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Modulation of epidermal proliferation and terminal differentiation in a promising ex vivo human skin model mimicking a psoriatic microenvironment

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Epidermal keratinocyte hyperproliferation is one of the key features involved in the formation/progression of psoriatic lesions and is driven by cytokines, among which TNF-α, IL-17, IL-22 and IL-23, secreted by both activated resident immune cells and keratinocytes (1). The network orchestrated by these cytokines is essential for the communication between resident cells and infiltrating cells and is due to redundancy, synergism and, sometimes, the reciprocal antagonism of cytokines. The aims of our study were to investigate whether the exposure of normal human skin to four main psoriatic cytokines, i.e. TNF-α, IL-17, IL-22, and IL-23 (cytokine mix) induced i) a modulation of epidermal proliferation and ii) a modification of keratinocyte terminal differentiation (TD). Human skin samples (n = 5) obtained from healthy 20-40 years-old women after plastic surgery, were exposed to the cytokine mix in a Transwell system at air-liquid interface as previously described (2). For each patient a control (ctr) group was not exposed to cytokine mix. Samples were harvested 5 (T5), 24 (T24), 48 (T48) and 72 (T72) hours after cytokine stimulation, processed for paraffin embedding and immunofluorescence analysis for the quantitative analysis of epidermal proliferation and the expression of the TD biomarkers, keratin (K) 10 and 17. A decrease of cell proliferation was evident starting from T5 in samples exposed to cytokine mix and was progressively more marked at later time points (**T5** ctr 47.44 ± 6.90 vs mix 23.07 ± 8.84; **T24** ctr 41.12 ± 12.78 vs mix 12.16 ± 1.53; **T48** ctr 25.88 ± 10.21 vs mix 2.19 ± 2.44; **T72** ctr 10.49 ± 2.52 vs mix 0.65 ± 1.02) ($p<0.05$). K17 expression was evident in samples exposed to the cytokine mix. Altogether the present results suggest that cell proliferation inhibition and K17 expression could be regarded as the basis for a later response to injury leading to psoriatic lesion formation/progression. In conclusion, this model allows to investigate the intimate interplay among different psoriatic cytokines and new insights may be of potential value for future clinical treatments.

References

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Keywords
Psoriasis; cytokines; keratins.