A Novel Type I Cytokine Receptor Is Expressed on Monocytes, Signals Proliferation, and Activates STAT-3 and STAT-5*

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Here we report the cloning of a novel type I cytokine receptor, gp130-like monocyte receptor (GLM-R), with homology to the interleukin-6 receptor signal transducing chain, gp130, and granulocyte colony-stimulating factor receptor. Human and murine GLM-R cDNAs encode open reading frames of 732 and 716 amino acids, respectively, and the corresponding genes are located in close proximity to gp130 genes on human chromosome 5 and mouse chromosome 13. GLM-R is specifically expressed on CD14-positive cells and is up-regulated more than 50-fold upon activation of those cells. To address the question of whether GLM-R is a signaling receptor, we constructed a chimeric molecule, consisting of the extracellular domain of human growth hormone (hGH) receptor, and the intracellular domain of GLM-R. When transfected into factor-dependent 32D cells, this chimeric molecule could signal for proliferation and activate signal transducer and activator of transcription (STAT)-3 and STAT-5 upon stimulation with hGH. Thus, GLM-R is a novel signaling receptor chain potentially involved in the development and function of monocytes and macrophages.

Helical cytokines control multiple biological processes, ranging from host defense to development and body homeostasis. This family of ligands, consisting of interleukin (IL)1 2, 3, 4, 5, 6, 7, 9, 11, 12, 13, 15, 21, 23, thymic stromal lymphopoietin (TSLP), granulocyte colony-stimulating factor (GCSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), erythropoietin (Epo), thrombopoietin (TPO), prolactin (PRL), growth hormone (GH), leukemia inhibitory factor (LIF), oncostatin-M (OSM), cardiotrophin-1 (CT-1), cardiotrophin-like cytokine (CLC), ciliary neurotrophic factor (CNTF), and leptin (OB), has been a rich source of molecules with highly specific biological effects and important therapeutic potential.

The helical cytokine family is defined by a common three-dimensional structure consisting of an anti-parallel four-helix bundle with a characteristic "up-up-down-down" topology (1, 2). Unfortunately, the lack of significant sequence homology has hampered the identification of novel members of this family by homology screens and, more recently, data mining. The cognate receptors, however, form a family of so-called type I cytokine receptors and share several structural motifs, including a cytokine receptor homology (CRH) domain with 2 pairs of conserved cysteine residues and a WSXWS sequence motif in the extracellular domain (3), a single transmembrane domain, and an intracellular domain without intrinsic enzymatic activity. These features allow for homology-based identification of novel receptors, which in turn can be used as tools to subsequently identify their ligands by a variety of different screening techniques (4–6).

Ligand binding induces homo- or heteromerization of at least two receptor subunits. In the former case, two identical receptor subunits form a homodimeric receptor that is sufficient for ligand binding and signaling (e.g. GH-R) (7), while in the latter case, a ligand-specific α-chain forms a high affinity receptor only in combination with a signal transducing β-chain, which is often shared among several ω-chains (e.g. IL-3, 5 and GM-CSF) (8). In either situation, ligand binding to the receptor leads to activation of cytoplasmic tyrosine kinases of the Janus kinase (Jak) family, which associate with the receptor subunits through conserved box-1 and box-2 motifs within the membrane proximal part of the intracellular domain (9). Jak activation leads to phosphorylation of cytoplasmic target proteins, in particular the intracellular domains of the receptors and members of the STAT protein family, which are recruited to phosphoryrosines on the receptor by means of their Src homology type 2 (SH2) domains (10, 11). Phosphorylation of STATs induces dimerization and translocation to the nucleus and results in specific activation of gene transcription (12). Seven STAT proteins are known to date (STATs 1, 2, 3, 4, 5a, 5b, and 6). Analysis of animals deficient for STAT isoforms indicates that STATs mediate many of the specific effects of cytokines (13), highlighting their key importance in cytokine receptor signaling. In addition to specific target gene regulation and in combination with other signaling pathways activated by cytokine receptors, such as mitogen-activated protein kinase and phosphatidylinositol 3-kinase, STATs can contribute to anti-apoptotic and mitogenic signals upon activation (9).

