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Forced Expression of Murine IL-17E Induces Growth Retardation, Jaundice, a Th2-Biased Response, and Multiorgan Inflammation in Mice

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IL-17 is a proinflammatory cytokine, and its in vivo expression induces neutrophilia in mice. IL-17E is a recently described member of an emerging family of IL-17-related cytokines. IL-17E has been shown to bind IL-17Rh1, a protein distantly related to the IL-17R, suggesting that IL-17E probably possesses unique biological functions. In this study, we have identified the murine ortholog of IL-17E and developed transgenic mice to characterize its actions in vivo. Biological consequences of overexpression of murine (m)IL-17E, both unique to IL-17E and similar to IL-17, were revealed. Exposure to mIL-17E resulted in a Th2-biased response, characterized by eosinophilia, increased serum IgE and IgG1, and a Th2 cytokine profile including elevated serum levels of IL-13 and IL-5 and elevated gene expression of IL-4, IL-5, IL-10, and IL-13 was observed in many tissues. Increased gene expression of IFN-γ in several tissues and elevated serum TNF-α were also noted. In addition, IL-17E induces G-CSF production in vitro and mIL-17E-transgenic mice had increased serum G-CSF and exhibit neutrophilia, a property shared by IL-17. Moreover, exposure to mIL-17E elicited pathological changes in multiple tissues, particularly liver, heart, and lungs, characterized by mixed inflammatory cell infiltration, epithelial hyperplasia, and hypertrophy. Taken together, these findings suggest that IL-17E is a unique pleiotropic cytokine and may be an important mediator of inflammatory and immune responses. The Journal of Immunology, 2001, 167: 6559 – 6567.

Interleukin-17 is a potent proinflammatory cytokine produced by activated T cells (1, 2). Although initially identified on the basis of homology with a protein encoded by HSV saimiri, it is now recognized as the prototype member of an expanding family comprised of at least six members (Refs. 3–5 and our unpublished observations). Subsequent characterization in vitro and in vivo has shown IL-17 to promote inflammatory responses in many peripheral tissues and to have substantial effects on hemopoiesis mediated by the induction of other cytokines, chemokines, and hemopoietic factors (6–11). In addition, IL-17 has been implicated in a number of human disease conditions, including rheumatoid arthritis, and organ transplantation (12–15). Recent members of the IL-17 family, including IL-17B, -C, and -E have also been identified on the basis of sequence homology between the family members. The biological functions of these new members remain to be characterized. However, initial characterizations suggest that each is capable of promoting the induction of other cytokines in cell culture systems (3, 5). Intraperitoneal administration of IL-17B was reported to induce neutrophil migration in mice (4).

The identification of IL-17Rh1 (also called IL-17ER, Evi27 or IL-17BR) as a receptor for IL-17E (5) and the observation that other IL-17R-like molecules are encoded in the human genome (our unpublished observations) suggest that members of the IL-17 family have a unique cognate receptor(s) and may therefore possess distinct biological functions. Interestingly, the murine ortholog of IL-17Rh1 was identified at Evi27, a common site of retroviral integration in BXH2 murine leukemias. The proviral integrations result in increased expression of the receptor, and its role in myeloid leukemia and growth and/or differentiation of hematopoietic cells has also been suggested (16). IL-17B has also been identified as a putative ligand for IL-17Rh1, although the apparent weaker binding suggests that it may use another, as yet unidentified, receptor (4). IL-17Rh1 transcripts are expressed in several adult tissues. In humans, abundant levels of IL-17Rh1 mRNA were detected in kidneys and liver, with lower abundance in testes, brain, small intestine, and other tissues. Similar expression patterns were observed in the mouse (5). Similar to IL-17, IL-17E was found capable of activation of NF-κB and stimulation of production of the proinflammatory chemokine IL-8 in cell cultures (5).

