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**IL-10 Suppresses Mast Cell IgE Receptor Expression and Signaling In Vitro and In Vivo**

Sarah Kennedy Norton,* Brian Barnstein,* Jennifer Brenzovich,* Daniel P. Bailey,* Mohit Kashyap,* Kelly Speiran,* Jill Ford, † Daniel Conrad, ‡ Stephanie Watowich, § Matthew R. Moralle, ¶ Christopher L. Kepley, § Peter J. Murray, †† and John J. Ryan‡‡

Mast cells are known for their roles in allergy, asthma, systemic anaphylaxis, and inflammatory disease. IL-10 can regulate inflammatory responses and may serve as a natural regulator of mast cell function. We examined the effects of IL-10 on in vitro–cultured mouse and human mast cells, and evaluated the effects of IL-10 on FcεRI in vivo using mouse models. IgE receptor signaling events were also assessed in the presence or absence of IL-10. IL-10 inhibited mouse mast cell FcεRI expression in vitro through a Stat3-dependent process. This down-regulation was consistent in mice tested in vivo, and also on cultured human mast cells. IL-10 diminished expression of the signaling molecules Syk, Fyn, Akt, and Stat5, which could explain its ability to inhibit IgE-mediated activation. Studies of passive systemic anaphylaxis in IL-10–transgenic mice showed that IL-10 overexpression reduced the IgE-mediated anaphylactic response. These data suggest an important regulatory role for IL-10 in dampening mast cell FcεRI expression and function. IL-10 may hence serve as a mediator of mast cell homeostasis, preventing excessive activation and the development of chronic inflammation. *The Journal of Immunology*, 2008, 180: 2848–2854.

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Materials and Methods

Animals

C57BL/6 mice were purchased from The Jackson Laboratory. CD68-IL-10 transgenic (Tg) 3 mice have been described previously (26). Passive systemic anaphylaxis (PSA) was performed using unanesthetized mice at 12 wk of age or older, with approval from the university animal care and use committee. STAT3 β and Tie2-Cre mice were provided by Drs. Takeda (Osaka University, Osaka, Japan) and Koni (Yale University, New Haven, CT) (27, 28) and were bred to yield β/β Cre and Cre - littermates as described (29).

Bone marrow-derived mast cell (BMMC) cultures

BMCC were derived from C57BL/6 and C57BL/6 × 129 mice by culture in complete RPMI (cRPMI) 1640 medium (Invitrogen Life Technologies) (containing 10% FBS, 2 mM l-glutamine, 100 U/ml penicillin, 100 μg streptomycin, 1 mM sodium pyruvate, and 1 mM HEPES; Biofluids), supplemented with 30% WEHI-3 cell-conditioned medium as described previously (30).

Tissue-culture conditions for human mast cells

All study protocols involving human tissues were approved by the Human Studies Internal Review Board at Virginia Commonwealth University (Richmond, VA). Surgical skin samples were obtained from Virginia Commonwealth University Medical Center, the Cooperative Human Tissue Network of the National Cancer Institute, or the National Disease Research Interchange. After removing s.c. fat by blunt dissection, residual tissue was cut into 1- to 2-mm fragments and digested with type 2 collagenase (1.5 mg/ml) and type 1 DNase (0.3 mg/ml) in HBSS for 2 h at 37°C. The dispersed cells were collected by filtering through a no. 80 mesh sieve and resuspended in HBSS containing 1% FCS (Biofluids), supplemented with 30% WEHI-3 cell-conditioned medium as described previously (30).

