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Effect of TNF-alpha and IL-17 on TLR expression and Langerhans cells phenotype in a three-dimensional model of normal human skin: a morphological study

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Toll-like receptors (TLRs) are essential for innate immunity and contribute to create the skin barrier. Their abnormal stimulation is involved in the development of several dermatological diseases, among which psoriasis. Tumor Necrosis Factor (TNF)-alpha and interleukin (IL)-17 play a pivotal role in the pathogenesis of psoriatic plaques and their proinflammatory activity can affect Langerhans cell (LC) phenotype. In a well characterized three-dimensional model of organotypic cultures of normal human skin [1-3] we evaluated the effect of TNF-alpha and IL-17 on the expression of TLR2 and 9 by immunofluorescence, on the ultrastructural morphology of keratinocytes and LCs by transmission electron microscopy (TEM). Human skin explants (n=7) were cultured at the air-liquid interface overnight in a Transwell system and exposed to 50 ng/ml IL-17 or 100 ng/ml TNF-alpha or a combination of both cytokines. Samples were harvested 24 (T24) and 48h (T48) after cytokines incubation. After incubation with IL-17 and IL-17+TNF-alpha, TLR2 immunostaining was not detectable in the basal layer, differently from controls and TNF-alpha-treated samples. Conversely, TLR9 expression was progressively induced in granular keratinocytes in all cytokine-exposed groups. By TEM, enlargements of intercellular spaces were evident especially and, after IL-17 treatment, LCs showed an activated phenotype. At T24 LCs number increased indicating that TNF-alpha and IL-17+TNF-alpha exert a chemoattractant activity, while at T48 only IL-17+TNF-alpha maintained this effect on trapping LCs in epidermis. TNF-alpha and IL-17 differently affect LCs behaviour and TLR expression, with a specific contribution to the inflammatory loop underlying the lesion formation. These results suggest that the simultaneous inhibition of the effect of different cytokines with a defined role in the pathogenesis of psoriasis could improve psoriasis treatment.

References

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Keywords

Transmission electron microscopy; proinflammatory cytokines.