Here, we have developed a transgenic mouse model overexpressing murine (m)IL-17E (mIL-17E) under the control of the muscle myosin L chain 2 gene promoter. We found that systemic overexpression of mIL-17E up-regulates gene expression of Th2 cytokines, including IL-4, IL-10, and IL-13 in many tissues. Serum levels of IL-13 and IL-5 as well as circulating IgE and IgG1 are increased in transgenic mice. Furthermore, these profound immunological changes in mIL-17E-transgenic (TG) mice are associated with pathological changes in multiple tissues, characterized by a mixed immune infiltration and epithelial cell hyperplasia.

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3 Abbreviations used in this paper: m, murine; TG, transgenic.

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Materials and Methods

Generation of mIL-17E-TG mice

All animal protocols were approved by an institutional use and care committee. The CDNA encoding for the mature mIL-17E protein with the putative signal sequence from human IL-17E was cloned into a plasmid containing rat myosin L chain promoter sequence (17, 18), followed by a sequence derived from the human growth hormone gene including the fourth and fifth exons and 3’ untranslated region plus poly(A) to improve the expression of the transgene. The expression cassette fragment was excised and purified, and injected into one-cell mouse eggs prepared from FVB × FVB matings. Genotyping was performed by PCR analysis of the DNA from tail biopsies using primers against specific sequences in the expression cassette. Expression levels of mIL-17E were determined by Taqman RT-PCR (PerkinElmer, Norwalk, CT) on total RNA samples derived from muscle biopsy.

Determination of gene expression

Total RNA samples from various mouse tissues were prepared using TRIzol reagent according to the manufacturer’s instructions (Life Technologies, Grand Island, NY). The mRNA expression levels for various murine cytokines, chemokines, adhesion molecules, and IL-17Rhi (IL-17E receptor) were determined by Taqman RT-PCR (PerkinElmer) using gene-specific primers and probes as follows. For mIL-6: primers, 5’-AGG CAG TTA AGG ACA AA-3’ and 5’-GGT TGC CGA GTA GTG CTC AA and probe, TAMARA. For mIL-17ER: primers, 5’-GCT GGA TAC TCC CGATTACAGAACCA; and probe, FAM CGACCGGGAGGTGGTGA-TGGCGT-TAMARA. For mIL-17: primers, 5’-GCT GGA TAC TCC CGATTACAGAACCA; and probe, FAM CGACCGGGAGGTGGTGA-TGGCGT-TAMARA. For mIL-17A: primers, 5’-GCT GGA TAC TCC CGATTACAGAACCA; and probe, FAM CGACCGGGAGGTGGTGA-TGGCGT-TAMARA. For mICAM-1: primers, 5’-CAGCCCGTAGTGCTGCAAG; and probe, FAM CAAATCGGTGACCCC; and probe, FAM CAGATGGTGCCCTGCTGCCCA-TAMARA. For mTNF-α: primers, 5’-AAA GGA TAG TTG AAG TCC TAA AGA ACA and 5’-GAG CTG CAG TA and 5’-CCT GCA GGC TCT ATC GGG-TCT AAG CTG; and probe, FAM CAC AGG GCA ACT GAG GCA GGC-5’-TCA AGA AGA AAT GTG GAT CAG CA and 5’-GAC TGG CAT GAG AAA G-3’. All animal protocols were approved by an institutional use and care committee (19). The expression of the transgene was determined by Taqman RT-PCR (PerkinElmer) using gene-specific primers and probes as follows. For mIL-17E: primers, 5’-GCT GGA TAC TCC CGATTACAGAACCA; and probe, FAM CGACCGGGAGGTGGTGA-TGGCGT-TAMARA. For mIL-17A: primers, 5’-GCT GGA TAC TCC CGATTACAGAACCA; and probe, FAM CGACCGGGAGGTGGTGA-TGGCGT-TAMARA. For mIL-17R: primers, 5’-GCT GGA TAC TCC CGATTACAGAACCA; and probe, FAM CGACCGGGAGGTGGTGA-TGGCGT-TAMARA. For mIL-17R: primers, 5’-GCT GGA TAC TCC CGATTACAGAACCA; and probe, FAM CGACCGGGAGGTGGTGA-TGGCGT-TAMARA. For mIL-17R: primers, 5’-GCT GGA TAC TCC CGATTACAGAACCA; and probe, FAM CGACCGGGAGGTGGTGA-TGGCGT-TAMARA. For mIL-17R: primers, 5’-GCT GGA TAC TCC CGATTACAGAACCA; and probe, FAM CGACCGGGAGGTGGTGA-TGGCGT-TAMARA. For mIL-17R: primers, 5’-GCT GGA TAC TCC CGATTACAGAACCA; and probe, FAM CGACCGGGAGGTGGTGA-TGGCGT-TAMARA. For mIL-17R: primers, 5’-GCT GGA TAC TCC CGATTACAGAACCA; and probe, FAM CGACCGGGAGGTGGTGA-TGGCGT-TAMARA.