Cytokines and reagents

DNP-specific mouse IgE was purified as described previously (31). Murine IL-3 and IL-10 were purchased from R&D Systems. Murine SCF was purchased from Peprotech. Cell Permeable STAT3 inhibitor peptide (STAT3i) was purchased from Calbiochem. Akt, p-Akt, STAT5, p-STAT5, Lyn, Syk Abs were purchased from Cell Signaling. Phospho-p38 was purchased from Cell Signaling. STAT3i was purchased from Calbiochem. Akt, p-Akt, STAT5, p-STAT5, or p38, or with a 1/5,000 dilution of β-actin overnight at 4°C with gentle rocking. Blots were washed five times for 10 min each in TBST, followed by incubation in 5% NFDM/TBST containing a 1/2,000 dilution of HRP-linked rabbit anti-IgG (Cell Signaling), or HRP-linked rabbit anti-mouse IgG at 1/2,000 (p38) or 1/10,000 (β-actin; Jackson Immunoresearch Laboratories). Size estimates for proteins were obtained using m.w. standards from Bio-Rad.

ELISA

IL-10, TNF-α, MIP-1α, and histamine were detected by standard ELISA kit as described by the manufacturer. IL-10 and TNF-α ELISA kits were purchased from BD Biosciences. A MIP-1α kit was purchased from R&D Systems. A Histamine kit was purchased from NeoGen. Serum IgE levels were measured by ELISA, as described previously (32).

IL-10 injection and ex vivo mast cell activation assay

C57BL/6 × 129 mice were injected i.p. twice daily for 5 days with 2 μg of IL-10 injection (PeproTech) in 100 μl of sterile PBS. Injections were 8 h apart, with the last injection 3 h before sacrificing animals. Peritoneal cells were harvested, resuspended at 10 6 cells/ml in cRPMI, and either analyzed for FcεRI expression (as indicated above) or activated ex vivo. Peritoneal cells activated ex vivo were plated at 200 μl/well and incubated with IgE (10 μg/ml) for 45 min at 4°C in cRPMI, washed, and resuspended in cRPMI supplemented with IL-3 (5 ng/ml) and SCF (50 ng/ml). Cells were activated with rat anti-mouse IgE (10 μg/ml) for 16–24 h. Cytokines were measured by ELISA.

Passive systemic anaphylaxis

C57BL/6 mice were injected i.p. with 50 μg of DNP-specific mouse IgE. Mice were injected i.p. 16 h later with 100 μg of DNP-albumin in PBS (Sigma-Aldrich). Body temperature was measured every 10 min for 30 min by rectal probe. After 30 min, mice were sacrificed, and blood was collected by cardiac puncture for serum analysis. Control mice were injected with PBS in place of IgE. These mice showed no significant change in body temperature (≤1°C), and had blood histamine levels near the limit of detection, ≥50 ng/ml.

Results

IL-10-mediated FceRI suppression requires STAT3 expression

IL-10 effects have been shown to be largely dependent on STAT3 expression in macrophages (33–35). To determine the importance of STAT3 in IL-10 effects on mast cells, we first used a population of STAT3-deficient mouse mast cells. We noted that these STAT3-deficient bone marrow cells did not develop into a uniform mast cell population, retaining some FcεRI-negative cells unlike the wild-type control population. However, we did find that the FcεRI-positive STAT3-deficient population showed no change in FcεRI expression when cultured ≥IL-10. By comparison, mast cells derived from littermate animals showed the expected decrease in FcεRI expression when treated with IL-10 (Fig. 1A), suggesting that STAT3 expression is required for IL-10-mediated FcεRI suppression. The importance of STAT3 was further supported by...
IL-3 Littermate or STAT3-deficient (knockout (KO)) BMMC were cultured in experiments using four to five populations each. Results are representative of two independent experiments using four to five populations each.

A/BRI expression.