EXPERIMENTAL PROCEDURES

Isolation of GLM-R cDNAs and Cloning of hGH-R-GLM-R Chimeric Receptor—Human GLM-R was first identified at the level of genomic DNA in the public data base (GenBank™ accession number AC008857). A cDNA encoding full-length human GLM-R was subsequently cloned from a pooled tissue cDNA library. Murine GLM-R was obtained by a combination of cross-species library screening and polyclonal antibody in the nucleus and results in specific activation of gene transcription (12). Seven STAT proteins are known to date (STATs 1, 2, 3, 4, 5a, 5b, and 6). Analysis of animals deficient for STAT isoforms indicates that STATs mediate many of the specific effects of cytokines (13), highlighting their key importance in cytokine receptor signaling. In addition to specific target gene regulation and in combination with other signaling pathways activated by cytokine receptors, such as mitogen-activated protein kinase and phosphatidylinositol 3-kinase, STATs can contribute to anti-apoptotic and mitogenic signals upon activation (9).
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Quantitative PCR Analysis of GLM-R Expression—Total RNA from human organs was obtained from CLONTECH (Palo Alto, CA), and total RNA from cell lines or sorted cells was isolated using the RNeasy kit and DNase I (Qiagen, Valencia, CA). Taqman™ quantitative reverse transcription-PCR using a sequence detector 7700 instrument was carried out according to the instructions of the manufacturer (Applied Biosystems, Foster City, CA). For each sample, duplicate test reactions and a control reaction into which no reverse transcriptase had been added were analyzed for GLM-R expression. Glucokinase (GK) was used as a housekeeper mRNA.

Production of Monoclonal Antibodies against GLM-R—A construct encoding the extracellular domain of human GLM-R fused to an octa-histidine tag was derived by recombinant PCR and cloned into a modified version of the pVLI393 baculovirus expression vector (BD Pharmingen, San Diego, CA). GLM-R-His6 was expressed in high-five insect cells (Invitrogen, Carlsbad, CA) and purified by nickel-nitritotriacetic acid affinity column. Monoclonal antibodies against GLM-R-His6 were raised in BALB/c mice.

Isolation of Blood Cell Subsets, FACS Analysis, and Activation of Monocytes—Heparinized blood was obtained with informed consent from healthy volunteers. 35 ml of a 1:2 dilution of blood in phosphate-buffered saline were layered over 15 ml of Ficoll-Hypaque (ICN Biomedicals, Costa Mesa, CA) and centrifuged for 30 min at 500 × g. Interphase peripheral blood mononuclear cells (PBMC) were recovered and washed once with phosphate-buffered saline. For RNA isolation, leukocyte subsets were separated using paramagnetic beads coupled to various marker antibodies according to the instructions of the manufacturer (Miltenyi, Auburn, CA). For FACS analysis, PBMC were incubated for 30 min on ice in a buffer containing 10 μg/ml total human IgG and 5 μg/ml murine IgG1 (Sigma) to prevent binding of GLM-R antibodies to Fc receptors expressed on some cell types. Cells were then stained with 1 μg per million cells of biotinylated anti-GLM-R (IgG1) or biotinylated isotype control antibody for 15 min following two washes with the same buffer. In a second round of staining, cells were simultaneously incubated with streptavidin-coupled phycoerythrin and various marker antibodies directly coupled to either fluorescein isothiocyanate or CyChrome™ (BD Pharmingen). Fluorescence was detected using an Epics-XL flow cytometry system (Beckman Coulter Inc.). For stimulation experiments, isolation of monocytes from PBMC was performed by a depletion strategy employing paramagnetic beads coupled to antibodies against CD3, CD7, CD19, CD45RA, CD56, and IgE (Miltenyi). We chose this approach to avoid activation of monocytes by ligation of the CD14 antigen, which would occur in a positive selection approach. These monocytes were stimulated in RPMI 1640 supplemented with 10% bovine calf serum (Beckman Coulter Inc.) and penicillin/streptomycin (LPS) (Sigma) and 100 ng/ml interferon-γ (IFN-γ) (R&D Systems, Minneapolis, MN) for 4 h.

