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A Role for IL-18 in Neutrophil Activation

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IL-18 expression and functional activity has been identified in several autoimmune and infectious diseases. To clarify the potential role of IL-18 during early innate immune responses, we have explored the capacity of IL-18 to activate neutrophils. Human peripheral blood-derived neutrophils constitutively expressed IL-18R (α and β) commensurate with the capacity to rapidly respond to IL-18. IL-18 induced cytokine and chemokine release from neutrophils that was protein synthesis dependent, up-regulated CD11b expression, induced granule release, and enhanced the respiratory burst following exposure to fMLP, but had no effect upon the rate of neutrophil apoptosis. The capacity to release cytokine and chemokine was significantly enhanced in neutrophils derived from rheumatoid arthritis synovial fluid, indicating differential responsiveness to IL-18 dependent upon prior neutrophil activation in vivo. Finally, IL-18 administration promoted neutrophil accumulation in vivo, whereas IL-18 neutralization suppressed the severity of footpad inflammation following carrageenan injection. The latter was accompanied by reduction in tissue myeloperoxidase expression and suppressed local TNF-α production. Together, these data define a novel role for IL-18 in activating neutrophils and thereby promoting early innate immune responses. The Journal of Immunology, 2001, 167: 2879–2886.

Interleukin-18 is a recently described member of the IL-1 cytokine family. Pro-IL-18 is cleaved by at least caspase 1 to yield an active 18-kDa glycoprotein (1). Initially characterized by its capacity to promote Th1 responses in synergy with IL-12 (2), IL-18 has been recently ascribed broader properties in the acquired immune response. Thus, it induces proliferation, IL-12Ra expression, and IFN-γ, TNF-α, and GM-CSF production by Th1 clones (3). However, at early stages of T cell differentiation, IL-18 can promote either Th1 or Th2 responses independently of IL-4 or IL-12, suggesting a broader role in functional T cell differentiation than that originally recognized (4). IL-18 enhances T cell and NK cell cytotoxicity and directly induces IFN-γ production by NK cells, suggesting some role in innate responses (5). IL-18 can also directly induce monokine production by macrophages that constitutively express IL-18R (6). Commensurate with a putative early role in immune responses, IL-18 mRNA is widely distributed, facilitating rapid generation of cytokine if required. Synthesis of IL-18 protein has been described thus far in macrophages, Kupffer cells, keratinocytes, fibroblasts, chondrocytes, and osteoblasts (6, 7–11). IL-18 is functionally regulated by IL-18 binding protein, a recently described Ig-like cytokine receptor that strongly suppresses developing Th1 responses through IL-18 neutralization (12).

IL-18 exerts important effects during host responses to infection. Thus, protective Th1 responses during murine Cryptococcus neoformans or Verruicella infections may be abrogated or enhanced by manipulation of IL-18 expression (13, 14), clearly indicating a role in microbial host defense. IL-18-deficient mice exhibit reduced responsiveness to Mycobacterium bovis, Propionibacterium acnes, and Leishmania major, associated with suppressed T cell/NK cell activation (5, 15). Moreover, we recently demonstrated that IL-18-deficient mice exhibit reduced capacity to kill Staphylococcus aureus in vivo associated with increased severity of septic arthritis (15). The precise mechanisms mediating the latter are currently unclear but could reflect impaired neutrophil function. Compatible with this, neutralization of IL-18 before LPS challenge reduces tissue myeloperoxidase (MPO)4 levels, suggesting that IL-18 is implicated at some stage in neutrophil activation (16). However, thus far, the direct effects of IL-18 on neutrophil function have not been defined.

Recent data indicate a role for IL-18 in the pathogenesis of several inflammatory disease states. IL-18 mRNA is up-regulated in nonobese diabetic mice and the murine IL-18 gene maps to the idd2 susceptibility locus (17). Similarly, IL-18 deficiency is associated with altered myeloid oligodenodrocyte glycoprotein peptide-specific autoreactive T cell responses and amelioration of autoimmune encephalomyelitis (18). In humans, IL-18 expression has been reported in psoriasis, inflammatory bowel disease, and sarcoidosis (19–21). We recently demonstrated that IL-18 is present in significant levels in the rheumatoid arthritis (RA) synovium (6), where it induces and sustains articular Th1 cell responses and independently promotes TNF-α production. IL-18-deficient mice develop significantly reduced incidence and severity of collagen-induced arthritis compared with wild-type mice, associated with suppressed TNF-α production and Th1 immune responses ex vivo (22). Finally, Ab-mediated IL-18 neutralization suppresses streptococcal cell wall-induced arthritis through an IFN-γ-independent

4 Abbreviations used in this paper used in this paper: MPO, myeloperoxidase; RA, rheumatoid arthritis; PB, peripheral blood; SF, synovial fluid; rh, recombinant human.