Although we have previously found that IL-10 suppressed murine mast cells, we also determined the effects of IL-10 on STAT5. We assessed protein expression after culture for 4 days in IL-3 ± IL-10, using Western blot analysis. Because Lyn is known to be a negative regulator of mast cell function (36–38), it was interesting to note that IL-10 treatment had no effect on Lyn expression (Fig. 3A). In contrast, IL-10 significantly suppressed expression of the activating kinases Syk and Fyn (Fig. 3A). Densitometry

We assessed protein expression after culture for 4 days in IL-3 ± IL-10, using Western blot analysis. Because Lyn is known to be a negative regulator of mast cell function (36–38), it was interesting to note that IL-10 treatment had no effect on Lyn expression (Fig. 3A). In contrast, IL-10 significantly suppressed expression of the activating kinases Syk and Fyn (Fig. 3A). Densitometry
showed an average 49.22% inhibition of Syk expression and 42.54% inhibition of Fyn expression in three BMMC separate populations. Thus, IL-10 had potent but selective inhibitory effects on downstream signaling proteins.

Because Syk and Fyn are involved in signal initiation, we expected IL-10 to inhibit the activation of downstream signaling molecules. To study this, mouse BMMC were cultured for 4 days in IL-3 ± IL-10, then stimulated with IgE + Ag for 5–15 min. Total and phosphoprotein expression was measured by Western blotting. As expected, FcεRI-mediated phosphorylation of both STAT5 and Akt was inhibited by IL-10. In contrast, p38 activation was unchanged (Fig. 3B). A striking aspect of this selective inhibition was that the reduction in STAT5 and Akt phosphorylation was matched by a loss of overall protein expression. Stat5 activation was the most affected, with densitometry showing an average 79.26% inhibition of STAT5 expression in three experiments. Thus, IL-10 appeared to suppress FcεRI signaling largely by blocking the expression of key signaling proteins, rather than by preventing their activation.

**IL-10 injection decreases FcεRI expression and IgE-mediated cytokine production**

To assess the in vivo effects of IL-10 on FcεRI, mice were injected with IL-10. To confirm the functionality of this model, IL-10 serum levels were quantified from IL-10- and PBS-injected mice. After 4 days of injections, IL-10-injected mice had significantly higher serum IL-10 levels than PBS-injected mice (Table 1). Peritoneal mast cells harvested from IL-10-injected mice had lower FcεRI expression than PBS-injected littersmates (Fig. 5B), demonstrating that IL-10 consistently suppressed FcεRI expression in vitro and in vivo.

Importantly, the changes in IgE receptor expression were not caused by altered IgE levels. Mean IgE levels in PBS-injected mice were 74.1 ± 7.3 ng/ml, which was not different from IL-10-injected mice with mean IgE levels of 70.1 ± 12.4 ng/ml (p = 0.78). In addition to its effects on FcεRI, IL-10 has been shown to inhibit Kit expression (39). We observed a slight but significant inhibition of Kit receptor expression, between 18 and 26% (data not shown). IL-10 injection also increased peritoneal cell numbers from 8.0 × 10^6 to 14.7 × 10^6 (n ≥ 4, p = 0.002), and also increased the percentage of mast cells in the peritoneum (Fig. 4C). These effects are in keeping with the ability of IL-10 to induce mast cell proliferation (40).

To assess the effects of decreased FcεRI expression on mast cell function, peritoneal cells were harvested from PBS- or IL-10-injected mice, and activated with anti-IgE ex vivo. In contrast to the effect of IL-10 on human mast cells (Fig. 2), mast cells harvested from IL-10-injected mice did not demonstrate reduced IgE-mediated degranulation (Fig. 4D; p = 0.18 when comparing activated cells harvested from PBS- or IL-10-injected mice). However, peritoneal cells from IL-10-injected mice produced significantly less TNF than their PBS-injected littersmates, indicating that IL-10 inhibited the late stage of FcεRI function (Fig. 4E). These results are in keeping with previous in vitro studies performed by our group and others with rodent cells (21, 22, 25), which demonstrated IL-10 inhibitory effects on cytokine production but not degranulation.