Histological analysis

Routine necropsy was performed. Tissues for light microscopy were collected and fixed overnight in 10% neutral buffered Formalin, embedded in paraffin, sectioned at 5 μm, and stained with H&E.

FACS analysis

Blood samples were collected and processed, and FACS analyses were performed on EPICS XL-MCL (Coulter, Miami, FL) using various Abs (BD PharMingen, San Diego, CA) according to the manufacturers’ instructions.

Measurement of serum proteins

Serum IgG1 and IgG2a levels were assessed using a sandwich ELISA. Anti-mouse IgG1- and IgG2a-coating Abs (BD PharMingen) were diluted to 1.0 and 2.5 μg/ml in PBS (pH 7.2), respectively, and added to separate 96-well plates (Nunc Immuno Plate Maxisorp; Nunc, Naperville, IL), then incubated overnight at 4°C. Plates were washed three times (0.05% Tween 20), blocked (0.5% BSA in PBS), and incubated for 2 h at room temperature with gentle agitation, then washed three times. Mouse IgG2a standard (Southern Biotechnology Associates, Birmingham, AL) was diluted to 400 ng/ml in assay buffer, and 2-fold serial dilutions were performed to create a seven-point standard curve ranging from 25 to 0.39 ng/ml. Mouse IgG2a standard (Southern Biotechnology Associates, Birmingham, AL) was diluted to 400 ng/ml in assay buffer, and 2-fold serial dilutions were performed to create a seven-point standard curve ranging from 25 to 0.39 ng/ml. Serum samples were serially diluted 2-fold in assay buffer to fall within the respective standard curve ranges. Standard or sample was added to each plate and incubated for 2 h at room temperature with gentle agitation, then washed six times. Biotinylated anti-mouse IgG1 and IgG2a Abs (BD PharMingen) were diluted 1:2000 in assay buffer and added to each plate at 100 μl/well, then incubated at room temperature for 1 h with gentle agitation and then washed six times. Streptavidin-HRP (Amersham Pharmacia Biotech, Piscataway, NJ) diluted 1:20,000 in assay buffer was added and incubated for 30 min at room temperature with gentle agitation, then washed six times. Tetramethylbenzidine substrate solution (Kirkegaard & Perry, Gaithersburg, MD) was added to each well, and color was allowed to develop for 4–6 min. The reaction was stopped with 1 M phosphoric acid, and absorbance was read at 450 nm. Serum IgG1 levels were assessed by sandwich ELISA using a mouse IgG1 OptEIA kit (BD PharMingen). Serum IL-5, IL-13, G-CSF, IFN-γ, and TNF-α were measured using ELISA kits (R&D Systems, Minneapolis, MN) according to the manufacturer’s instructions.

Recombinant proteins and cell cultures

NIH-3T3 and ST2 cells were grown in high glucose DMEM with 10% heat-inactivated FBS, 2% m1-glutamine, and 1% penicillin, streptomycin. The cultures were initiated at 5,000 per 60-mm culture dish. All cultures were grown in triplicate. At 24 h, factors were added to the cultures; 4 and 24 h later, conditioned media were removed and frozen for ELISA, and cells were lysed for RNA extraction in the dish using an RNeasy kit according to the manufacturer’s instructions (Qiagen, Valencia, CA). The rIL-17 was purchased from R&D Systems. IL-17E was prepared as previously described (5).