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mechanism (23). These data indicate that IL-18 is of importance during development and sustaining inflammatory pathologic states.

In the present study, we have explored the hypothesis that the functional role of IL-18 in innate immune responses may extend to neutrophil activation, and that this property of IL-18 may be of importance in chronic inflammatory diseases. Neutrophil infiltration is a feature of many autoimmune lesions including psoriasis, inflammatory bowel disease, and RA, although their qualitative and quantitative contribution therein is unclear. In RA, neutrophils constitute up to 90% of synovial fluid (SF) cells and are present also at the cartilage-pannus junction. Activated neutrophils secrete many of those cytokines and extracellular matrix-degradative enzymes implicated in RA pathogenesis (reviewed in Refs. 24 and 25). Circulating neutrophils in RA patients exhibit several features indicative of partial activation (24, 26). The present report documents for the first time direct biologic effects of IL-18 upon neutrophils. IL-18 enhanced adhesion molecule expression, respiratory burst, and chemokine production by peripheral blood (PB) neutrophils through constitutive IL-18R expression. Because prior to vivopriming could alter subsequent neutrophil function, we extended our studies to include neutrophils derived from RA synovium, which demonstrates that IL-18 induces high levels of proinflammatory cytokine production and degranulation by tissue neutrophils.

Materials and Methods

Isolation of neutrophils

PB from normal donors (n = 11) or RA PB (n = 11) and SF (n = 14) samples were collected from patients who satisfied the American College of Rheumatology 1987 criteria (27). Neutrophils were isolated as previously described (28) and resuspended in complete RPMI 1640 medium supplemented with 10% heat-inactivated fetal bovine serum, 100 IU penicillin, and 100 μg/ml streptomycin (all obtained from Life Technologies, Paisley, U.K.). The purity of the isolated neutrophils was assessed by FACS analysis and found to be 95% pure with <1% CD14, <2% CD19, and <2% CD3 cells.

RT-PCR and quantification of mRNA

The presence of IL-18R on neutrophils at the mRNA level was investigated by RT-PCR. RNA was extracted from purified neutrophils using RNAzol B (Biogenesis, Poole, U.K.), and cDNA was generated by reverse transcription using the SuperScript II system (Life Technologies) according to the manufacturer’s recommendations. PCR analysis of the cDNA was conducted using the recommended reaction mix (Life Technologies) according to the following primers: IL-18R, 5′-ACCTGTGATTAGTTGGGGG-3′ and 5′-ACTCATGCCACCTACCCTCC-3′; β-actin, 5′-AGGCCTGATCTCCTTCTGCTAC-3′ and 5′-CCACCTGTGGCCATCTAGGGG-3′ (Sigma-Genosys, Pampisford, U.K.). Reaction conditions were as follows: denaturing at 94°C for 40 s followed by 35 cycles of denaturing at 94°C for 40 s, annealing at 56°C for 30 s, and extending at 72°C for 60 s. The 305-bp product was confirmed by cloning into TA vector (Invitrogen, Groningen, The Netherlands) and sequencing with T7 DNAse polymerase kit (Amer sham, Little Chalfont, U.K.) according to the manufacturer’s protocol. Finally, cDNA levels of murine TNF-α and hypoxanthine phosphoribosyltransferase were quantitated by real-time PCR using an ABI prism 7700 sequence detector according to the manufacturer’s instructions (PerkinElmer Applied Biosystems, Foster City, CA). Amplification was achieved using an initial cycle of 50°C for 2 min and 95°C for 10 min followed by 40 cycles of 95°C for 15 s and 50°C for 1 min. The cDNA levels during the linear phase of amplification were normalized against hypoxanthine phosphoribosyltransferase controls. Calculations were made in triplicate and expressed as mean ± SD.

