in the pathobiology of allergic contact and irritant contact dermatitis [8] and conclude this review with a discussion of the next step beyond induction of cutaneous inflammation, to the active stages of more fully evolved psoriatic lesions.

By using the same sort of molecular probes that were useful in detecting various cytokines, adhesion molecules, and chemotaxins as described above for early and late allergic contact dermatitis, we obtained biopsies from the advancing margins of untreated psoriatic plaques [10]. In these experiments TNF-α was not found in the epidermal keratinocyte as observed for this dermatitis but in the dermal dendrocyte of the psoriatic lesion. However, the epidermal keratinocyte was observed to be the principal source of other key molecular mediators of the psoriatic process such as transforming growth factor-alpha, ICAM-1, and IL-8. Based on the aberrant phenotype of cultured keratinocytes that has been repeatedly passaged since removal from their psoriatic plaque [9], we postulated at least five different pathways by which mutant clones of psoriatic keratinocytes could contribute to the pathobiology of psoriasis [7]. These proposed pathways include: altered growth regulatory reactions between cytokine-activated keratinocytes and T cells, induction of angiogenesis, and induction of autoreactive T lymphocytes. For all of these different pathways the key concept is that the epidermal keratinocytes plays an active and dynamic patricipatory role in the disease process. It is still too early to be certain exactly how the psoriatic gene mutation expresses itself in the keratinocytes, but clearly a credible case can be made for considering the keratinocyte as a centrally important constituent of the overall initiation and perpetuation of the complex multifactorial skin phenomenon known as psoriasis. Because it can produce primary cytokines such as TNF-α, immunomodulating cell surface molecules such as ICAM-1 and HLA-DR as well as T cell/-monocyte/macrophage chemotactic polypeptides, we consider the keratinocyte to be a key immunocyte within the epidermis of skin. In conclusion, it is abundantly clear that keratinocytes can not only actively participate in epidermal barrier formation but functionally initiate and propagate inflammatory and immune-mediated reactions in a wide variety of skin diseases.

References

1. Baker H (1986) The skin as a barrier. In: Rook A (ed) Textbook of dermatology, 4th edn. Oxford-Blackwell, London, pp 356–357
2. Barker JNWN, Mitra RS, Griffiths CEM, Dixit V, Nickoloff BJ (1991) Keratinocytes as initiators of inflammation. Lancet 337: 211–214
3. Braun-Falco O, Christophers E (1974) Structural aspects of initial psoriatic lesions. Arch Dermatol 251: 195–110
4. Elias PM, Brown BE (1978) The mammalian cutaneous permeability barrier: defective barrier function in essential fatty acid deficiency correlates with the abnormal intercellular lipid deposition. Lab Invest 39: 574–583
5. Griffiths CEM, Barker JNWN, Kunkel SL, Nickoloff BJ (1979) Modulation of leukocyte adhesion molecules, a T cell chemotaxin (IL-8) and a regulatory cytokine (TNF-α) in allergic contact dermatitis (rhus dermatitis). Br J Dermatol 124: 519–526
6. Morhenn VB (1988) Keratinocyte proliferation in wound healing and skin diseases. Immunol Today 9: 104–107
7. Nickoloff BJ (1991) The cytokine network in psoriasis. Arch Dermatol 127: 871–884
8. Nickoloff BJ (1992) Role of epidermal keratinocytes as key initiators of contact dermatitis due to allergic sensitization and irritation. Am J Contact Dermatitis 3: 65–69
9. Nickoloff BJ, Mitra RS, Elder JT, Fisher GJ, Voorhees JJ (1989) Decreased growth inhibition by recombinant gamma interferon is associated with increased transforming growth factor-α production in keratinocytes cultured from psoriatic lesions. Br J Dermatol 121: 161–174
10. Nickoloff BJ, Karabin GD, Barker JNWN, Mitra RS, Sarma V, Elder JT, Kunkel SL, Dixit V (1991) Cellular localization of interleukin-8 and its inducer tumor necrosis factor-alpha in psoriasis. Am J Pathol 138: 129–140
11. Piquet PF, Grau GE, Hauser C, Vasalli P (1991) Tumor necrosis factor is a critical mediator in hapten-induced irritant and contact hypersensitivity reactions. J Exp Med 173: 673–679
12. Proksch E, Feingold KR, Qiang MM, Elias PM (1991) Barrier function regulates epidermal DNA synthesis. J Clin Invest 87: 1668–1673
13. Shuster S (1971) Research into psoriasis — the last decade. BMJ 3: 236–239