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A Soluble Form of IL-13 Receptor α1 Promotes IgG2a and IgG2b Production by Murine Germinal Center B Cells

Johanne Poudrier,* Pierre Graber,* Suzanne Herren,* Denise Greten,* Greg Elson,*† Claude Berney,* Jean-François Gauchat,*† and Marie H. Kosco-Vilbois2*

A functional IL-13R involves at least two cell surface proteins, the IL-13Rα1 and IL-4Rα. Using a soluble form of the murine IL-13Rα1 (sIL-13R), we reveal several novel features of this system. The sIL-13R promotes proliferation and augmentation of Ag-specific IgM, IgG2a, and IgG2b production by murine germinal center (GC) B cells in vitro. These effects were enhanced by CD40 signaling and were not inhibited by an anti-IL4Rα mAb, a result suggesting other ligands. In GC cell cultures, sIL-13R also promoted IL-6 production, and interestingly, sIL-13R-induced IgG2a and IgG2b augmentation was absent in GC cells isolated from IL-6-deficient mice. Furthermore, the effects of the sIL-13R molecule were inhibited in the presence of an anti-IL-13 mAb, and preincubation of GC cells with IL-13 enhanced the sIL-13R-mediated effects. When sIL-13R was injected into mice, it served as an adjuvant-promoting production to varying degrees of IgM and IgG isotypes. We thus propose that IL-13Rα1 is a molecule involved in B cell differentiation, using a mechanism that may involve regulation of IL-6-responsive elements. Taken together, our data reveal previously unknown activities as well as suggest that the ligand for the sIL-13R might be a component of the IL-13R complex or a counterstructure yet to be defined. The Journal of Immunology, 1999, 163: 1153–1161.

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3 Abbreviations used in this paper: GC, germinal center; sIL-13R, soluble IL-13 receptor; LD, low buoyant density; IL-6KO, IL-6 deficient; wt, wild type; CD40L, CD40 ligand; FDC, follicular dendritic cell; LN, lymph node.
ROLE OF IL-13Rα1 IN MOUSE GERMINAL CENTER B CELL ACTIVATION

A

B

C

D

E

sIL-13R:

- alone
- + anti-IL-4R

F

G

CT4S proliferation (cpm)

IL-4 concentration (pg/ml)

no sIL-13R
+ sIL-13R (10 µg/ml)
recently found that a soluble form of IL-13Rα1 is immunoprecipitated from activated human T cell supernatants (35). Soluble forms of IL-13Rα2 have also been identified in mouse urine and serum (22). These observations suggest that their might be other ligands or functions for the IL-13R. Indeed, the data reported here using a soluble form of the murine IL-13Rα1 (sIL-13R) suggest a novel role for this protein in B cell activation and differentiation.

Materials and Methods

**Mouse, Ags, and immunizations**

Animals were kept under specific pathogen-free conditions. Male BALB/c mice (Janvier, France) were used between 8–12 wk of age. Male BALB/c mice (Janvier, France) and IL-6 deficient (IL-6KO; C57BL/6) mice were gifts from Dr. Manfred Kopf (Basel Institute for Immunology, Basel, Switzerland) (38), were used between 8–12 wk of age. Mice received either a single dose of DNP-OVA (300 µg) s.c. and were sacrificed on day 7, or were primed and boosted as stated above and sacrificed on day 5.

