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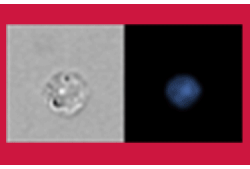
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CUTTING EDGE

Cutting Edge: Interleukin 17 Signals through a Heteromeric Receptor Complex

Dean Toy, David Kugler,* Martin Wolfson,† Tim Vanden Bos,† Jesse Gurgel,‡ Jonathan Derry,§ Joel Tocker,* and Jacques Peschon[1]**

IL-17 is an inflammatory cytokine produced primarily by a unique lineage of CD4 T cells that plays critical roles in the pathogenesis of multiple autoimmune diseases. IL-17RA is a ubiquitously expressed receptor that is essential for IL-17 biologic activity. Despite widespread receptor expression, the activity of IL-17 is most classically defined by its ability to induce the expression of inflammatory cytokines, chemokines, and other mediators by stromal cells. The lack of IL-17 responsiveness in mouse stromal cells genetically deficient in IL-17RA is poorly complemented by human IL-17RA, suggesting the presence of an obligate ancillary component whose activity is species specific. This component is IL-17RC, a distinct member of the IL-17R family. Thus, the biologic activity of IL-17 is dependent on a complex composed of IL-17RA and IL-17RC, suggesting a new paradigm for understanding the interactions between the expanded family of IL-17 ligands and their receptors. The Journal of Immunology,* 2006, 177: 36–39.

Interleukin 17 is an inflammatory cytokine initially identified as a transcript selectively expressed by activated T cells encoding a protein with significant sequence identity (~60%) to the *Herpesvirus saimiri* protein HVS13 (1). IL-17RA is a ubiquitously expressed receptor identified as a mammalian counterstructure for HVS13 and subsequently shown to bind IL-17 with high affinity (2). Leukocytes from mice lacking IL-17RA fail to bind IL-17, and Abs against IL-17RA inhibit the activity of IL-17 on human epithelial cells, indicating that IL-17RA is critical for IL-17 function (3, 4).

IL-17 is expressed by a unique lineage of CD4 T cells (Th17) that develop in response to IL-23, in particular under conditions in which Th1 and Th2 development are suppressed (5–8). Recent work indicates that IL-17 is a key mediator of autoimmune disorders, including rheumatoid arthritis, psoriasis, inflammatory bowel disease, and asthma, and plays a role in host defense (9–13).

At the time of discovery, IL-17 and IL-17RA were structurally unique and did not fall into any known cytokine or cytokine receptor families. More recently, five additional IL-17-like ligands (IL-17B–F) and four additional IL-17R-like receptors (IL-17RB–E) have been identified (9). The most recently identified ligand, IL-17F, is structurally most similar to IL-17 and is dependent upon IL-17RA for function (4, 14–16).

Based on crystallographic analyses, the homodimeric cytokines IL-17 and IL-17F have structural features in common with cystine knot family growth factors (15). Members of this family are also homodimeric and have been shown to bind and signal through both homodimeric and heteromeric counterstructures (17, 18). In contrast, additional subunits for IL-17RA or any other IL-17R family member have not been described.

We sought to establish a system whereby the function of IL-17RA could be manipulated in vitro. Mouse fibroblasts lacking IL-17RA (IL-17RA$^{-/-}$) are unresponsive to both IL-17 and IL-17F. Surprisingly, full responsiveness to either ligand is not restored following transduction of human IL-17RA. These data suggest that human IL-17RA is unable to productively associate with mouse protein(s) essential for signaling. We identify IL-17RC, a related IL-17R family member sharing 23% amino acid sequence identity with IL-17RA, as an essential component of the IL-17R.

Materials and Methods

Cytokines, Abs, ELISAs, and clones

Murine and human IL-17 and IL-17F, murine TNF, polyclonal Abs against IL-17RA and IL-17RC, and all ELISA kits were obtained from R&D Systems and used according to the manufacturer's specifications. Human IL-17:Fc and mAbs against human and mouse IL-17RA were generated internally (2, 19, 20). Multianalyte panel analyses of cell culture supernatants was performed by Rules Based Medicine. cDNAs encoding human and mouse IL-17RA have been described previously. Human IL-17RC, encoding an open reading frame identical with that previously described (isoform 2, GenBank accession no. NP_703190.1) was obtained from a human pancreas cDNA library. Human IL-17RA:Fc and human IL-17RC:Fc were prepared as described using the respective extracellular domains (2).