Neutrophil cytokine production in response to IL-18

Neutrophils were placed in 96-well flat-bottom plates (Nunc, Roskilde, Denmark) at 2 × 10⁶ cells/ml in complete RPMI 1640 medium supplemented with 10% FCS (Life Technologies) and stimulated with recombinant human (rh)IL-18 (6) at 1, 10, or 100 ng/ml for 24 h at 37°C. To determine whether de novo protein synthesis is induced by IL-18 activation, cycloheximide or actinomycin D (both at 2 μg/ml, obtained from Sigma-Aldrich, Poole, U.K.) was added to cells for 30 min before IL-18 addition. Finally, dexamethasone and methotrexate (both at 1 μM, obtained from Sigma) were used in inhibition studies. Culture supernatants were stored at −20°C until estimated by ELISA.

ELISA

IL-1α and IL-8 were detected using paired Abs (R&D Systems, Oxon, U.K.), and TNF-α was also detected using paired Abs (BD PharMingen, San Diego, CA). Recombinant IL-1α and IL-8 were obtained from R&D Systems, and TNF-α was a gift from Dr. G. R. Adolf (Boehringer Ingelheim Research and Development, Vienna, Austria). The detection limit for TNF-α and IL-1α was <10 pg/ml, IL-8 was <20 pg/ml. Lactoferrin was detected as previously described (29).

FACS analysis

To assess the purity of PB and SF neutrophils, cells were labeled with Abs against CD3, CD14, CD15, and CD19 (all obtained from Sigma) according to the manufacturer’s recommendations. Neutrophil IL-18R expression was determined by FACS analysis with monoclonal anti-IL-18R (R&D Systems) as previously described (6). Neutrophil activation was assessed by CD11b expression. Briefly, heparinized venous blood was diluted 1/10 in IMDM supplement with 2 mM -glutamine, 100 IU penicillin, and 100 μg/ml streptomycin (all obtained from Life Technologies). Cells were cultured for 1 h at 37°C either in the presence or absence of 100 ng/ml rhIL-18 and then labeled with anti-CD11b (Sigma). Propidium iodide (Sigma) and annexin V (BD PharMingen) staining for apoptosis was conducted according to the respective manufacturer’s recommendations, and cells were observed for signs of apoptosis up to 24 h cultured either in medium alone or with 100 ng/ml rhIL-18. All stained cells were analyzed using a BD Biosciences (San Jose, CA) FACS Calibur with CellQuest software.

Effect of IL-18 on neutrophil respiratory burst

Mediators such as GM-CSF and TNF-α have been shown to have “priming” effects on neutrophils, altering the subsequent respiratory burst in response to stimuli such as immune complexes, PMA, or the bacterial chemoattractant FMLP. Neutrophils were placed in 24-well flat-bottom plates (Nunc) at 10⁷ cells/ml in medium with 10% FCS and stimulated with 100 ng/ml rhIL-18 for 1 h at 37°C. Neutrophils were transferred to triplicate wells of a luminometer microtiter plate in the presence of 10 μM luminol solution (Sigma). A total of 1 μM IMLP (Sigma) was added, and the plate was read immediately in a MLX microtiter plate luminometer (Dynex, Middlesex, U.K.).

In vivo estimation of IL-18 function

Carrageenan-induced inflammation was initiated in BALB/c mice as described previously (30). Neutralizing monoclonal anti-IL-18 Ab or control Ab (both at 25 μg/animal, obtained from R&D Systems) was administered i.p. 30 min before and 24 h after carrageenan injection into the right hind footpad. The change in footpad thickness between the right and left hind limbs was measured with a dial caliper (Kroepelin, Munich, Germany). In some experiments, 4- to 5-week-old male BALB/c mice received i.p. injection (0.5 ml total volume) of recombinant murine IL-18 (R&D Systems) at doses indicated or of PBS, and neutrophil accumulation within the peritoneal cavity was calculated at various times thereafter as previously described (31). Briefly, after IL-18 or PBS injection, the animals were killed and the peritoneal cavity cells were harvested by washing the cavity with 5 ml PBS containing 1 mM EDTA. The volume recovered was similar in all groups tested. Total counts were performed in a cell counter (Coulter Counter CBCS; Coulter, Miami, FL) and differential cell counts enumerated on cytocentrifuge (Shandon, Pittsburgh, PA) slides stained with Rosenfeld. The differential count (200 cells) was performed under a light microscope and the results presented as number of neutrophils per cavity.

