Original Article

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Integrative Responses to IL-17 and TNF-α in Human Keratinocytes Account for Key Inflammatory Pathogenic Circuits in Psoriasis

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Psoriasis is a complex inflammatory disease mediated by tumor necrosis factor (TNF)-α and cytokines secreted by specialized T-cell populations, e.g., IL-17, IL-22, and IFN-γ. The mechanisms by which innate and adaptive immune cytokines regulate inflammation in psoriasis are not completely understood. We sought to investigate the effects of TNF-α and IL-17 on keratinocyte (KC) gene profile, to identify genes that might be coregulated by these cytokines and determine how synergistically activated genes relate to the psoriasis transcriptome. Primary KCs were stimulated with IL-17 or TNF-α alone, or in combination. KC responses were assessed by gene array analysis, followed by reverse transcriptase-PCR confirmation for significant genes. We identified 160 genes that were synergistically upregulated by IL-17 and TNF-α, and 196 genes in which the two cytokines had at least an additive effect. Synergistically upregulated genes included some of the highest expressed genes in psoriatic skin with an impressive correlation between IL-17/TNF-α-induced genes and the psoriasis gene signature. KCs may be key drivers of pathogenic inflammation in psoriasis through integrating responses to TNF-α and IL-17. Our data predict that psoriasis therapy with either TNF or IL-17 antagonists will produce greater modulation of the synergistic/additive gene set, which consists of the most highly expressed genes in psoriasis skin lesions.