Cell line derivation and characterization

The generation of B6.129-Il17ra⟨tm1Koll⟩ (IL-17RA$^{-/-}$) mice has been described previously (3). Primary tail fibroblasts from age- and sex-matched C57BL/6 and IL-17RA$^{-/-}$ mice were immortalized by transduction with a SV40 large T Ag-encoding retrovirus as described (21). cDNAs encoding murine and human IL-17RA and IL-17RC were cloned into the mouse stem cell

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virus retroviral backbone, and viruses were generated and used according to the manufacturer's specifications (Clontech Laboratories). Immortalized fibroblasts were transduced with mouse stem cell viruses encoding IL-17RA or IL-17RC, selected in 5 μg/ml puromycin (InvivoGen) for 7 days, and then sorted for expression by staining with either human IL-17:Fc or a monoclonal Ab against human IL-17RA as described (2, 20).

Immunoprecipitations

HEK 293 cells were transfected with expression constructs encoding human IL-17RA and/or carboxyl-terminal Flag-tagged human IL-17RC. Cells were lysed in PBS containing 1% (v/v) Triton and Complete proteinase mixture (Roche). Lysates were immunoprecipitated on ice for 2 h with either 20 μg of anti-Flag M2 mAb or 20 μg of anti-human IL-17RA mAb. Immunoprecipitates were collected on protein A and protein G UltraLink beads (Pierce). Beads were washed in lysis buffer, and the material was resolved by electrophoresis on 4–20% SDS-polyacrylamide gels, Western blotted with goat polyclonal Abs against either human IL-17RC or human IL-17RA (R&D Systems), and developed with an Alexa Fluor 680-conjugated anti-goat Ab (Invitrogen Life Technologies).

Results and Discussion

Human IL-17RA fails to complement mouse IL-17RA deficiency

IL-17RA engagement on fibroblasts leads to the induction of inflammatory chemokine and cytokine expression (22–24). We sought to develop a system in which IL-17RA variants could be introduced into IL-17RA$^{-/-}$ fibroblasts and assayed for their ability to induce known IL-17 target genes. Immortalized IL-17RA$^{+/+}$ cells, but not IL-17RA$^{-/-}$ cells, are responsive to IL-17 and IL-17F with respect to CXCL1 expression. (Fig. 1*a*). Both populations are responsive to IL-1, indicating that IL-17RA$^{-/-}$ cells are not broadly defective in chemokine expression. Responsiveness was restored in IL-17RA$^{-/-}$ cells stably transduced with a virus encoding mouse IL-17RA. However, IL-17RA$^{-/-}$ cells stably transduced with a virus encoding human IL-17RA responded poorly to human IL-17 and IL-17F (Fig. 1*a*). Costimulation with TNF, which is known to synergize with IL-17 (25), could not reverse this defect (data not shown). These defects were not restricted to CXCL1 production as assessed using a multianalyte panel that included the known IL-17 target genes *CXCL2*, *IL-6*, and *GM-CSF* (data not shown). IL-17RA$^{-/-}$ cells expressing either mouse or human IL-17RA were equally capable of ligand binding (Fig. 1*b*). These data indicate that human IL-17RA is capable of binding IL-17 when expressed in a mouse cell but inefficiently delivers IL-17 and IL-17F signals.