Statistical analysis

For body weights, hematological analysis, and FACS of PBMC, statistical significance was determined by Student’s t test. Gene expression data were statistically analyzed by ANOVA using StatView software (Calabasas, CA). A value of p < 0.05 was taken as significant.

Results

Identification of mIL-17E

The murine ortholog of IL-17E was identified through sequence comparison with expressed sequence tag information (accession no. AI430337) present in GenBank. Several cDNA clones were subsequently isolated, and the longest cDNA clone encoded a partial signal sequence and the predicted mature protein of murine IL-17E, which was 85% identical to human IL-17E and 17–22% identical to other members of the IL-17 family (Fig. 1A). Attempts including 5’ racing, failed to identify cDNA that contained an initiation codon. Analysis of mRNA expression in several mouse tissues indicated that mIL-17E is expressed in brain, heart, and testes. Little expression was detected in liver, lung, or spleen (Fig. 1B).

mIL-17E-TG mice have elevated liver enzymes and are jaundiced and growth retarded

TG mice have not been previously reported for any member of the IL-17 family. Attempts to generate transgenic mice that ubiquitously overexpress mIL-17E were unsuccessful (9). The reason for this failure remains unknown, but it is probable that overexpression of potent proinflammatory cytokine, such as IL-17 during early development may be lethal. Thus, rat skeletal myosin L chain 2 promoter was chosen to overexpress mIL-17E in TG mice (17,
18), as this promoter is known to direct a high level gene expression starting 6–9 days after birth, presumably giving rise to circulating mIL-17E. The mice were housed in a specific pathogen-free environment, and multiple founders were analyzed. All TG pups were significantly smaller than their non-TG littermates by 1 wk of age. This difference in body weights was retained at 3, 4, 6, 12, and 13 wk of age (Fig. 1C and data not shown), suggesting that the TG mice were growth retarded. At 6 wk of age, most of the TG founder mice were jaundiced (Fig. 1D), indicating bilirubin deposition in the tissues. Consistent with this, serum levels of bilirubin were significantly elevated in the mIL-17E-TG mice (1.78 mg/dl (TG) vs 0.05 mg/dl (non-TG); *p* = 0.008). In addition, serum...
FIGURE 2. mRNA levels of various genes in TG vs non-TG mice. Gene expression in various tissues was examined by a real-time quantitative RT-PCR using gene-specific primers and probes as described in Materials and Methods. The mRNA levels of various genes were normalized over those of 18S. Relative mRNA expression values (TG vs non-TG) are shown as the fold increase. The data are from analysis of six TG and six non-TG mice and are presented as the range of increase. A, Gene expression profile in livers. B, Gene expression profile in kidneys. C, Gene expression profile in lungs. D, IL-17ER mRNA is upregulated in TG mice. The fold increase is represented as the mean ± SD (n = 5).
levels of liver enzymes were markedly elevated, including alkaline phosphatase (886.7 U/L (TG) vs 223 U/L (non-TG); $p = 0.018$), alanine aminotransferase (252 U/L (TG) vs 45 U/L (non-TG); $p = 0.008$), and amylase (21414 U/L (TG) vs 3606 U/L (non-TG); $p = 0.015$), suggestive of liver damage in the mIL-17E-TG mice.

