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

MINOCYCLINE INHIBITS KERATINOCYTE PROLIFERATION VIA MODULATING CA2+/LYSOSOME/IL-1α SYSTEM

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Background: Minocycline has long been used in the treatment of acne vulgaris for its anti-bacterial and anti-proinflammatory properties. Our preliminary study found minocycline may also exert an anti-proliferative action on keratinocytes. As IL-1α, a key proinflammatory cytokine in acne pathogenesis, could modulate cell growth in various experimental models, we hypothesized that the anti-proliferative action of minocycline may be related to its regulation of IL-1α production.

Objective: We aimed to determine the anti-proliferative role of minocycline in keratinocytes and identify the underlying mechanisms.

Materials and Methods: Minocycline was administrated in HaCaT cells or skin explants co-cultured with 4% formalin-killed Propionibacterium acnes (P.acnes). Keratinocyte proliferation was determined by crystal violet, flow cytometry and immunohistochemistry analysis of Ki67. IL-1α expression was measured using ELISA and western blot. Since regulation of IL-1α production could be caspase-1 dependent or independent, we utilized inhibitors of caspase-1, lysosome phagocytosis and lysosomal enzyme activity, respectively, to address which pathway minocycline may interfere with.

Results: Cell growth decreased by over 40% when treated with 10 uM minocycline. Ki67 expression in skin explants also decreased by minocycline. Analysis of culture supernatants and cell lysis showed an over 6-fold increase in IL-1α production in cells treated with P.acnes. Minocycline could normalize the IL-1α production induced by P.acnes. Cell proliferation induced by IL-1α overexpression was decreased by 39.2±6.5%, indicating that minocycline may downregulate cell growth via modulation of IL-1α production. Moreover, IL-1α production was normalized when lysosome activation or lysosomal enzyme activity was impaired, not caspase-1. Using a fluorescent Ca2+-imaging technique, we found minocycline could inhibit Ca2+ influx induced by P.acne. This suggested that the ability to chelating calcium of minocycline may stabilize lysosome activity and thus reducing IL-1α production and cell proliferation.

Conclusions: Minocycline could exert an anti-proliferative action against keratinocytes by modulating intracellular calcium signaling to stabilize the lysosome/IL-1α system.