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NEWS & VIEWS

Groundbreaking Discoveries in Clinical & Basic Science

Neuron–macrophage interaction in the healing process of the skin

The skin is the largest organ of the human body. It controls body temperature and hydroelectrochemical balance, protects the organism, and maintains its integrated structures. Immunologically, the skin is endowed with a complex network of immune-functioning cells consisting of macrophages, Langerhans cells, and dendritic cells, as well as sensory neurons that detect damage.

The skin is frequently exposed to ultraviolet (UV) radiation, which, although critical for life, can also be a source of important alterations. The recent work by Hoeffel et al [1] focuses on the injury caused by UVC radiation, being the most harmful type of radiation although it does not penetrate naturally the earth's atmosphere.[2] UV radiation contributes to a variety of skin alterations, including inflammation, degenerative aging, and cancer.[2] Inflammation is a response to harmful conditions and stimuli such as tissue damage. A successful acute inflammatory response results in the elimination of the tissue damage followed by a resolution and repair phase, which is mediated mainly by tissue resident and recruited macrophages.[3] The number of macrophages increases during the inflammatory phase, peaks during the phase of granulation tissue, and declines during the maturation phase. Initially, proinflammatory macrophages infiltrate after injury to clean the wound of bacteria, debris, and dead cells. As the tissue begins to repair, the overall macrophage population transitions to one that promotes anti-inflammatory effects and the migration and proliferation of fibroblasts, keratinocytes, and endothelial cells to restore the dermis, epidermis, and vasculature, respectively.[3]

Since macrophages play an important role in tissue repair, it is important to elucidate the precise mechanisms by which these cells restore tissue homeostasis. In this sense, the detailed study by Hoeffel et al. elucidated the tissue repair cascade generated.[1] They described the pathway that begins from the nonpeptidergic GINIP$^+$ sensory neurons releasing TAFA4 after skin exposure to UV. This promotes the production of IL-10 by embryonic-derived resident TIM4+ macrophages. The continuous release of IL-10 is essential for the maintenance of resident macrophage survival and for controlling inflammation. It also recruits fewer proinflammatory monocytes and more monocytes with an anti-inflammatory profile, leading to tissue repair and recovery of homeostasis (Figure 1).

TAFA4 is a secreted protein that attracts macrophages by chemotaxis through the formyl peptide receptor 1 (FPR1) in vitro, and it has been shown to be upregulated upon LPS-stimulation on macrophages.[4] However, Hoefel et al have not found TAFA4 expression on CD206+ dermal macrophages or by bone marrow-derived macrophages following LPS stimulation. Furthermore, the authors have also not observed a chemotactic effect of TAFA4 on macrophages. They have proposed the existence of another receptor, different from FPR1, responsible for inducing its effect on dermal macrophages after skin injury.

IL-10 is a cytokine with potent anti-inflammatory properties that maintains the balance of the immune response. Hoefel et al. have shown in their work that macrophages and mast cells are the main IL-10 producers after irradiation; however, TAFA4 was only able to modulate IL-10 production in the macrophage population. This correlates with other tissues, such as the small intestine, where macrophages play an important role in maintaining gastrointestinal homeostasis through IL-10 production.[5] Moreover, IL-10 deficiency in macrophages after drug-induced injury compromised the recovery of the small intestine epithelial barrier. In this regard, IL-10 has been proposed to be an attractive therapeutical target in inflammatory bowel diseases such as ulcerative colitis and Cronh's disease, but clinical results in humans have been disappointing without a clear beneficial effect. One possible explanation that has been proposed is that the cytokine is cleared before reaching its target due to its short half-life.[6] Therefore, treatment with TAFA4 may result in the release of IL-10 in a more sustained manner and may be an alternative to IL-10 administration to treat other inflammatory skin diseases, such as pemphigus vulgaris and atopic dermatitis.

Abbreviations: FPR1, formyl peptide receptor 1; GINIP, Galphai-interacting protein; TAFA4, TAFA Chemokine Like Family Member 4; UV, ultraviolet; UVC, ultraviolet range C.