Culture and Transfection of 32D Cells—32D cells were maintained in RPMI 1640 supplemented with 10% bovine calf serum, 1-glutamine and penicillin/streptomycin (Invitrogen). Conditioned medium from WEHI-3B cells was used as a source of IL-3 and added to the culture at 5–10% final concentration. Cells were transfected by electroporation and bulk selected in 0.4 mg/ml G418 (Invitrogen) for 10 days. G418-resistant cells were then stained with a monoclonal antibody against hGH-R (Genentech, South San Francisco, CA), and single positive cells were sorted by FACS into individual wells of 96-well plates. After 1 week of expansion, clones were re-examined by FACS for hGH-R surface expression and by proliferation assay for factor dependence. Three clones with significant hGH-R expression and low background proliferation were selected for further experiments.

Proliferation Assay—Cells were starved for 20 h in complete medium without growth factors at a density of 5 × 10^3 cells/ml. Subsequently, 5 × 10^3 cells were co-cultured with 96-well plates containing different concentrations of hGH- or WEHI-3B-conditioned supernatants or their dilutions. Cells were allowed to proliferate for 22 h with addition of 1 μCi of [3H]thymidine per well during the last 6 h of the incubation period. Thymidine incorporation was determined using a Top Count liquid scintillation counter according to the manufacturer’s instructions (Packard Instruments, Meriden, CT).

Analysis of STAT Activation—10^5 cells per condition were washed
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RESULTS

We first identified GLM-R by screening the public human genomic data base for molecules with cytokine receptor homology domains and used this sequence information to clone the corresponding human cDNA from a pooled tissue library. Only one major open reading frame was present, and it encoded a protein of 732 amino acids (aa) residues with characteristic features of type I cytokine receptors (Fig. 1A). A predicted signal peptide of 19 aa is followed by a cytokine receptor homology domain (aa 20–227) with two pairs of conserved cysteines and a WSDWS signature motif. Three modules with homology to fibronectin type III domains (aa 228–324, 325–420, 421–516) complete the extracellular domain, and a single transmembrane region (aa 517–539) connects to an intracellular domain of 193 amino acids (aa 540–732). Within the cytoplasmic tail, a box-1 motif (aa 550–563) typically involved in the association with cytoplasmic tyrosine kinases of the Jak family, and four tyrosine residues that may serve as docking sites for downstream signaling molecules with SH2 domains are present.

A slightly shorter murine homolog of 716 amino acids was cloned from a spleen library and shows 59.1% identity and 67.5% similarity to the human molecule (Fig. 1B). All hallmark features except the second pair of cysteines and two cytoplasmic tyrosine residues are conserved between the two sequences. The lack of the cysteines in the murine protein does not appear to be due to alternative mRNA splicing, since analysis of murine genomic sequences did not reveal the presence of an alternative exon with those features (not shown).

Human GLM-R is most homologous to the IL-6 signal transducer chain, gp130 (19), at 24.73% identity, followed by GCSF-R (20) and IL-12Rβ2 (21) (23.94 and 20.09% identity, respectively) (Fig. 1C). Interestingly, analysis of genomic sequences indicated that GLM-R and gp130 are separated by only 24 kilobases (kb) on human chromosome 5, and by 19 kb in a synthetic region on mouse chromosome 13. In light of the relatively low level of sequence conservation, this chromosomal localization pattern further confirms that mGLM-R and hGLM-R are true homologs.

To gain insight into the potential function of this receptor, we next sought to determine the expression pattern of GLM-R. The abundance of this transcript was generally so low that we were unable to reliably detect it by Northern blot analysis in any organ (not shown). Supporting low expression levels is a total lack of human expressed sequence tags (EST) corresponding to GLM-R in the public data base. We therefore analyzed GLM-R expression in a comprehensive panel of human total RNAs by real time quantitative PCR (Taqman™), using primers located in exon 11 (Fig. 2A). Highest levels of GLM-R transcript were detected in testis, prostate, thymus, bone marrow, and trachea. GLM-R amplification product from testis RNA became detectable after 25 cycles of PCR (thymus, 26 cycles; prostate, 27 cycles), whereas rpl-19 amplification product was detectable after 18 cycles (thymus, 17 cycles; prostate, 18 cycles). Therefore, GLM-R expression in testis was roughly 22- or 128-fold lower than rpl-19 expression (thymus, prostate, 28- or 512-fold lower). Using a similar calculation, it can be determined that in most tissues, GLM-R is expressed at 103-105-fold lower levels than rpl-19.