IL-17RC is an essential component of the IL-17R

One explanation for the inability of human IL-17RA to efficiently signal in a mouse cell is that it is incapable of productively associating with a mouse protein(s) essential for activity. We considered the possibility that other members of the IL-17R family might associate with IL-17RA to mediate IL-17 responsiveness. IL-17RC is a widely expressed orphan IL-17R family member (26). Surprisingly, the IL-17 ligand binding defect of IL-17RA$^{-/-}$ cells can be "rescued" by transduction with a virus encoding human IL-17RC (Fig. 1*b*). These results, together with BIAcore analyses (data not shown) indicate that IL-17 is a potential ligand for IL-17RC. Despite the ability of IL-17RC to bind IL-17, IL-17RA$^{-/-}$ fibroblasts expressing human IL-17RC do not produce *CXCL1* or any other known IL-17 target genes present on the multianalyte panel in response to human IL-17 and IL-17F (Fig. 2*a* and data not shown), suggesting that this receptor is unable to mediate a classical IL-17 signal in the absence of IL-17RA. Strikingly, however, IL-17RA$^{-/-}$ fibroblasts expressing both human IL-17RA and human IL-17RC respond to human IL-17 and IL-17F (Fig. 2*a*). Thus, the failure of human IL-17RA to signal in a mouse cell can be complemented by the cointroduction of human IL-17RC. A human IL-17RC variant lacking a cytoplasmic domain remains competent to bind IL-17 at the cell surface (Fig. 1*b*) but fails to complement activity in this system (Fig. 2*a*). Mouse fibroblasts express endogenous IL-17RC mRNA (data not shown), although the observation that IL-17RA$^{-/-}$ cells fail to appreciably bind IL-17 suggests that its presence on the cell surface is low enough to escape detection by flow cytometry using IL-17:Fc (Fig. 1*b*).

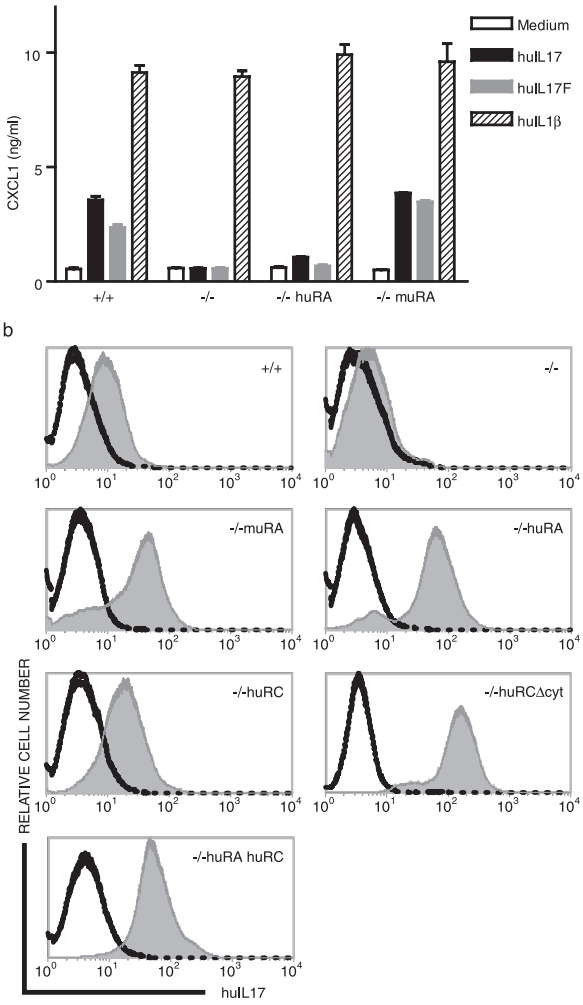

FIGURE 1. IL-17 and IL-17F responses in mouse cells lacking IL-17RA. *a*, Immortalized wild-type fibroblasts (+/+), IL-17RA-deficient fibroblasts (−/−), and IL-17RA-deficient fibroblasts stably transduced with retroviruses encoding mouse IL-17RA (−/−muRA) or human IL-17RA (−/−huRA) were stimulated in the presence of 50 ng/ml human IL-17 (huIL17) or IL-17F (huIL17F) for 18 h, and culture supernatants were assayed for the presence of CXCL1 by ELISA. Cells were independently stimulated with 1 ng/ml human IL1β (huIL1β) as a positive control. Cultures were analyzed in triplicate. Averages and SEM values are depicted. *b*, Immortalized wild-type fibroblasts (+/+), IL-17RA-deficient fibroblasts (−/−), and IL-17RA-deficient fibroblasts stably transduced with retroviruses encoding mouse IL-17RA (−/−muRA), human IL-17RA (−/−huRA), human IL-17RC (−/−huRC), both human IL-17RA and human IL-17RC (−/−huRAhuRC), or a cytoplasmic domain deletion variant of human IL-17RC (−/−huRCΔcyt) were analyzed by flow cytometry by staining with 1 μg/ml human IL-17:Fc (shaded histograms) or a negative control Fc (open histograms).