**Abs and reagents**

The Abs and visualizing reagents included GK1.5 (rat anti-mouse CD4), 53.6.78 (rat anti-mouse CD8), T24 (rat anti-mouse Thy 1), and MS-114 (rat anti-mouse MHC II) from the American Type Culture Collection (Manassas, VA). 209 mAb (FDC-M2, rat anti-mouse FDC) (29), goat anti-mouse IgM Texas Red, Cy5-streptavidin, and FITC-streptavidin (Southern Biotechnology Associates, Birmingham, AL), mouse anti-rat IgG F(ab')2-FITC (Jackson ImmunoResearch Laboratories, West Grove, PA); and rat IgG2b anti-mouse IL-13 (R&D Systems, Abingdon, U.K.). The rat IgG2b anti-mouse IL-6 mAb as well as a biotinylated anti-IL-6 Ab used for detection of IL-6 by ELISA were purchased from PharMingen (San Diego, CA). The rat IgG2b anti-mouse IL-6Rα and rat IgG2b anti-mouse neutralizing IL-4Rα mAbs were obtained from Genzyme (Cambridge, MA). The neutralizing activity of the anti-IL-4Rα mAb was verified on the IL-4-dependent cell line CT4S (data not shown). FJK-45 (rat anti-mouse CD40) was a gift from Dr. T. Rolink (Basel Institute for Immunology). The murine rIL-2 protein was generated in-house. Mouse rIL-4 was purchased from ImmunoKontakt (Frankfurt am Main, Germany), while rIL-6 and rIL-13 were obtained from PharMingen and R&D Systems, respectively. The generation of the soluble human CD40 ligand (sCD40L) has been reported previously (39). Rat IgG1, rat IgG2a, and rat IgG2b (Serotech, Oxford, U.K.) were used for isotype controls (data not shown).

**mRNA for IL-6**

Semiquantitative RT-PCR was performed as described previously (40, 41).

**Production of rsIL-13R**

*Source of cells and culture conditions.* The cell lines HEK-293, COS7, and SP9 were obtained from the American Type Culture Collection and cultured according to their specifications. The EBNA-1-expressing HEK-293 derivative was maintained according to the instructions of the supplier (In vitr ogen, L eek, T he Neth erlands).

**Production of sIL-13R.** To produce a cDNA derivative encoding a tagged form of the cytoplasmic region of the mouse IL-13Rα1, murine spleen cDNA (17) was subjected to RT-PCR using a mix of the primers AGGGCGTGCAGGCGGCGCCAGCGCCTGCTG and AAAACTTCTCACAGGGTCACATGGGAAGGAACAG. The amplified mouse IL-13Rα1 cDNA was cloned into the vector pcR2.1 (Invitrogen) and fully sequenced. To generate a cDNA derivative encoding a soluble derivative of mIL-13Rα1, the cDNA fragment in pcR2.1 was digested with the restriction enzymes AccI and BamHI and ligated to a synthetic DNA fragment:

1. CTACACACTG AGAGATGAGG TCAGACAGA GTGATTGATT GTACAGAGA CAAACACTG ACTGAGTCG
2. GACAGGTG ATGGCAAGAC AGAGATTGAG TTGAGAAGCT ACCCAGAGAA ATCCAGACTC
3. CTCACTACCT TCACACAGCT ATTGCTCAGT TGGTGGTAGG TTAGTGGAT
4. CAGGCGGCGCCAGCGCCTGCTG
5. AAAACTTCTCACAGGGTCACATGGGAAGGAACAG

which had been produced by annealing and ligation of 5’ phosphorylated oligonucleotides. The insert was checked by DNA sequencing. The modified cDNA encodes for the extracellular domain of the murine IL-13Rα1
The sIL-13R binds to GC cells and promotes IL-6 production. A, GC cells cultured for 2 days were incubated with sIL-13R followed by the biotinylated mAb 179 (anti-Tag) and FITC-streptavidin. Gating on the large blast cell population using FACS revealed sIL-13R binding (open area) vs the control (filled area; mAb 179 and FITC-streptavidin). B, The sIL-13R promotes IL-6 secretion in GC cultures. GC cells were cultured with and without sIL-13R (10 μg/ml), in the presence or the absence of CD40 stimulation (anti-CD40, 10 ng/ml). The level of IL-6 in 7-day culture supernatants was measured by ELISA and compared with that in a standard rIL-6 control culture. The data are representative of four experiments. *, p < 0.005 between medium alone/sIL-13R; **, p < 0.015 between sIL-13R/rIL-6 and anti-CD40.