**Overexpression of mIL-17E in TG mice induces gene expression of cytokines in multiple tissues**

To understand the in vivo consequences of the overexpressed mIL-17E, we first examined the gene profiles of both Th1 and Th2 cytokines. mIL-17E receptor, mIL-17ER, is expressed in multiple tissues, especially abundant in liver and kidneys (4, 5). Thus, we measured expression of inflammatory cytokines in these tissues using quantitative RT-PCR assays. The transcripts for Th2 cytokines IL-4 and IL-10 were significantly induced in liver, and IL-4, IL-10, and IL-13 in kidneys from TG mice (Fig. 2, A and B). Interestingly, we found that some of these cytokines were also dramatically induced in lungs (IL-4 and IL-10; Fig. 2C), heart (IL-10 and IL-13; data not shown), spleen (IL-4, IL-6, and IL-13; data not shown), and intestines (IL-4, IL-5, IL-9, and IL-10; data not shown) where normally a very low abundance of mIL-17ER was detected (4, 5), suggesting that these tissues were also responsive to IL-17E. We thus measured the mIL-17ER expression in these tissues in TG mice. Remarkably, mIL-17ER mRNA was substantially increased in multiple tissues, especially heart and lung (increased by 64- and 16-fold, respectively; Fig. 2D) and consistent with the idea that IL-17E may enhance its signaling in peripheral tissues by up-regulation of its own receptor. These cytokine profiles suggest that IL-17E may drive a Th2-like response. However, when the gene expression levels of Th1 cytokines were measured (e.g., IFN-γ and TNF-α), we also observed elevated levels of these messages in several tissues (Fig. 2A and data not shown). Thus, the inflammatory response induced by mIL-17E may not be strictly Th2 in character.

**mIL-17E-TG mice have increased serum IL-5 and IL-13 and circulating IgE and IgG1**

To determine whether the elevated gene expression described above gave rise to circulating cytokines and further affected Ab generation, we measured serum levels of several cytokines and Abs using specific ELISAs. Both Th2 cytokines, IL-13 and IL-5, were increased in mIL-17E-TG mice (Fig. 3A). However, serum TNF-α was also induced in TG mice (Fig. 3A). Induction of serum IFN-γ was not detected (data not shown) despite increased IFN-γ mRNA in some tissues (Fig. 2). In addition, both serum IgE and IgG1 (characteristic of the Th2 response) were significantly elevated in the TG mice, but serum levels of IgG2a (Th1 in character) were not altered (Fig. 3B). Along with the increased circulating eosinophils (see below), these findings suggest that IL-17E induces a systemic Th2-biased response.

**Overexpression of mIL-17E causes neutrophilia and eosinophilia in TG mice**

In vivo expression of IL-17 via adenoviral-mediated delivery causes neutrophilia in mice (9), but no effect on eosinophils has been reported. To understand whether overexpression of mIL-17E had a similar effect, FACS analyses of PBMC were performed using specific cell surface markers. CD3⁺T cells or CD19⁺B cells were significantly reduced in TG mice compared with those of non-TG mice (Fig. 4A). However, there was no change in the CD4⁺:CD8⁺ ratio (data not shown). When PBMC were stained for GR-1⁺ neutrophils, we found that TG mice had significantly increased circulating neutrophils (Fig. 4B). Consistent with these findings, the absolute cell counts of neutrophils were increased by 8- to 10-fold in TG mice. Interestingly, the absolute counts of eosinophils were also dramatically increased (Fig. 4C), but the absolute number of lymphocytes was only slightly reduced (Fig. 4C). FACS analyses of cells isolated from spleen and lymph nodes also showed significantly increased neutrophils in the TG mice (data not shown). When lymphocytes from spleen and lymph nodes were examined, we found that CD3⁺ T cells were reduced by 20% (only significant in male TG mice; $p = 0.009$). In contrast, CD19⁺ B cells appeared to be increased in the TG mice, but this was not statistically significant (data not shown). Additional experiments are needed to examine the direct impact of IL-17E on the lymphocyte population. These findings suggest that IL-17E stimulates hemopoiesis and causes neutrophilia and eosinophilia in vivo. Although the underlying molecular mechanism remains to be further elucidated, these effects may be mediated in part by increased IL-5 and G-CSF (Figs. 2 and 3 and see below).