**Chronic overexpression of IL-10 inhibits mast cell FcεRI expression and suppresses anaphylaxis**

Although IL-10 injection demonstrated the consistent effects of IL-10 in vivo, we sought a model that could be used for long-term studies. To observe the effects of chronic IL-10 overexpression, we used CD68-IL-10-transgenic mice. Transgenic mice expressed an average of 1626 pg/ml IL-10 in serum samples, while their wild-type littersmates had undetectable IL-10 levels (Fig. 5A). This concentration of IL-10 is similar to the amount required for FcεRI suppression in vitro (25). We noted a trend toward higher IgE levels in naive IL-10-transgenic mice compared with their littersmates, although no significant difference was noted. Littersmates had mean IgE levels of 236.7 ± 47.28 ng/ml, while IL-10 transgenics had mean IgE levels of 856.1 ± 401.9 ng/ml. This is consistent with the stimulatory effects of IL-10 on B cells (41, 42). In contrast to IL-10 injection, transgene expression did not affect mast cell numbers (data not shown).

Despite the fact that elevated IgE levels are known to enhance FcεRI expression (43), CD68-IL-10Tg mice demonstrated lower FcεRI expression on peritoneal mast cells compared with littersmates (Fig. 5B), consistent with our in vitro and IL-10 injection.
mast cell homeostasis, leading to chronic inflammation. We have
disease progression. Understanding mast cell signaling is therefore a critical
aspect of developing new clinical interventions and predicting
viable of significant and broad pathology when aberrantly acti-
appears poised to rapidly respond to infection, but is also ca-
trophil recruitment (45, 46). Collectively, mast cell activation
of TNF after contact with bacterial ligands, and subsequent neu-
mice succumb to infection in bacterial peritonitis and pneumonia
asite elimination (1). Even more dramatically, mast cell-deficient
infection with parasites, mast cell hyperplasia correlates with par-
protective role in bacterial and parasitic infections. In response to
developing treatment strategies for a variety of illnesses.
standing of how mast cell function is regulated is important for
syndrome, due to elevated postmortem
cells have even been suspected to play a role in sudden infant death
syndrome, sudden infant death syndrome victims (44). Therefore, our under-
sing that despite these inherent differences, IL-10 has similar ef-
variable that differ between mouse and human mast cells, partic-
expression on mouse mast cells (30), but has the reverse effect on
expression in vivo, despite the presence of
mediated activation. We detected a 30% decrease in surface Fc
mediated suppression, showing IL-10-mediated suppres-
sion and function in vitro, and subsequently induce mast cell ap-
ntermediate differentiated human mast cells (53). There are many
variables that differ between mouse and human mast cells, partic-
culture systems and growth factors. Therefore, it is compel-
ghat despite these inherent differences, IL-10 has similar ef-
effects on mouse and human mast cells.
We also found that IL-10 can act in vivo. IL-10 injection
pressed mast cell FcεRI expression in vivo, despite the presence of
IgE as an opposing force. The down-regulation we observed in
in vivo may be at best a partial explanation for suppressing IgE-
mediated activation. We detected a 30% decrease in surface FcεRI
after IL-10 injection, which would likely leave many more recep-
tors on the cell surface than are required for activation. In contrast,
omalizumab therapy, a clinically effective monoclonal anti-IgE ca-
pable of preventing IgE binding to FcεRI, reduces surface IgE
receptor expression >90% (54, 55). Because this partial inhibitory
effect on surface receptor expression did not appear to fully explain
the ability of IL-10 to repress FcεRI signaling, we further inves-
tigated IL-10 effects on FcεRI signal transduction downstream.
IL-10 treatment of mouse BMMC revealed an interestingly se-
selective suppressive effect on FcεRI signaling. We found it partic-
ularly striking that IL-10 suppressed expression of Fyn, Syk, Akt,
and STAT5—molecules with critical functions in mast cell acti-
vation—without altering Lyn expression. Lyn is argued to be a

studies. To further assess the effects of IL-10 overexpression on
mast cell function in vivo, we used IgE-mediated PSA. CD68-IL-
Tg mice demonstrated a reduced anaphylactic response com-
pared with littermates. This was noted by a mitigated drop in body
temperature 30 min after Ag challenge (Fig. 5C). Surprisingly, this
improvement was not matched by changes in serum histamine lev-
els, which were elevated in both littermate and transgenic mice.
IL-10 transgene expression did suppress IgE-mediated cytokine
production, as CD68IL-10Tg mice had much lower serum MIP-1α
levels post-Ag challenge. These data support the contention that
IL-10 can suppress mast cell activation and related anaphylactic