MPO assay

Footpads were removed 24 h after carrageenan challenge, and the content of MPO was determined as described previously (16). Neutralizing activity of the test or Student’s t test as indicated.
Results
Neutrophils express IL-18R

We first sought evidence of IL-18R expression. Neutrophils derived from both normal donors and RA patients constitutively expressed IL-18R α- and IL-18R β-chain mRNA (Fig. 1A). Surface expression of IL-18Rα was confirmed by FACS in PB samples from both normal donors and RA patients. No significant difference in the level of expression was observed in PB derived from RA or normal donors (Fig. 1B). Similar data were obtained using a whole-blood culture FACS method, indicating that such expression was unlikely to reflect partial activation during purification (data not shown). These data suggest that IL-18 could initiate early biologic effects on neutrophils. To determine whether IL-18R expression (data not shown). To investigate potential mechanisms underlying this observation, we examined up-regulation of CD11b. PB neutrophils from RA patients expressed significantly higher basal levels of CD11b than normal donors, indicating partial prior activation in vivo. Incubation of PB neutrophils from either normal donors or RA patients with rhIL-18 resulted in a significant increase in CD11b expression compared with control cells (Table I). Maximal CD11b expression was similar in RA and normal donor groups.

Table I.  IL-18 up-regulates CD11b expression in normal and RA PB neutrophils

<table>
<thead>
<tr>
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<th>CD11b Expression (Mean Fluorescence Intensity)</th>
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<tr>
<td></td>
<td>PN</td>
</tr>
<tr>
<td>Normal</td>
<td>36.2 ± 15.9</td>
</tr>
<tr>
<td>RA</td>
<td>148.0 ± 51.7</td>
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a PB neutrophils were cultured either with medium alone or in the presence of rhIL-18 (100 ng/ml) for 1 h, after which CD11b expression was measured by FACS analysis. Data are expressed as mean fluorescence intensity ± SD. A significant increase in CD11b was observed in RA PB neutrophils when compared with normal donors. *, p < 0.05 by Mann-Whitney U test. Furthermore, IL-18 induced CD11b up-regulation from both normal and RA-derived PB neutrophils. **, p < 0.05 vs medium control.

IL-18 modulated neutrophil adhesion molecule expression

Constitutive expression of IL-18Rα indicated that IL-18 could exert early effects on neutrophil adhesion. The i.p. injection of recombinant murine IL-18 into BALB/c mice induced rapid influx of neutrophils that was maximal at 4 h and reduced by 48 h (Fig. 2, A and B). Similar data were obtained when IL-18 was injected in an identical protocol into C3H/HEJ mice, indicating that low-level LPS contamination is unlikely to explain our observations (data not shown). To establish a time course, 20 ng IL-18 was injected, and neutrophil accumulation was estimated at the time points shown (Fig. 2). Values of p < 0.05 vs PBS control group by Mann-Whitney U test. Data are presented as the mean ± SEM and are representative of five separate experiments with five mice per group.

FIGURE 1.  Neutrophils express IL-18R mRNA and protein. A, RT/PCR was used to detect IL-18R α-chain and β-chain expression. Lanes 1–3, IL-18Rα expression; lanes 4–6, IL-18Rβ expression; L, ladder. Lanes 1 and 4 are representative of normal PB-derived neutrophils, 2 and 5 of positive control, and 3 and 6 of negative control. B, Cell surface expression of IL-18Rα on neutrophils was analyzed by FACS analysis of normal PB neutrophils (n = 6), RA PB (n = 7), and RA SF (n = 12). Data are presented as the mean ± SEM of each group, *, p < 0.05, by Student’s t test.

FIGURE 2.  IL-18 administration induced accumulation of neutrophils in the peritoneal cavity of 4- to 5-wk-old male BALB/c mice. Mice received 0, 20, or 60 ng recombinant murine IL-18 in a total volume of 0.5 ml PBS. Neutrophil accumulation was measured after 4 h (A). Thereafter, to establish a time course, 20 ng IL-18 was injected, and neutrophil accumulation was estimated at the time points shown (B). *, Values of p < 0.05 vs PBS control group by Mann-Whitney U test. Data are presented as the mean ± SEM and are representative of five separate experiments with five mice per group.
IL-18 induced chemokine and cytokine production by neutrophils