**mIL-17E induces the expression of neutrophil-specific chemokine GROs and adhesion molecules**

Like IL-17, IL-17E stimulates IL-8 production in cell cultures (1, 5). To determine the effect of mIL-17E on the gene expression of other chemokines and adhesion molecules in vivo that might contribute to the immune infiltrate in tissues (see blow), we examined mRNA levels for GROα, monocyte chemoattractant protein-1, ICAM-1, and VCAM-1 in multiple tissues from the TG mice. The GROα mRNA was significantly induced in liver, kidneys, lungs, and heart, while ICAM-1 was increased in liver and VCAM-1 in kidneys (Fig. 2, A and B, and data not shown). These findings that mIL-17E may induce production of chemokines and adhesion molecules in epithelial cells, endothelial cells, and fibroblasts in various tissues, contributing to the recruitment of neutrophils, lymphocytes, and other infiltrating cells.

**IL-17E stimulates G-CSF production**

IL-17 stimulates the production of G-CSF, a potent inducer of granulopoiesis, in vivo and from stromal cells in vitro (7, 9, 19).
To determine whether G-CSF was induced by IL-17E in vivo, its mRNA levels in TG tissues were measured. G-CSF mRNA levels were markedly increased in liver, kidneys, and spleen (Fig. 2, A and B, and data not shown). Consistent with this, serum G-CSF was also dramatically induced in TG mice (Fig. 5A). IL-17 directly stimulates G-CSF production from stromal cells, NIH-3T3, and ST2 (7). To determine whether IL-17E has a similar activity, NIH-3T3 and ST2 were treated with rIL-17E. Like IL-17, IL-17E stimulated G-CSF mRNA (Fig. 5, B and C). G-CSF protein production from NIH-3T3 cells was confirmed by ELISA (Fig. 5D). These findings suggest that IL-17E induces G-CSF production, and the increased G-CSF may contribute to the granulopoiesis seen in mIL-17E-TG mice.

Overexpression of mIL-17E causes multiorgan inflammation

A comprehensive histological tissue survey showed that mIL-17E-TG mice had chronic inflammation in multiple tissues. Tissues consistently affected include liver, heart, lungs, lymph node, kidneys (renal pelvis and mild glomerular changes), spleen, and urinary bladder. Inflammation in these tissues was comprised of mixed infiltrates of neutrophils, eosinophils, lymphocytes, plasma cells, and macrophages. In the liver, all mIL-17E-TG mice evaluated had severe cholangihepatitis with adenomatous hyperplasia of bile ducts, periportal fibrosis, and variable oval cell hyperplasia (Fig. 6, B vs A). Special stains, including Warthin Starry and periodic acid-Schiff, were negative for Helicobacter sp. and fungal elements, respectively (data not shown). In the lungs, mIL-17E-TG mice consistently develop diffuse interstitial and peribronchial inflammation, with more severe changes in the highest expressing founders (Fig. 6, C and D). In addition to the mixed inflammatory cell infiltrate described above, alveolar spaces were filled with numerous macrophages that were occasionally multinucleated and often distended with long, thin, cytoplasmic crystals, similar to those reported in the lungs of other mutant mouse models that have eosinophilic inflammation (20, 21). Consistent with these studies, crystals seen in the mIL-17E TGs were stained with eosin, but not periodic acid-Schiff or Congo Red. All IL-17E-TG mice examined had splenomegaly (data not shown). Splenic weights showed that, on the average, the mIL-17E-TG spleen weighed up to four times more than that of the non-TG littermates. Histologically, the splenomegaly was attributable to extensive extramedullary hemopoiesis (data not shown). Lymph nodes were also enlarged in the IL-17E TGs due to expansion of medullary and cortical sinuses by numerous plasma cells (data not shown). Thymic weights were slightly reduced (data not shown). These histological findings suggest that ubiquitous expression of mIL-17E causes profound pathological and immunological changes in multiple organs.
Discussion

IL-17E is a recently identified member of the IL-17 cytokine family. Although IL-17E appears to be a proinflammatory cytokine and induces IL-8 production in human cells, no in vivo biological activity has been described. To understand the in vivo action of this cytokine, we have generated and characterized TG mice that ubiquitously express the mIL-17E. The mIL-17E-TG mice exhibit growth retardation, jaundice, and striking multiorgan inflammation associated with mixed infiltrate.