Discussion
Mast cells are best known for their role in allergy and asthma,
where they serve as an initiator of inflammation (1). This patho-
logical role has been expanded by the recent demonstration that
mast cells function in mouse models of multiple sclerosis, inflam-
matory arthritis, cardiovascular disease, and colitis (3–7). Mast
cells have even been suspected to play a role in sudden infant death
syndrome, due to elevated postmortem β-tryptase levels in some
sudden infant death syndrome victims (44). Therefore, our under-
standing of how mast cell function is regulated is important for
developing treatment strategies for a variety of illnesses.

In contrast to their pathological functions, mast cells have a
protective role in bacterial and parasitic infections. In response to
infection with parasites, mast cell hyperplasia correlates with par-
asite elimination (1). Even more dramatically, mast cell-deficient
mice succumb to infection in bacterial peritonitis and pneumonia
models (45, 46). This protective function stems from rapid release
of TNF after contact with bacterial ligands, and subsequent neu-
trophil recruitment (45, 46). Collectively, mast cell activation
appears poised to rapidly respond to infection, but is also ca-
pable of significant and broad pathology when aberrantly acti-
vated. Understanding mast cell signaling is therefore a critical
aspect of developing new clinical interventions and predicting
disease progression.

Allergy and allergic asthma may be caused in part by a loss of
mast cell homeostasis, leading to chronic inflammation. We have
postulated that in a normal response, mast cells can proliferate and
induce inflammation for 3–6 days, at which point cytokines such as
IL-4, IL-10, and TGF-β1 inhibit mast cell function (47). Our
previous data showed that these cytokines suppress FcεRI expres-
sion and function in vitro, and subsequently induce mast cell ap-
optosis (25, 30, 48–50). Of these cytokines, IL-10 and TGFβ1 are
well-documented for their immunosuppressive capabilities. Loss of
IL-10 function has been shown to cause colitis (13), while
TGF-β1 deficiency results in widespread autoimmunity (51, 52).

Our previous work with IL-10 used mouse mast cells and in
vitro assays. In the current study, we demonstrate the consistency of
IL-10-mediated suppression, showing IL-10-mediated suppres-
sion of FcεRI expression and function on human skin and lung
mast cells. This consistency is important, because some cytokine
effects vary between species. For example, IL-4 suppresses FcεRI
expression in mouse mast cells (30), but has the reverse effect on
terminally differentiated human mast cells (53). There are many
variables that differ between mouse and human mast cells, partic-
ularly culture systems and growth factors. Therefore, it is compel-
ing that despite these inherent differences, IL-10 has similar ef-
effects on mouse and human mast cells.

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and STAT5—molecules with critical functions in mast cell acti-
vation—without altering Lyn expression. Lyn is argued to be a