Neutrophils are abundant in inflammatory lesions, and their ability to produce inflammatory mediators has recently been recognized. PB neutrophils produced high levels of IL-8 in a dose-dependant manner in response to IL-18, providing a further mechanism whereby IL-18 may promote neutrophil recruitment into inflammatory lesions (Fig. 3A). Of interest, IL-8 production to IL-18 was reduced in RA donors. This may reflect concomitant drug therapy, because preincubation with either dexamethasone or methotrexate ablated IL-18-mediated cytokine release (Fig. 3B). Low levels of IL-1α production were observed from PB neutrophils derived from normal donors only (Fig. 3C). Finally, a minority of patient and normal PB donor neutrophils produced low levels of TNF-α (data not shown). Thus, the potential for ex vivo cytokine release appeared to be qualitatively and quantitatively altered by prior in vivo activation. To determine whether de novo protein synthesis was required for cytokine production, neutrophils were cultured in the presence of actinomycin D and cyclohexamide, leading to highly significant suppression of all cytokine production (Fig. 4, A–D). Thus, de novo cytokine synthesis, rather than granule release, most likely explains our observations.

Effects of IL-18 on neutrophil degranulation

The presence of a neutrophil granule constituent, lactoferrin, in culture supernatants may serve as a surrogate marker for neutrophil degranulation (24). Lactoferrin release increased dose dependently in response to IL-18 (Fig. 5). Furthermore, lactoferrin release in response to IL-18 (100 ng/ml) was significantly higher from SF neutrophils than from RA or normal PB neutrophils, commensurate with in situ activation in the synovial compartment.

Effects of IL-18 on respiratory burst

Prior incubation of neutrophils with IL-18 led to significant enhancement of the response to fMLP (p < 0.05) that was evident in normal and in RA-derived PB neutrophils (Fig. 6). However, SF neutrophils failed to respond to fMLP following preincubation with IL-18. This is consistent with the previously described phenomenon of neutrophil “exhaustion” with respect to respiratory burst (32).

IL-18 did not modulate neutrophil apoptosis

Antiapoptotic effects of innate cytokines including IL-15 and GM-CSF have been previously observed for neutrophils (33, 34). Therefore, we investigated whether IL-18 can promote neutrophil survival at sites of inflammation. After up to 24 h of incubation with IL-18 (100 ng/ml), apoptosis was determined by propidium iodide and annexin V staining. No difference was observed in IL-18-treated cells compared with medium controls at any time point (data not shown).
Anti-IL-18 Ab suppresses neutrophil-mediated inflammation in vivo

Finally, we investigated whether in vivo neutralization of IL-18 could modify neutrophil-mediated acute inflammatory responses. Anti-IL-18 Ab was administered to BALB/c mice before footpad carrageenan challenge. Anti-IL-18 recipient mice exhibited significantly reduced paw pad edema compared with control mice ($p < 0.01$; Fig. 7A). Consistent with this, tissue MPO activity was significantly reduced in anti-IL-18-treated mice (Fig. 7B). Cytokine mRNA expression assessed by real-time PCR demonstrated significant suppression of footpad TNF-α expression (Fig. 7C). Importantly, lymph node cytokine mRNA (by TaqMan PCR) and cellular proliferation and cytokine production (IFN-γ, TNF-α, and IL-6) to anti-CD3 in draining lymph node cultures was unaltered in anti-IL-18-treated mice (data not shown), suggesting that the primary effects of Ab administration were manifest locally.

Discussion

The present report clearly demonstrates that IL-18 plays an important role in neutrophil activation. Our data define a novel pathway whereby IL-18 can amplify acute inflammation through promoting neutrophil adhesion and migration, cytokine and chemokine production, granule release, and respiratory burst. Such effects are of relevance in vivo because IL-18 administration induced peritoneal neutrophil recruitment, whereas Ab-mediated neutralization of IL-18 suppressed the development of carrageenan-induced acute inflammation. These data strongly support the notion that the biologic effects of IL-18 extend beyond promoting
Th1-type responses to include an important role in developing innate immune responses. By implication, regulation of IL-18 may be an important determinant in the evolution of responses from acute to the acquired or chronic phase.

