DERMATOPATHOLOGY

INTERLEUKIN (IL)-17/IL-36 AXIS IN THE CROSSTALK BETWEEN ENDOTHELIAL CELLS AND KERATINOCYTES IN INFLAMMATORY SKIN RESPONSES

Cm Failla [(1)] - C Albanesi [(1)] - L Capriotti [(1)] - C Scarponi [(1)] - L Mercurio [(1)] - F Facchiano [(2)] - M Morelli [(1)] - M Cordella [(2)] - G Pagnanelli [(3)] - A Cavani [(4)] - S Madonna [(1)]

Idi-irccs, Laboratory Of Experimental Immunology, Rome, Italy [(1)] - Istituto Superiore Di Sanità (iss), Oncology And Molecular Medicine Department, Rome, Italy [(2)] - Idi-irccs, I Dermatology Division, Rome, Italy [(3)] - National Institute For Health, Migration And Poverty (nihmp), Scientific Coordination, Rome, Italy [(4)]

Introduction. In inflammatory skin conditions, such as psoriasis, vascular enlargement is associated to endothelial cell proliferation, release of cytokines and adhesion molecule expression. IL-17 is a pro-inflammatory cytokine mainly secreted by T helper 17 cells that is critically involved in psoriasis pathogenesis. IL-36α and IL-36γ are also inflammatory cytokines up-regulated in psoriasis and induced by various stimuli, including IL-17.

Objective. Our objective is to provide a deep analysis of IL-17/IL-36 role in human dermal endothelial cells (HDMEC) that could highlight not only the effects on modulating leukocyte trafficking across vessels but also the initial damages on endothelial cells leading to systemic co-morbidities.

Materials and Methods. We analyzed membrane molecule expression in human dermal microvascular endothelial cells (HDMEC) by real-time RT-PCR, Western blotting and cytofluorimetric analysis. HDMEC conditioned medium was used in Bio-Plex ProTM assays. Cultured human keratinocytes were treated with selected inflammatory cytokines and their supernatant was then used to stimulate HDMEC in the presence or absence of cytokine inhibitors.

Results. We confirmed expression of IL-17 and IL-36 receptors in HDMEC. IL-17 and IL-36 treatment augmented HDMEC proliferation and STAT3 and ERK1/2 phosphorylation. IL-17 or IL-36 synergized with tumor necrosis factor (TNF)-α to induce the secretion of inflammatory chemokines and membrane expression of ICAM-1. Co-treatment with IL-17, IL-36 and TNF-α of keratinocytes resulted into secretion of increased amount of the angiogenic factors of the vascular endothelial growth factor (VEGF) family. However, IL-36 and not VEGF-A derived from IL-17-treated keratinocytes was responsible for HDMEC proliferation and ICAM-1 expression.

Conclusion. Our data demonstrated that IL-17 and IL-36 are highly involved in endothelial cells/keratinocytes crosstalk in inflammatory skin and that IL-36 represents the pro-angiogenic mediator of IL-17.