FIGURE 5. Chronic IL-10 overexpression suppresses FcεRI expression and function in vivo. Serum
and peritoneal cells were collected from CD68-IL-10Tg and littermate mice. A, Serum IL-10 levels were quan-
tified by ELISA. B, FcεRI expression on peritoneal cells was determined by flow cytometry. C–E, Body temper-
ature change, serum histamine, and MIP-1α were de-
termined 30 min after PSA challenge. Data shown in
C–E are from one of three representative experiments
using a total of 18 littermates and 11 IL-10Tg mice.
negative regulator of FcεRI signaling, so its continued expression may serve to inhibit IgE-mediated activation (37, 38). In contrast, Fyn and Syk represent the apical end of IgE signaling, while Akt and STAT5 are linked to mast cell cytokine production (11, 38). Like its repression of FcεRI levels, IL-10 partially reduced expression of these signaling molecules, typically in the range of 50% suppression (Fig. 3). The combined effect of fewer surface receptors and reduced signaling resulted in reduced cytokine production, but did not affect degranulation in the mouse system. This is in contrast to human mast cells, which showed reduced degranulation and cytokine production. These data offer two areas for future studies. It will be interesting to dissect the suppressive effects of IL-10 on mouse vs human mast cells, to determine the mechanism providing species-restricted inhibition of degranulation, a clinically important event in mast cell activation. Related to this issue, Gonzalez-Espinosa et al. (56) recently showed that weak IgE-mediated signals could elicit cytokine production without degranulation. Their study indicates that the signaling threshold for cytokine production is lower than that for degranulation—hence, we would have expected IL-10 to exert its more prominent effect on histamine release. Yet, we and others have consistently found the reverse effect of IL-10 both in vitro and in vivo (21, 22, 25). How this threshold effect is attained and altered by IL-10 is a focus of our current studies.

The consistent ability of IL-10 to suppress FcεRI expression and function both in vivo and across species supports our focus on the molecular mechanisms of IL-10 function. We are currently investigating how IL-10 suppresses protein expression and the role of STAT3 in this process. Our current work includes studies of how IL-10 inhibits expression of FcεRI-signaling molecules, and the role of STAT3 in this process. If these effects occur at the protein level, they could be partly explained by induction of suppressor of cytokine signaling family proteins and subsequent ubiquitination (57). Although Stat3 appears to be critical for the effects of IL-10, we found that Stat3-deficient mast cells differentiate incompletely and hence may be a difficult model in which to study the effects of IL-10.

Because IL-10 polymorphisms correlate with increased incidence of atopic disease (58), it is tempting to speculate that loss of IL-10-mediated suppression is part of the disease etiology, and that IL-10 normally functions to limit mast cell activation. In our in vivo experiments showed that raising IL-10 levels via injection or transgene expression suppressed mast cell function. These experiments also revealed an interesting effect on mast cell numbers. Although short-term (4-day) injection with IL-10 raised mast cell numbers, we found no such effect in the IL-10Tg mice with chronically high IL-10 levels (Figs. 4 and 5, and data not shown). IL-10 has been shown to both increase and decrease mast cell proliferation (40, 59). Interestingly, the suppressive effects on proliferation were found in an in vivo model in which IL-10 levels were elevated for >17 days (59), suggesting that chronic IL-10 may suppress mast cell proliferation. Our own in vitro work supports this contention. We have found that IL-10 in combination with IL-4 initially promotes mast cell proliferation, but by day 6 of culture this effect has reverted to cell cycle arrest and apoptosis (50). One wonders if the linkage of IL-10 promoter polymorphisms to atopic disease is related to loss of this late suppressive effect on mast cell numbers and function.

Consistent with our mouse in vitro studies (25), IL-10 had no effect on histamine release in IgE-challenged CD68−/−IL-10Tg mice. However, chronic IL-10 still improved the drop in body temperature noted during the immediate vasodilatory phase of anaphylactic shock. This appears to reflect some other function of IL-10, possibly on the release of mast cell mediators other than histamine, or on smooth muscle cell responsiveness. A striking and consistent effect of IL-10 was its blockade of IgE-mediated cytokine production in vivo. We chose to measure MIP-1α because it is a representative inflammatory cytokine/chemokine (60). The role of mast cells in atopy, and especially in nonallergic inflammatory diseases, may hinge on production of cytokines and subsequent inflammatory cell recruitment (61). If this is the case, IL-10 or small molecules mimicking IL-10 signaling may prove to be efficacious clinical interventions.

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Disclosures
The authors have no financial conflict of interest.

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