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Differential effects of C5a on human and mouse mast cells may be mediated by C5aR and C5L2

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Rationale

The complement anaphylatoxin 5a (C5a) is an inflammatory mediator associated with the pathology of inflammatory diseases such as sepsis. C5a mediates its pro-inflammatory effects via interaction with two C5a receptors, C5aR and C5L2. C5aR initiates G protein-coupled receptor signaling while C5L2 is not coupled to G proteins and its role in C5a-mediated immune processes is not well understood. We hypothesized that mast cells (MC) expressed C5aR and/or C5L2 and that C5a activated MC through these receptors.

Methods

Human MC (LAD2) and bone marrow-derived MC (BMMC) were stimulated with C5a and degranulation was determined by measurement of β-hexosaminidase release. BMMC were cultured from bone marrow of wild type and CL52 knock-out mice in interleukin-4 (300U/ml) and stem cell factor (50ng/ml). Tumor necrosis factor (TNF), granulocyte macrophage colony-stimulating factor (GM-CSF), monocyte chemotactic protein-1 (MCP-1) and interferon-inducible protein-10 (IP-10) production was measured by cytometric bead array. Expression of C5aR and C5L2 receptors was analyzed by quantitative PCR (qPCR) and flow cytometry.

Results

C5a (100ng/ml) stimulated LAD2 degranulation (25%) and production of TNF (22±1.3pg/ml), GM-CSF (15±0.4pg/ml), MCP-1 (53±3.6pg/ml) and IP-10 (32±4.3pg/ml). qPCR showed that LAD2 expressed mRNA for C5a and C5L2 and flow cytometry showed that LAD2 expressed surface C5L2 but not C5aR. BMMC from wild type mice expressed both C5aR and C5L2 but did not degranulate in response to C5a. However, BMMC from C5L2 knock-out mice expressed C5aR but not C5L2 and degranulated (14.5±0.8%).

Conclusions

LAD2 express C5L2 but not C5aR and respond to C5a by releasing granule contents, cytokines and chemokines suggesting that C5L2 is an excitatory receptor in human MC. BMMC expressing C5aR but lacking C5L2 degranulate in response to C5a suggesting that C5L2 may function as a decoy receptor in mouse MC. These data show the potential importance and complexity of C5a and its two receptors in immune responses.

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