Keratinocyte-derived tumor necrosis factor and the physiopathology of the skin

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Introduction

Keratinocytes have emerged in recent years as cells producing a wide variety of cytokines, notably interleukin (IL)-1, IL-3, IL-6, IL-8, several colony-stimulating factors (CSFs), transforming growth factor (TGF)-α, TGF-β, platelet-derived growth factor (PDGF), and tumor necrosis factor (TNF)-α, reviewed in [1]. The capacity to produce these mediators implies that keratinocytes are not just the constituents of a barrier between the outside world and the body, but rather are active participants.

The production of TNF-α and IL-1 is of particular importance for the pathophysiology of the skin since these cytokines are nowadays recognized as the cytokines of inflammation; it is, indeed, unlikely that an inflammatory disease ever occurs in their absence. Furthermore, injection of IL-1 or TNF reproduces the whole spectrum of the alterations observed in inflammatory disease, such as vascular leak, leukocyte sequestration, necrosis, and fibrosis. As reviewed in [9], IL-1 and TNF are functionally homologous despite the fact that they are structurally unrelated and interact with different surface receptors.

The keratinocyte-derived IL-1 already has a history; IL-1-like activity has been detected within normal epidermis since 1981 [21, 29, 41]. The production of IL-1 by keratinocytes as well as the IL-1-inducing agent have been reviewed [1]. In contrast keratinocyte-derived TNF has only been described recently and I will therefore focalize here on keratinocyte-derived TNF-α. Because of the abundance of keratinocytes, keratinocyte-derived TNF has a major importance not only for the physiopathology of the skin, but also for the whole organism and particularly the immune system.

Production of TNF by keratinocytes

In vitro

Several epidermal cell lines (derived from squamous cell carcinoma) of mouse or human origin contain TNF-α mRNA and can be shown to release TNF under
some conditions [25, 46]. Effective stimulating agents are LPS, haptens, UVB irradiation and TNF itself, but not IL-1 (Table 1 and Fig. 1). TNF production in vitro seems to be critically dependent upon the culture conditions, notably the cell density, and the presence of various growth factors in the culture medium [1, 27]. Cell crowding apparently leads to inhibitory concentration of prostaglandins.

The secretion of TNF by keratinocytes is suggested by its presence in the keratinocyte supernatant, but the secretion rate does not appear to be comparable to that of macrophages. In our study of the mouse keratinocyte cell line PAM 212 we observed abundant TNF mRNA (Fig. 1) (comparable to that observed in LPS-stimulated macrophages), but variable amount of TNF protein within the supernatant. This raises the possibility of a complex regulation occurring at translation or during maturation and secretion of a TNF precursor, as has been described for other cells [8]. As mentioned before, this might be greatly influenced by the culture conditions.

![Fig. 1. A keratinocyte cell line PAM-212 was cultured alone or was stimulated with lipopolysaccharide (LPS; 10 µg/ml), tumor necrosis factor (TNF; 10 µg/ml) or interleukin-1 (IL-1; 10 µg/ml) and its RNA extracted after 60 min. A Northern blot was prepared and hybridized with a probe specific for TNF-α. Arrow indicates the position of the TNF mRNA](image-url)