The biological consequences of IL-17E exposure have both interesting similarities and clear distinctions to those reported for IL-17. Like IL-17, IL-17E impacts diverse tissues. This reflects in part the broad expression of its receptor (4, 5, 22). IL-17E promotes substantial neutrophilia, a response that may be due to the observed induction of G-CSF. IL-17 has also been shown to induce the production of G-CSF and promote neutrophilia (6, 7, 9, 19). Similarly, both IL-17 and IL-17E induce the local production of chemokines that target neutrophils such as GROα and IL-8 (5, 8). Furthermore, both IL-17 and IL-17E are associated with increased expression of ICAM-1 and other inflammatory cytokines (1, 17). Although we could not exclude the possibility that some of the actions elicited by IL-17E might be mediated by IL-17, serum IL-17 was not elevated in IL-17E-TG mice (data not shown). Additional experiments using Abs against IL-17 or cells or mice deficient in IL-17/IL-17R are required to address these issues. In contrast, IL-17E overexpression resulted in the promotion of a systemic Th2-biased immune response. This response has not been noted with chronic IL-17 exposure (9). It should be mentioned that IL-17 can be produced by both Th1 and Th2 subsets, and it has not been strongly associated with either the Th1 or Th2 response (23, 24). The Th2 feature of this response in the TG mice was characterized by cytokine profile, the presence of increased serum IgE and IgG1, and an increase in eosinophil number. It was noted that in vivo expression of IL-17 increased the peripheral white blood cell count and 2-fold increases in lymphocytes (6, 9). In contrast, mIL-17E-TG mice appeared to be slightly lymphopenic. Further studies are required to understand the effect of IL-17E on lymphopoiesis and subtypes of lymphocytes. These comparisons should be viewed with caution, since the phenotype of IL-17-TG mice has not been reported.

Long-term exposure to IL-17E causes multiorgan inflammation. The inflammatory infiltrate in IL-17E-TG mice is comprised of...
cosinophils; however, mixed cellular infiltrates, including neutrophils and lymphocytes, are frequently present and may result from secondary necrosis or induction of proinflammatory chemokines. Epithelial hyperplasia was observed in multiple tissues. Interestingly, the IL-17Rh1 message is elevated in multiple tissues in the TG mice, suggesting that the spectrum of tissues upon which IL-17E can act is influenced by the regulation of receptor expression. In a survey of human cell lines by PCR for expression of IL-17Rh1 mRNA, message was detectable in nearly all cell lines examined and was detectable in cells of various hemopoietic lineages (our unpublished observations). In this context, the complete mechanisms by which IL-17E promotes the development of inflammation and a TH2-immune profile are as yet unclear, but may reflect, at least partially, direct actions on cells of the immune system.

Microbial lipopeptides have recently been identified as the first demonstrated pathological inducers of IL-17 production (23). Lipopeptides are known to signal through the Toll-related receptor 2 (25, 26). This suggests that normal IL-17 function may relate the defense against pathogens. Consistent with this, IL-17R has recently been shown to be required for host defense against bacterial pneumonia (27). The immunological or pathological source of IL-17E remains to be identified, but IL-17E mRNA is expressed at very low levels in peripheral tissues (5). It is likely that there exist stimuli, as yet unidentified, that induce elevated expression of IL-17E. The phenotype of the IL-17E-TG mice also resembles an immunune response to pathogens, with an increase in several Th1 cytokines. A. D. Goddard, D. G. Yansura, R. L. Vandlen, W. I. Wood, et al. 2001. IL-17E, a novel proinflammatory ligand for the IL-17 receptor homolog IL-17Rh1. J. Biol. Chem. 276:1660. J. J. Pin, P. Garrone, E. Garcia, S. Saeland, et al. 1996. T cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines. J. Exp. Med. 183:2596.

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