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Morphological analysis of JAK1 intracellular pathway activation after pro-inflammatory psoriatic cytokines exposure: inside-out and outside-in the epidermis

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For their normal growth, cells depend on a continuous flow of signals from the environment. The Janus kinases (JAK) 1 transducers signalling pathway is a pleiotropic cascade used to transduce a multitude of signals among cells. A variety of ligands including cytokines, hormones, growth factors, and their receptors stimulate the JAK1 pathway. Cytokines, a large and very heterogeneous family of small and generally soluble glycoproteins, both control multiple biological processes as haematopoiesis, inflammation, and immunity playing a central role in cell-cell communication. Their action is mediated by the binding to specific receptors on the cell surface, thus transducing biological information to target cells [1]. Pro-inflammatory cytokines play a pivotal role in several inflammatory illnesses including psoriasis. Among them, interleukin (IL)-17, IL-22, IL-23 and tumor necrosis factor (TNF)-alpha play a central role. In the formation and progression of the psoriatic lesion a typical marker is keratin (K) 17 which is correlated with psoriasis severity. The aims of this study were to evaluate the early, direct, and specific effects of pro-inflammatory psoriatic cytokines i) on the activation of the intracellular pathway JAK1 and ii) on the correlation with the induction of K17 expression in a three-dimensional model (3D) of human skin (n=7) by immunofluorescence. Biopsies were cultured overnight epidermal side-up in a Transwell system and exposed to 50 ng/ml IL-17, or 100 ng/ml IL-22, or 50 ng/ml IL-23 or 100 ng/ml TNF-alpha. Samples were harvested 24 (T24), 48 (T48), and 72 (T72) hours after cytokine incubation.

In samples not exposed to cytokines, a JAK1 slight labelling was observed throughout the epidermis, decreasing at T72 in the lower layers. At T24, IL-17 and IL-22, but not IL-23 and TNF-alpha, induced an expression of JAK1 in the spinous layer. At T72, JAK1 immunostaining decreased in all samples, similarly to controls. K17 immunopositivity was induced and progressively increased with time in the suprabasal layers of epidermis in all experimental groups, with the exception of the TNF-alpha group. These results suggest that cytokines exert parallel effects on JAK1 pathway activation and K17 induction.

In conclusion, this 3D model, reproducing some features of psoriatic microenvironment, represents an useful experimental approach to dissect the specific role of each cytokine in the different steps of psoriatic lesion formation.

References

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Keywords

3D model, psoriasis, immunofluorescence, transmission electron microscopy, keratin 17