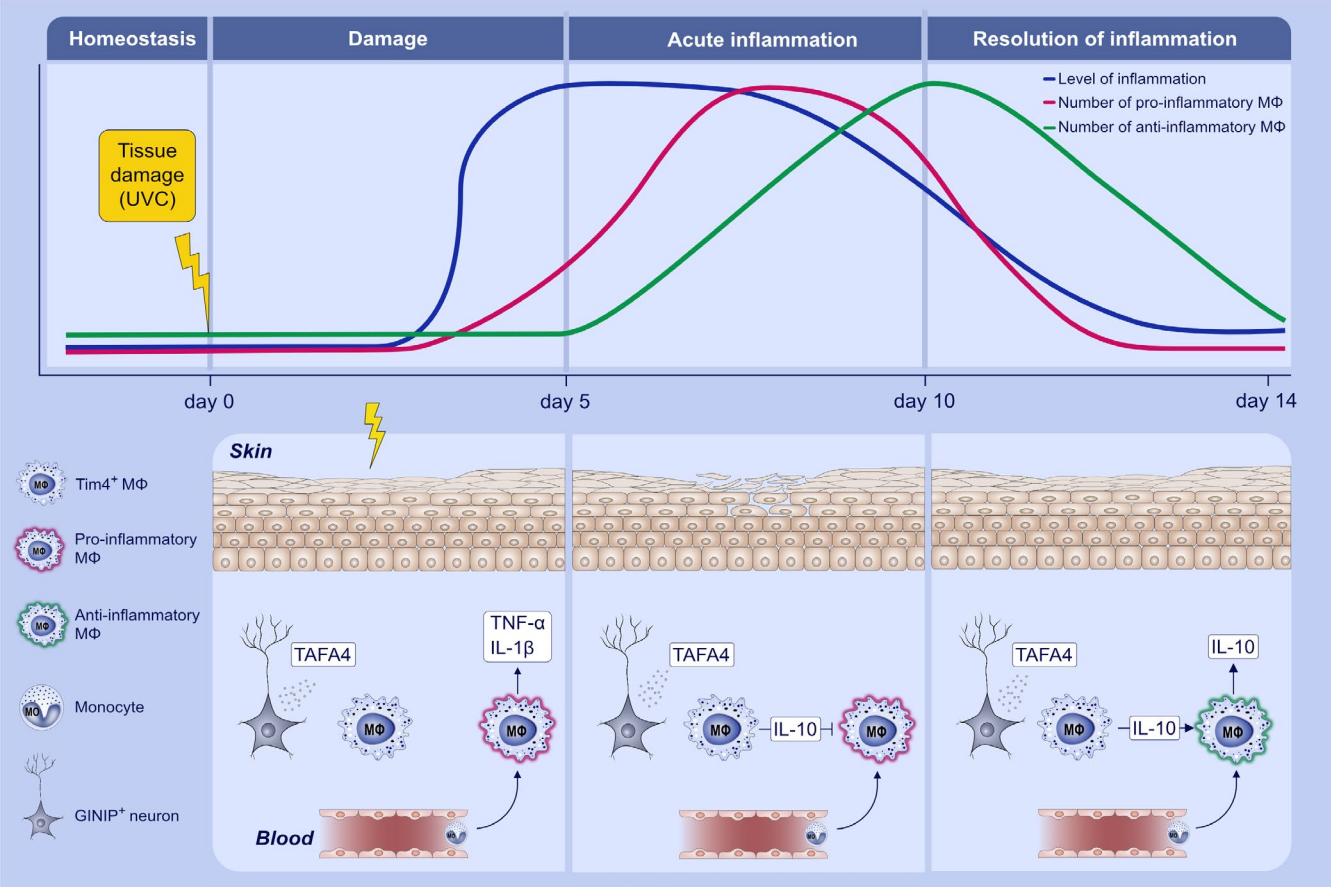

FIGURE 1 Sequent phases of skin repair upon UV exposure. After tissue irradiation, there is an inflammatory phase where monocyte-derived cells recruited to the site of injury acquire a proinflammatory phenotype, secreting high levels of TNF-α and IL1-β, contributing to tissue damage. The release of TAFA4 by GINIP+neurons is essential to control the inflammation and to enter into the repair phase, as it induces the secretion of IL-10 by tissue resident macrophages, which favors their own survival and promotes the recruitment of monocytic cells with anti-inflammatory properties, reducing skin inflammation and fostering tissue regeneration

KEYWORDS

IL-10, neurons, radiation, resident macrophages, TAFA4

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CONFLICT OF INTEREST

The authors declare no competing interests.

AUTHOR CONTRIBUTION

The authors approved the final version of the manuscript as submitted and agreed to be accountable for all the aspects of the work.

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