ACNE, ROSACEA, AND RELATED DISORDERS (INCLUDING HIDRADENITIS SUPPURATIVA)

EFFECT OF ORAL ISOTRETINOIN ON THE NUCLEO-CYTOPLASMIC DISTRIBUTION OF FOXO1- AND FOXO3 PROTEINS IN SEBACEOUS GLANDS OF PATIENTS WITH ACNE VULGARIS

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Background: Oral isotretinoin is the most effective anti-acne drug with the strongest sebum-suppressive effect caused by sebocyte apoptosis. It has been hypothesized that upregulation of nuclear FoxO transcription factors and p53 mediate isotretinoin-induced sebocyte apoptosis in vivo. This hypothesis has recently been challenged by studies with SZ95 immortalized sebocytes demonstrating a decrease in nuclear FoxO1 and an increase in phosphoinositide-3-kinase/AKT signalling in isotretinoin-treated SZ95 immortalized sebocytes.

Objectives: It is the aim of our study to analyse the distribution of the pro-apoptotic transcription factors FoxO1 and FoxO3 in the nuclear and cytoplasmic compartments of human sebocytes before and during isotretinoin treatment of acne patients.

Methods: Immunohistochemical analysis of skin biopsies with antibodies distinguishing phosphorylated and non-phosphorylated human FoxO1 and FoxO3 proteins was performed before initiation of isotretinoin treatment, six weeks after initiation of isotretinoin therapy, and in acne-free control patients not treated with isotretinoin.

Results: Our in vivo study demonstrates a significant increase in the nucleo-cytoplasmic ratio of non-phosphorylated FoxO1 and FoxO3 during isotretinoin treatment of acne

patients.

Conclusions: Translational evidence indicates that upregulation of nuclear FoxO1 and FoxO3 is involved in isotretinoin-induced pro-apoptotic signalling in sebocytes promoting the observed upregulation of tumour necrosis factor-related apoptosis-inducing ligand (TRAIL). Isotretinoin-mediated upregulation of p53 is a possible pathway for the promotion of FoxO expression, a potential requirement that is disturbed by Simian virus 40 large T antigen-mediated inactivation of p53 in immortalized sebocytes. Immortalized sebocytes are thus not a suitable model for studying acne treatment involving p53/FoxO/TRAIL-dependent death signalling induced by isotretinoin exposure.