followed by six histidines and the tag CLEPYTACD, an epitope recognized by a specific mAb (mAb 179, Affymax, Palo Alto, CA). The soluble murine IL-13Rα1 cDNA insert was recloned in pFastBac1 (Life Technologies, Basel, Switzerland) using the restriction enzymes KpnI and NotI. Recombinant baculovirus was generated with a BAC-TO-BAC kit (Life Technologies) and used to infect SF-9 cells expanded in SF900II medium (Life Technologies). The SF-9 culture medium was concentrated, filtered, and applied to a column packed with 50 ml of Ni-NTA-resin (Qiagen, Basel, Switzerland) pre-equilibrated in 50 mM Tris-HCl (pH 7.5), 300 mM NaCl, and 10% glycerol; buffer I. The resin was first washed with 500 ml of buffer I supplemented with 0.1% (w/v) Tween-20, followed by a second 500-ml wash with buffer I. The bound proteins were eluted with buffer I containing 500 mM imidazol. The eluate was then dialyzed against 0.1 M Tris-HCl (pH 7.5). The recovered fraction contained ~80% of monomeric sIL-13Rα1 as verified by SDS-PAGE. The LPS content measured as described previously (42) was 1.6 EU/mg. To use the molecule in bioassays, the sIL-13R was generated to be LPS free, as reported previously (35). This soluble form comprises the extracellular domain of the IL-13Rα1 cDNA insert cloned in pFastBac1 (Life Technologies). Briefly, following enzymatic digestion with collagenase 4188 (Worthington Biomedical, Freehold, NJ) plus DNase I (Sigma, St. Louis, MO), the low density (1.060–1.065 g/ml) cells were isolated on Percoll (Pharmacia, Uppsala, Sweden) gradients, and adherent cells were removed following a 1-h incubation at 37°C. The resulting population has been previously shown to contain >75% B cells, 10% T cells, 10% FDC, and <5% tingible body macrophages (43).

Assessment of proliferation and Ag-specific Ab production
GC cells or LD B cells were cultured in round-bottom 96-well plates at a density of 2 × 10^5 cells/well, in Iscove’s modified Dulbecco’s medium (Life Technologies, Paisley, Scotland) supplemented with 5% FCS (CanSera, Rexdale, Ontario), L-glutamine (Life Technologies), 2-ME, and antibiotics. Proliferation was assessed by the incorporation of [3H]thymidine (Amersham, Aylesbury, U.K.) for the final 18 h of a 42-h culture period.
Ab titers in day 7 cell culture supernatants were assayed by using standard ELISA procedures. Briefly, DNP- or OVA-specific Abs were detected using either DNP-BSA or OVA (1 μg/ml)-coated flat-bottom 96-well plates (Nalge Nunc International, Naperville, IL), respectively. HRP-coupled goat anti-mouse IgM, IgG1, IgG2a, and IgG2b Abs (Southern Biotechnology Associates) were used to reveal individual Ig isotypes. O-phenylenediamine (Sigma) was used as the substrate. Data are represented as OD read out at 490/570 nm. For all experiments, an inactivated form of sIL-13R was added to the cultures and was shown to have no effect (data not shown).

Assessing sIL-13R activity in vivo

The sIL-13R was injected into wt and IL-6KO mice, according to the following protocol. On day 0, mice received 200 μg of OVA s.c. together with 100 μg of either sIL-13R or an inactivated form of sIL-13R (boiled at 100°C for 10 min). On days 2 and 4, 100 μg of either sIL-13R or inactivated sIL-13R was injected s.c. Mice were then sacrificed on day 7 after the primary immunization.

Detection of sIL-13R binding by FACS

GC cells were incubated with the tagged sIL-13R (40 μg/ml) for 1 h on ice. Binding was subsequently revealed using the biotinylated anti-Tag mAb 179 and FITC-streptavidin. Immunolabeling was performed on ice in FACS buffer (1× PBS, 1% BSA, and 0.01% sodium azide), and the fluorescence intensity was analyzed using a FACS Calibur (Becton and Dickinson, San Jose, CA).

Statistics

Statistical analyses were performed according to Student’s t tests.

Results

The sIL-13R promotes IgG2a and IgG2b isotype production by murine GC cells

To explore the possible role of IL-13R in B cell activation, the effect of sIL-13R was investigated using murine GC cells. As shown in Fig. 1, the addition of sIL-13R enhanced the ability of GC cells to produce Ag-specific IgM, IgG2a, and IgG2b. Furthermore, CD40 stimulation slightly enhanced this effect. In contrast,

![Graph](image1.png)

**FIGURE 5.** Effect of injecting sIL-13R in vivo. The wt and IL-6KO mice were immunized with OVA (100 μg/mouse; day 0) and coinjected with either sIL-13R or an inactivated form of sIL-13R (100 μg/injection; days 0, 2, and 4). Mice were sacrificed on day 7, and GC cells were isolated from draining LNs. Cells were cultured for 7 days, and the OVA-specific Ab levels within these supernatants were assayed by ELISA. The results are representative of the mean for three mice per group. ***, p = 0.005; **, p = 0.003; *, p = 0.002 (compared with the control group).