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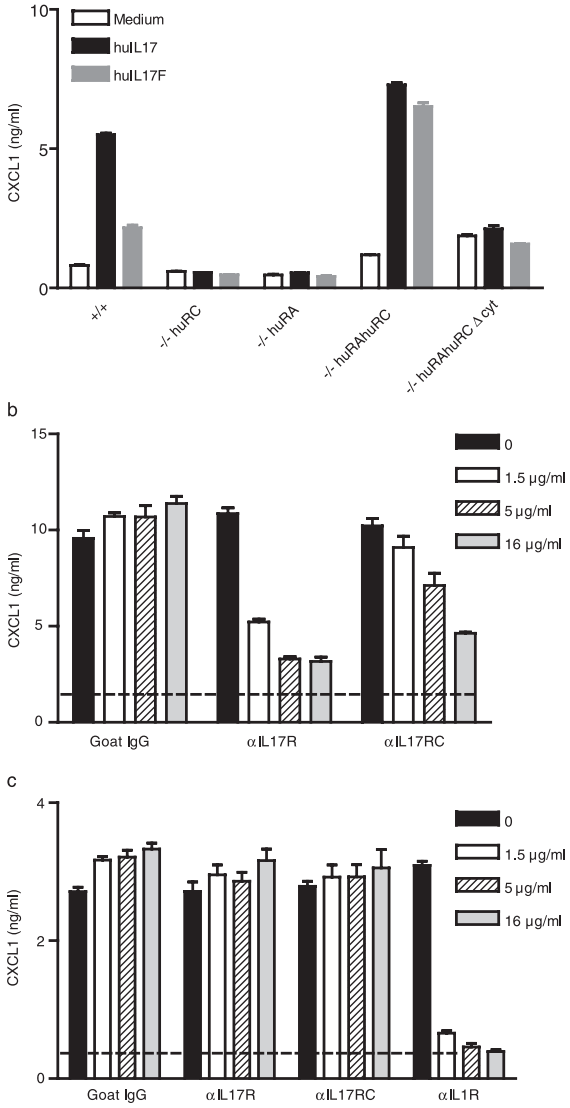

FIGURE 2. IL-17RC is a functional component of the IL-17R. *a*, Immortalized wild-type fibroblasts (+/+) and IL-17RA-deficient fibroblasts stably transduced with retroviruses encoding human IL-17RC (−/−huRC), human IL-17RA (−/−huRA), both human IL-17RA and human IL-17RC (−/−huRAhuRC), or both human IL-17RA and a cytoplasmic domain deletion variant of human IL-17RC (−/−huRAhuRCΔcyt) were stimulated in the presence of 50 ng/ml human IL-17 (huIL17) or IL-17F (huIL17F) for 18 h, and culture supernatants were assayed for the presence of CXCL1 by ELISA. *b*, Wild-type mouse fibroblasts were stimulated for 18 h with 50 ng/ml mouse IL-17 in the presence of the indicated concentrations of a control goat IgG, a mAb against mouse IL-17RA (αIL17R), or a polyclonal Ab against mouse IL-17RC (αIL17RC), and culture supernatants were assayed for the presence of CXCL1 by ELISA. *c*, Wild-type mouse fibroblasts were stimulated for 18 h with 1 ng/ml human IL1β in the presence of the indicated concentrations of a control goat IgG, a mAb against mouse IL-17RA (αIL17R), a polyclonal Ab against mouse IL-17RC (αIL17RC), or a mAb against mouse type 1 IL1R (αIL1R), and culture supernatants were assayed for the presence of CXCL1 by ELISA. The medium control CXCL1 levels are indicated with a horizontal dashed line. Cultures were analyzed in triplicate. Averages and SEM values are depicted.

To further examine a role for IL-17RC in IL-17 and IL-17F signaling in unmanipulated cells, wild-type mouse fibroblasts were stimulated with mouse IL-17 in the presence of Abs against either IL-17RA or IL-17RC. As shown in Fig. 2*b*, a polyclonal Ab against mouse IL-17RC can inhibit IL-17 responsiveness in a dose-dependent manner. This polyclonal Ab does not inhibit IL-1 responsiveness, nor does it block binding of IL-17 to mouse IL-17RA (Fig. 2*c* and data not shown), in agreement with the considerable sequence divergence between IL-17RA and IL-17RC (26). Thus, Abs against either IL-17RA or IL-17RC can specifically inhibit the activity of IL-17 on mouse fibroblasts.