Because type I cytokine receptors frequently play a role in blood cell development and function, and because GLM-R expression levels were comparably high in thymus and bone

FIG. 2. Expression pattern of GLM-R by Taqman™ and FACS. In panels A, B, D, and E, GLM-R mRNA expression levels are given as arbitrary units calculated from the expression of GLM-R mRNA and expression of a housekeeping gene mRNA, rpl-19. A, tissue distribution of GLM-R transcripts in human organs. B, expression of GLM-R in sorted human blood cells. C, detection of GLM-R expression by FACS on human blood cells. Freshly isolated PBMC were double stained with biotinylated antibodies and streptavidin-conjugated phycoerythrin in combination with marker antibodies coupled to fluorescein isothiocyanate or CyChrome. Histograms are gated on cells positive for the indicated markers. Gray histograms, stained with biotinylated isotype antibody; white histograms, stained with biotinylated anti-GLM-R. D, expression of GLM-R in human cell lines. E, up-regulation of GLM-R transcripts in monocytes from three healthy volunteers upon activation with LPS/IFNγ for 4 h. ND, not detectable.
marrow, we were interested in the expression of GLM-R on different blood cell types. To this end, we isolated PBMC from healthy human volunteers by Ficoll density gradient centrifugation, and separated the different cell subsets using paramagnetic beads coupled to antibodies against CD4 (helper T cells), CD8 (cytotoxic T-cells), CD14 (monocytes), CD19 (B-cells), and CD56 (natural killer cells). Taqman™ PCR was then performed on RNA isolated from those cell fractions, using primers located in exon 11 of human GLM-R (Fig. 2B). Again, the absolute levels of GLM-R expression were low, but CD14-positive and, to a lesser extent, CD56-positive cells displayed significantly higher expression than CD4-, CD8-, or CD19-positive cells. This expression pattern was confirmed by FACS analysis with monoclonal antibodies raised against the extracellular domain of GLM-R. GLM-R protein was only detectable at low to moderate levels on CD14-positive cells, and was barely detectable on CD56-positive cells. No GLM-R was expressed on CD4-, CD8-, or CD19-positive cells. Similar results were obtained from four independent blood donors, and a representative set of histograms is shown in Fig. 2C. Compatible with the monocytesspecific expression of GLM-R, we found high levels of GLM-R transcripts in two monocytic human cell lines, THP-1 and U937 (Fig. 2D), whereas all other cell lines tested did not express GLM-R. Finally, we found that GLM-R was induced between 56- and 91-fold in freshly isolated human monocytes after 4 h of stimulation with a combination of 1 μg/ml LPS and 100 ng/ml IFN-γ (Fig. 2E). Again, GLM-R induction was confirmed at the protein level by FACS (not shown). Up-regulation of GLM-R was not observed upon activation of T or B cells with appropriate stimuli, suggesting that this is a phenomenon restricted to monocytes (not shown).

To address whether GLM-R is capable of transmitting a signal upon activation, we constructed a chimeric molecule consisting of the extracellular and transmembrane domains of human GH (hGH) receptor, joined to the cytoplasmic region of human GLM-R (Fig. 3A). This construct was stably transfected into IL-3-dependent murine 32D cells (22), and three clones staining positive with an anti-hGH-R antibody were used for further analysis (Fig. 3B). All clones gave comparable results in subsequent assays.

First, we examined whether the hGH-R/GLM-R chimera could signal for proliferation when stimulated with hGH (Fig. 3C). We found that only hGH-R/GLM-R-transfected cells were able to proliferate in a dose-dependent manner in response to hGH, while both transfected and parental cells proliferated comparably in IL-3 (Fig. 3D).

