TITLE: Oncostatin M induction of monocyte chemoattractant protein 1 (MCP-1) in human epidermal keratinocytes is inhibited by anti-oncostatin M receptor β monoclonal antibody KPL-716

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ABSTRACT

Oncostatin M (OSM), a member of the gp130 cytokine family, is involved in T_H2 inflammation, epidermal integrity, and fibrosis. The effect of OSM on MCP-1 was evaluated with and without interleukin (IL)-4, IL-13, and anti-OSM receptor β (OSMRβ) monoclonal antibody, KPL-716, in human epidermal keratinocytes (HEK) and human dermal fibroblasts (HDF) in vitro. Cells were stimulated with OSM, leukemia inhibitory factor (LIF), IL-31, IL-13, alone or in combination, and separately with OSM, OSM+IL-4, and increasing concentrations of KPL-716. MCP-1 levels in supernatants were determined by ELISA. MCP-1 and receptor chain mRNAs were measured (Nanostring). OSM (50 ng/mL) strongly induced MCP-1 protein ($P<.05$ in HEK or HDF) and mRNA ($P<.001$ in HEK or HDF) at 24 hrs. In HEK, OSM (but not LIF or IL-31) induced phosphorylation of STAT3 or STAT1 and synergized with either IL-13 or IL-4 in elevating MCP-1 ($P<.01$). Results were similar for OSM in HDF; LIF or IL-31 minimally activated STAT3 but not MCP-1. A dose-dependent increase in MCP-1 production was

observed for IL-4 or IL-13 in combination with OSM (P<.01) but not with LIF or IL-31. OSM significantly stimulated mRNA for the receptor chains of type II IL-4 receptor (HEK, P<.05; HDF, P<.01) and type II OSM receptor (HEK, P<.05; HDF, P<.01), but not for chains of LIF receptor or IL-31RA. KPL-716 significantly attenuated the cellular MCP-1 response to OSM (P<.0001) and the synergistic response to OSM+IL-4 (at 5 and 20 ng/mL; P<.0001) in HEK. Anti-IL-31 receptor α or isotype control antibody had no significant effect on the OSM– and OSM+IL-4-induced responses. These data show that OSM synergizes with IL-4/13, and that LIF or IL-31 do not in this system. Potent inhibition of OSM activity suggests therapeutic potential of KPL-716 in T_H2-mediated diseases distinct from KPL-716 inhibition of IL-31.

KEYWORDS: Interleukins, Chemokines, Keratinocytes

DISCLOSURES:

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