IL-17RA and IL-17RC physically associate

To determine whether IL-17RA and IL-17RC physically associate within cells, native human IL-17RA and C-terminally Flag-tagged human IL-17RC were overexpressed in HEK 293 cells. Expression of each subunit was confirmed by Western blot analyses. Human IL-17RA is present in immunoprecipitates brought down with the anti-Flag monoclonal M2 Ab used to immunoprecipitate IL-17RC (Fig. 3*a*), and IL-17RC is present in immunoprecipitates brought down with an Ab against IL-17RA (Fig. 3*b*). Thus, IL-17RA and IL-17RC are capable of associating in vitro, supporting a model in which IL-17 and IL-17F signaling is mediated by a heteromeric receptor complex containing, minimally, IL-17RA and IL-17RC chains.

Implications of IL-17RA and IL-17RC association

Signaling triggered by ligand-induced activation of type 1 receptors is dependent on receptor subunit association (27). In the case of receptor homodimerization, ligand-independent signaling can be achieved by forced receptor overexpression. Ligand-independent chemokine expression is not observed in fibroblasts overexpressing either IL-17RA or IL-17RC alone (Fig. 2*a*). The observation that forced coexpression of IL-17RA and IL-17RC is also insufficient to drive ligand-independent signaling (Fig. 2*a*) suggests the possibility that yet additional

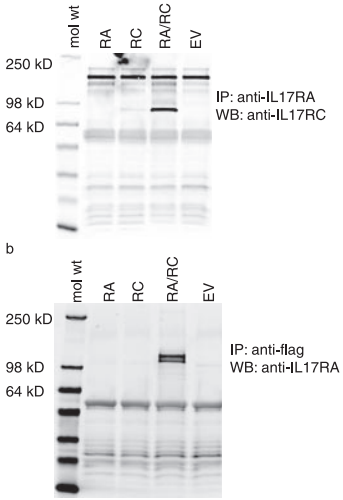

FIGURE 3. IL-17RA and IL-17RC physically associate. HEK 293 cells were transiently transfected with human IL-17RA (RA), human IL-17RC (RC), human IL-17RA plus human IL-17RC (RA/RC), or vector alone (EV). *a*, Human IL-17RC was immunoprecipitated (IP) from the indicated transfected HEK 293 lysates using an anti-Flag mAb, and the resulting immunoprecipitates were analyzed for the presence of IL-17RA by Western blot (WB) analysis. *b*, Human IL-17RA was immunoprecipitated (IP) from the indicated transfected HEK 293 lysates using an anti-IL-17RA mAb, and the resulting immunoprecipitates were analyzed for the presence of IL-17RC by Western blot (WB) analysis.

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receptor components are involved. Alternatively, ligand-induced receptor conformational changes may be essential for activity irrespective of receptor density. IL-17RA was recently shown to self-associate on the cell surface in the absence of ligand (28). Interestingly, association was reduced in the presence of IL-17. One intriguing explanation for these data is that IL-17RA is maintained in an inactive, homotypic state in the absence of IL-17. It is plausible that ligand binding alters the conformation of IL-17RA to favor a productive, heterotypic interaction with IL-17RC.

IL-17RC was recently shown to protect cells from TNF-induced apoptosis when overexpressed in transfected human cells (29). This protection is not mediated through canonical survival pathways and is apparently not dependent upon known IL-17 family ligands. Additionally, the panel of genes reported to be activated in IL-17RC-overexpressing cells does not include any of the inflammatory chemokines and cytokines classically associated with IL-17RA activation (29). These results suggest that IL-17RC may have biologic functions independent of IL-17RA. Similarly, cross-linking of overexpressed IL-17RE, a newly described orphan member of the IL-17R family, can activate a mitogenic pathway (30). Thus, the cellular outcomes of signaling through IL-17R family receptors are likely dependent upon both homotypic and heterotypic receptor interactions. The results of this report suggest that such heterotypic interactions can involve multiple IL-17R family members and provide a potential framework for elucidating the ligand specificities and biologic activities of current orphan IL-17 and IL-17R family members.

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Disclosures

D. Troy, D. Kugler, M. Wolfson, T. Vanden Bos, J. Gurgel, J. Tocker, and J. Peschon are all stockholding employees of Amgen. J. Derry was an employee of Amgen during all phases of the work described, but recently left the company.

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