![Graph](image2.png)

**FIGURE 6.** The sIL-13R-induced proliferative responses occur independently of IL-6. GC cells isolated from wt (A and B) and IL-6KO mice (A) were cultured with either medium alone or with mouse sIL-13R (10 μg/ml; A and B) in the presence or the absence of neutralizing anti-IL-4Ra mAb used at 10 μg/ml (B). [3H]Thymidine ([3H]Tdr) incorporation (counts per minute) was measured after 2 days. *, p < 0.005 compared with medium alone.
IgG1 production was not influenced by sIL-13R, with or without CD40 costimulation (for p values, see Fig. 1). Because IL-13Rα1 has been reported to associate with the IL-4Rα chain (44), the effect of blocking with a neutralizing anti-IL-4Rα mAb was tested. However, this had no effect on the sIL-13R activity (Fig. 1E). This result is in agreement with the observation that sIL-13R does not bind to IL-4Rα-transfected cells (data not shown). Furthermore, sIL-13R did not increase the proliferative response by the IL-4-dependent cell line, CT4S (Fig. 1F). Finally, sIL-13R had no effect on the IL-2-dependent parent cell line, CTLL (Fig. 1G). These results show that sIL-13R does not compete or synergize with IL-4 for signaling in an IL-4Rα-dependent manner.

The sIL-13R activity is linked to IL-6

It has been reported that both IgG2a and IgG2b secretion are selectively impaired in IL-6KO mice (45). These results prompted us to investigate whether sIL-13R was working through a pathway involving IL-6. The results presented in Fig. 2 show that blocking IL-6 responses using either anti-IL-6R- or anti-IL-6-neutralizing mAbs impaired in vitro production of IgG2a and IgG2b by GC cells without similarly affecting IgG1 production. IgM production was also decreased by both mAbs (data not shown). The sIL-13R activity was decreased in the presence of these mAbs, suggesting that the sIL-13R might use an IL-6-dependent pathway. Isotype control mAbs did not generate this effect (data not shown).

The sIL-13R binds to GC cells and promotes IL-6 secretion

By flow cytometry, it was determined that the large GC cell population could bind sIL-13R after culture for 24 and 48 h (data not shown and Fig. 3A). In addition, IL-6 production was increased by a mean of 30% when GC cells were cultured with sIL-13R (Fig. 3B). The level of IL-6 ranged from 1–25 ng/ml. These results concur with our recent findings that the recombinant human sIL-13R molecule binds to human monocytes and promotes IL-6 production (see Footnote 4). Finally, CD40 stimulation also promoted IL-6 secretion and together with sIL-13R triggered a greater production than either stimulus alone (Fig. 3B). The data were confirmed by PCR analysis at the RNA level (data not shown).

GC cells from IL-6ko mice are unresponsive to sIL-13R

Considering our observations that sIL-13R promoted the production of both IgG2a and IgG2b, and that this effect could be neutralized with anti-IL-6 reagents, GC cells isolated from IL-6-deficient mice were studied. As shown in Fig. 4A, the sIL-13R-mediated effect was only observed in the presence of rIL-6. Similar results were obtained for IgG2a responses (data not shown). In addition, in cultures of purified B cells that do not secrete IL-6

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FIGURE 7. The effects of sIL-13R are related to the presence of IL-13. GC cells isolated from wt mice were incubated with or without sIL-13R (10 μg/ml; A and B) in the presence or the absence of a neutralizing anti-IL-13 mAb (10 μg/ml; A) or rIL-13 (10 ng/ml) that had been preincubated with the GC cells for 1 h on ice before culture (IL-13; B). The presence of DNP-specific Ab levels in day 7 supernatants was assayed by ELISA. *, p < 0.005 compared with sIL13R alone.