The Jak/STAT pathway is critical for transmitting the signal generated by cytokine receptors (9), and STAT proteins were

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**Fig. 3.** Introduction of the hGH-R/GLM-R chimeric receptor into 32D cells and proliferation assay. A, sequence of the junction of hGH-R transmembrane domain and GLM-R intracellular domain. The amino acids predicted to be within the transmembrane (tm) region are boxed. B, FACS analysis of 32D cells overexpressing the chimeric receptor. Cells were stained with a monoclonal anti hGH-R antibody or an isotype control antibody (black), followed by a fluorescein isothiocyanate-coupled goat anti-mouse antibody. C and D, thymidine incorporation in response to growth hormone- (C) or WEHI-3B-conditioned medium (D). A representative experiment is shown. Circles, parental 32D cells; squares, hGH-R/GLM-R-transfected cells.

**Fig. 4.** STAT activation by the hGH-R/GLM-R chimera. A and B, electrophoretic mobility shift assay using the m67 (A) and βCAS (B) probes. Cells were stimulated with 10 ng/ml IL3 or 100 ng/ml hGH, and complexes were supershifted with polyclonal antibodies as indicated. C, tyrosine phosphorylation of STAT-3 and STAT-5. Phosphorylated proteins were immunoprecipitated from stimulated cell lysates with anti-phosphotyrosine antibodies and detected by Western blot, using polyclonal antibodies specific for STAT-3 and STAT-5.
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Previously shown to transmit many of the specific effects of cytokines (13). To analyze which of the STAT proteins are activated upon stimulation of the chimeric receptor with hGH, we performed EMSA. We used a mutated form of the serum-inducible element of the fos promoter (m67) (17) to test for STAT-1, STAT-3, and STAT-4 activation, and the mammary gland factor response element of the β-casein gene (βCAS) (18) to test for STAT-5 and STAT-6 activation. Upon hGH stimulation, hGH-R-GLM-R-transfected cells displayed formation of a strong complex on the m67 probe, while parental cells did not respond. This complex was completely supershifted with an antibody against STAT-3 (Fig. 4A). A less intense yet clearly identifiable complex was present when extracts were incubated with the βCAS probe, and this complex was supershifted completely with an antibody against STAT-5 (Fig. 4B). STAT-3 and STAT-5 were also activated upon stimulation with IL-3 in both parental and transfected cells, as described previously (23, 24) (Fig. 4, A and B). To exclude the presence of interferon-stimulated gene factor 3, a complex containing activated STAT-1 and STAT-2, we also tested our extracts on the interferon-stimulated response element (ISRE) (25) probe, but did nor observe any hGH-specific gelshifts (not shown). Thus, no STAT molecules other than STAT-3 and STAT-5 are activated by hGH-R-GLM-R under these conditions. Specific activation of STAT-3 and STAT-5 upon activation of hGH-R/GLM-R was confirmed by phosphotyrosine immunoprecipitation followed by Western blot with antibodies specific for STAT-3 and STAT-5 (Fig. 4C).

**Discussion**

Here we describe a novel molecule that displays the typical architecture and structural features of type I cytokine receptors. It shares significant homology to known members of this receptor family, most notably gp130 and GCSF-R and is found in close physical proximity to gp130 on human chromosome 5 and mouse chromosome 13.

GLM-R was found to be expressed predominantly on activated monocytes. In support of this finding, GLM-R was expressed in two monocytic cell lines, THP-1 and U937, but not in a number of other cell lines of lymphoid and myeloid origin. Furthermore, strong induction of GLM-R upon stimulation with LPS and IFNγ was seen in monocytes and in the two cell lines (not shown). Together, these expression data suggest that monocytes and possibly macrophages are a likely site of physiologic activity of this receptor, and prompt further analysis of the subtle balance of STAT activation.

Taken together, our data suggest that GLM-R is a receptor for a yet unknown helical cytokine that likely acts on monocytes and possibly also macrophages. Using the receptor as a tool, it will hopefully be possible to identify this ligand, which is critical to the further understanding of the biological function of GLM-R.

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