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The seven-transmembrane receptor, C5L2, is a stimulatory receptor on human mast cells

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Background

Complement anaphylatoxin 5a (C5a) is a powerful inflammatory mediator involved in the pathology of inflammatory diseases such as chronic idiopathic urticaria. C5a binds to two receptors, C5aR, a G protein-coupled receptor, and C5L2, a 7-transmembrane receptor deficient in G protein coupling. The role of C5L2 in human mast cells (huMC) is unknown. We hypothesized that huMC express C5aR and/or C5L2 and C5a activates huMC to produce pro-inflammatory mediators through one or both of these receptors.

Methods

C5aR and C5L2 expression on the huMC line, LAD2, was analyzed by quantitative PCR and flow cytometry. Degranulation was measured by β-hexosaminidase assay. Eicosanoids and cytokines/chemokines production was measured by ELISA and cytometric bead array. C5L2 expression was knocked-out using C5L2 shRNA lentiviral particles (LvP) and a stably C5L2$^-$ cell line was selected for further analysis of C5L2 function.

Results

LAD2 expressed mRNA for C5aR and C5L2. However, flow cytometry analysis showed that LAD2 expressed surface C5L2 but not C5aR. C5a stimulated LAD2 to produce TNF (22±1.3pg/ml), GM-CSF (15±0.4pg/ml), MCP-1 (53±3.6pg/ml) and IP-10 (32±4.3pg/ml). C5a failed to degranulate LAD2 and generate eicosanoids. C5L2 shRNA LvP completely knocked-out C5L2 expression. C5L2-depleted LAD2 did not respond to C5a while control shRNA-treated LAD2 did.

Conclusions

LAD2 express C5L2 but not C5aR, and C5a induces production of cytokines/chemokines suggesting that C5L2 is an excitatory receptor in huMC. Knock-down of C5L2 abrogates C5a function. This is the first study to demonstrate a functional role of C5L2 in huMC. The observation that C5L2, not C5aR, may be more important in complement-mediated activation of huMC may provide novel insights into treatment of complement-mediated inflammation.

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