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Effects was assessed. As shown in Fig. 7, the possible involvement of IL-13 in generating the sIL-13R effect on IgG2b production was observed in GC cells isolated from wt and IL-6KO mice injected with both sIL-13R and Ag compared with that in cells from mice given the inactivated form. Surprisingly, the sIL-13R had opposite effects on IgG1 levels, with an enhancement in the IL-6KO cells vs a decrease in cells in wt mice. Taken together, these experiments suggest that sIL-13R might act as an adjuvant for Ab production. The mechanism may be associated with regulating members of the IL-6R/gp130 family or, alternatively, an unknown counterstructure that also uses IL-6 signaling pathways.

Proliferative responses induced by sIL-13R are not IL-6 dependent

Next, the effect of sIL-13R on GC cell proliferation was assessed. In contrast to the in vitro effects of sIL-13R on Ab production, sIL-13R augmented the proliferation of GC cells isolated from either wt or IL-6KO mice (Fig. 6A). The sIL-13R-induced proliferation was also not inhibited by blocking of the IL-4Rα (Fig. 6B). Similarly, purified LD B cells were also induced to proliferate with sIL-13R in the absence of IL-6 (data not shown).

IL-13 is involved in the sIL-13R-mediated increase of IgG2a and IgG2b

The possible involvement of IL-13 in generating the sIL-13R effects was assessed. As shown in Fig. 7A, the sIL-13R-mediated increase in both IgG2a and IgG2b secretion by GC cells was inhibited in the presence of a neutralizing anti-IL-13 mAb. IgG1 production was not affected. This suggested that the ligand to which sIL-13R binds may involve IL-13. To test this hypothesis GC cells were preincubated with IL-13 for 1 h, and then the sIL-13R was added. As shown in Fig. 7B, this protocol greatly enhanced the effect of sIL-13R alone. IgG1 levels were not affected. This increase in IgG2a and IgG2b production by cells preincubated with IL-13 may be the consequence of receptor-ligand interactions that involve IL-13 on either B cells or other cell types within the GC cultures.

Discussion

In an attempt to understand the biological significance of the IL-13R in B cell activation, a soluble form of the IL-13Rα1 chain was generated. Using this, we observed that LD B and GC cell proliferation is induced and IgM, IgG2a, and IgG2b production is promoted, without modifying IgG1 secretion. The results from the in vitro experiments at first suggested that sIL-13R signaling was independent on IL-6. However, as IgG2a and IgG2b responses were reconstituted in IL-6KO mice that had been injected with sIL-13R, and also that sIL-13R induced proliferation of IL-6KO GC cells and purified LD B cells, the latter incapable of producing IL-6, the data, rather, support a role for sIL-13R in regulating the expression of IL-6R/gp130 family components. Indeed, the increased Ab production obtained following in vivo administration of sIL-13R in an IL-6-deficient environment may reflect the activity of other molecules that use IL-6R/gp130, such as IL-11, leukocyte inhibitory factor (LIF), oncostatin M (OSM), cardiomyophin-1 (CT-1), and ciliary neurotrophic factor (CNTF) receptors (46). Thus, we do not favor the idea that sIL-13R directly regulates IL-6 production. Instead, sIL-13R probably affects the IL-6R/gp130 complex, affecting IL-6 in an autocrine fashion.

The nature of the ligand for the soluble form of IL-13R has yet to be defined. However, our results suggest that it may involve IL-13 already complexed to the cell surface of GC cells. This may be via the membrane form of IL-13Rα1, especially given its specific distribution to GC B cells and FDCs (J. Poudrier et al., manuscript in preparation). Our results are consistent with an IL-4Rα-independent IL-13R-mediated signaling, because the neutralizing anti-IL-4Rα mAb did not block the effects generated by sIL-13R. The plausibility of an IL-4Rα-independent mechanism is consistent with the intracytoplasmic characteristics of IL-13Rα1. It possesses box 1-like and box 3-like motifs (17, 19–21), necessary for binding to Janus protein kinase (25) and activation of STAT3 (47), respectively. Interestingly, STAT3 is involved in gp130 signaling for regulation of IL-6 responsiveness (46, 48). This alternative receptor complex for IL-13 is possibly activated upon homodimerization and/or heterodimerization with other chains yet to be characterized. In the model presented here, sIL-13R may segregate membrane IL-13Rα1 from its usual partner, IL-4Rα (44), and provide alternative signals to GC cells than that of IL-4 (4).