Several recent data indicate an important role for IL-18 in host defense to a broad range of microbes, including C. neoformans, Y. enterocoliticus, M. bovis, P. acnes, L. major, and S. aureus (5, 13–14). IL-18-mediated protective effects have been proposed to operate mainly through regulation of T cell and NK cell activation and enhanced monokine production (5, 35). Our data indicate that polymorphonuclear cell activation will also be of importance, especially during Gram-positive bacterial infection, in which neutrophil function is paramount. We demonstrated constitutive IL-18R expression, indicating that IL-18-dependent responses may be rapidly recruited. Several reports indicate that IL-18 is present at an early stage following S. aureus infection (36, 37). Addition of IL-18 binding protein in vitro promptly downregulates IFN-γ production following S. epidermidis infection in whole-blood cultures (38). We have also observed that intracellular IL-18 protein expression is detectable within 15 min of S. aureus (Cowan strain) ingestion by human monocytes (data not shown). Our data suggest that, following microbial challenge, IL-18 can rapidly enhance neutrophil recruitment and killing activity. Commensurate with this, IL-18-deficient mice exhibit reduced killing of S. aureus in vivo (15), suggesting that the IL-18-dependent pathways elucidated here may be of critical importance.

Higher levels of IL-18R expression were detected in neutrophils derived from RA SF than from blood. Wide variability was observed in the magnitude of neutrophil IL-18R expression between individuals and in cells from different tissue compartments. Because samples were collected and treated in a similar manner, it is unlikely that processing artifact can explain all of the observed variation. Given its relative importance in regulating acquired and innate responses, it is likely that IL-18R α-chain expression will be tightly regulated. Whereas IL-18R expression on T cells is regulated in part by IL-12, the factors that alter IL-18R expression on neutrophils are unknown and are being sought in our laboratory. IL-18R is a member of the Toll/IL-1R family, suggesting that the IL-18/IL-18R system has evolved as a component of the innate response (39). Pathways that modulate IL-18R will likely modulate potential neutrophil function and may in due course have implications for Toll/IL-1R family regulation on neutrophils and other cell types.

Sustained IL-18 expression has been reported in a number of chronic inflammatory disease states including RA, inflammatory...
bowl disease, and sarcoidosis (6, 20, 21). The mechanisms whereby IL-18 could contribute to disease pathogenesis remain poorly defined. An important component of the present study was to determine whether effects of IL-18 on neutrophils could extend beyond acute inflammation (e.g., carrageenan induced) to include some contribution to chronic synovitis. In RA, proposed mechanisms whereby IL-18 can drive synovitis include regulation of local Th1 responses, direct effects on proinflammatory monokine production, enhanced NO production, and direct effects on chondrocytes and matrix degradation (6, 11). Commensurate with high levels of IL-18R expression, synovial neutrophils retained a high degree of responsiveness to IL-18, leading to significant cytokine and chemokine production. The quantitative contribution of neutrophils to cytokine expression in RA is unclear but could be considerable given their abundance within the synovial compartment. That IL-18 also induced degranulation is of importance because granule contents of synovial neutrophils include collagenase, cathepsin G, gelatinase, elastase, and phospholipase A2, all of which may be of functional significance in promoting articular destruction. Although neutrophils are detected in low numbers at the cartilage-pannus junction (25, 40), the majority are trafficked to SF. Thus, IL-18-activated neutrophils could contribute directly to altered cartilage turnover, because SF directly bathes the cartilage matrix, or could modulate synovial lining layer cells through adjacent release of cytokines or chemokines (25).

It is of interest that recent effective therapeutic developments in RA, namely TNF-α blockade and leflunomide, exhibit powerful effects on neutrophil recruitment in vivo (41, 42). RA PB neutrophils expressed higher basal levels of CD11b yet produced significantly less IL-8 in response to IL-18 than normal PB. We also observed suppression of the IL-18 response in vitro by corticosteroid and to a lesser extent by methotrexate. In contrast, the effects of IL-18 on respiratory burst and granule release were similar on RA and normal PB neutrophils. This suggests complex regulation of discrete neutrophil functions, amenable to distinct interventions. PB neutrophils from RA patients exhibit evidence of prior activation compared with normal PB controls that could further explain variable responses to IL-18 observed in this study.

Taken together, our data suggest a role for IL-18 in innate neutrophil lead responses in addition to its clearly deleterious role in T cell maturation. Our data have two-edged consequences for therapeutic targeting of IL-18. IL-18 blockade may abrogate host toxic neutrophil responses in addition to its clearly deleterious role in T cell maturation. Hence, therapeutic targeting of IL-18, IL-18 blockade may abrogate host toxic neutrophil responses in addition to its clearly deleterious role in T cell maturation.