A possible contribution of IL-13Rα2 in the type I IL-13R is presently under investigation. Interestingly, there is increasing evidence that IL-13Rα2 is present in human tonsilar GC B cells (21, 49). Although IL-13Rα2 does not appear to possess signaling capabilities, it could be important for strengthening binding to IL-13, as has recently been demonstrated for mouse IL-13Rα2 (23). Our views are shared by those of Donaldson et al. (23), whereby IL-13Rα2 may have a complementary role with membrane IL-13Rα1 in facilitating the formation of a high affinity IL-13R signaling complex. The possibility that sIL-13R binds directly to IL-13Rα1 or IL-13Rα2 chains has been ruled out by binding experiments on transfectants (see Footnote 4; J.-F. Gauchat, unpublished observations). However, it is possible that either IL-13 or another component is required to generate a complex involving sIL-13R that would bind to these surface receptors.

Until now, the similarities between IL-4 and IL-13 activities have been explained by the fact that both IL-4 and IL-13 can signal through the type II IL-4R. This is composed of the IL-4Rα and IL-13Rα1 chains (44). However, the possibility that the IL-13Rα1 may provide STAT3 signaling elements could reconcile observations for the distinctive biological patterns seen between IL-4 and IL-13. For example, it has been shown recently that the clearing of certain pathogens was IL-13, rather than IL-4, dependent (50–53). In contrast to IL-4-deficient mice (IL-4KO), IL-13-deficient mice (IL-13KO) could not clear certain strains of nematodes (51, 53), a phenotype shared by the IL-4Rα and STAT6-deficient mice (STAT6KO) (52). These observations suggest that an IL-13-dependent signaling must occur that is undeliverable by IL-4.

The effects of sIL-13R are biologically significant, because a soluble form of IL-13Rα1 exists physiologically (35). However, these observations may also mimic homotypic interactions between GC B cells that express IL-13Rα1 on their surface (J. Poudrier et al., manuscript in preparation) and/or heterotypic interactions involving GC B cells and FDCs. Given our observation that sIL-13R increases IL-6 production by GC cells in vitro, it is possible that binding of sIL-13R on FDCs regulates IL-6 production by potentiating the expression of IL-6R/gp130 family components. The increased IL-6R/gp130 expression by B cells then allows for the production of more IgG2a and IgG2b isotypes in response to IL-6. The fact that these isotypes are generated later in
GC cell reactions is consistent with an additional round of proliferation induced by sIL-13R and the requirement for this event to induce Ig class switching (54).

These results are consistent with those of other reports showing that IL-13 can promote IL-6 production. Indeed, in vivo administration of IL-13 to mice augmented the production of IL-6 (55, 56). The effect of IL-13 in potentiating IL-6 production has also been shown in human endothelial cells (57) and human keratinocytes (58), whereas decreased IL-6 production was observed in human monocytes (1). The overall effect of IL-13 on both murine and human IL-6 production appears to vary depending on the cell population studied. Based on our data, these effects may not be direct but, instead, occur via the regulation of receptors or ligands necessary for such events to occur.

We thus provide evidence for an IL-4Rα-independent, type I IL-13R. This IL-13R seems to allow for murine B cells to respond to IL-13 and appears to be a likely candidate as a B cell differentiation molecule involved in silenced GC reactions and possibly regulating events taking place during B cell maturation. Indeed, the expression of IL-13Rα1 within lymphoid organs is restricted to B cells, follicles, and GCs, and B cell–sensitive DCs such as FDCs, but not T cells or interdigitating DCs (J. Poudrier et al., manuscript in preparation).

The observation that mice injected with sIL-13R deviate their Ag-specific production toward IgG2a and IgG2b is of interest in the field of IgE-mediated asthma. Given that IgG2a and IgG2b are the most potent at fixing complement (45), understanding the sIL-13R pathway is also of interest for defining antiviral vaccination strategies.

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