Role of M-CSF-dependent macrophages in colitis is driven by the nature of the inflammatory stimulus

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Macrophage colony-stimulating factor (M-CSF) is a critical trophic and differentiation factor for macrophages and osteoclasts (37). Mice with a defect in the M-CSF encoding region exhibit osteopetrosis and have been shown to be deficient in osteoclasts, monocytes, and tissue macrophages (28). A single nucleotide (T) insertion 262 bp downstream from the initiation codon resulted in a frame shift and the creation of a stop 21 bp downstream of the insertion. M-CSF-deficient (op/op) mice have provided a useful tool in the investigation of the role macrophages in a variety of conditions. Macrophages are derived into several subsets, based on exposure to panels of chemokines and growth factors such as granulocyte macrophage colony-stimulating factor (GM-CSF) and M-CSF (2, 23). Both M-CSF and GM-CSF have been implicated in the differentiation of macrophages with counterinflammatory properties, and M-CSF enhances the IL-10-dependent suppressor activity of macrophages (26). Experimental colitis induced by tri- or dinitrobenzene sulfonic acid (TNBS or DSS) or by oral administration of dextran sulfate sodium (DSS) are two of the most widely used models of intestinal bowel disease (IBD) (for reviews, see Refs. 13 and 32). The hapten-induced model of colonic inflammation in which 2,4,6-TNBS is delivered induces a Th1 cell-mediated colitis (29). The hapten DNBS also induces a similar colitis in mice, characterized by mucosal ulceration and transmural inflammation (33).

The DSS model is also a well-characterized model of colitis that develops following exposure to DSS in the drinking water. Mice develop symptoms such as diarrhea, rectal bleeding, and weight loss (8, 12, 30). The underlying histology reveals erosion of the epithelium and distortion of crypt architecture. This is accompanied by an influx of macrophages and granulocytes and changes in T cell activation although the model is not associated with a classical Th-1 response.

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In the present study, we used these models of colitis to examine the role of M-CSF-dependent macrophages in the inflammatory processes, using M-CSF-deficient op/op mice. Our results indicate that although the absence of M-CSF-dependent macrophages increased the severity of DNBS colitis, the absence of these cells reduced the severity of DSS colitis. Thus M-CSF-dependent macrophages play a dominant pro- or counterinflammatory role in colitis, depending on the manner in which inflammation is induced.

MATERIALS AND METHODS

Animals. M-CSF-deficient mice (op/op) as well as heterozygotes +/? breeding pairs were purchased from Jackson (Bar Harbor, ME) and kept under specific pathogen-free conditions in McMaster University central animal facilities. A colony was obtained by breeding +/op mice. Mutant mice are characterized by osteopetrosis and lack of incisors, due to the absence of osteoclasts, derived from the same precursors as M-CSF-dependent macrophages (43). Nonhomozygous mice are +/op or +/+; are phenotypically indistinguishable from each other (therefore named +/?), and do not present either osteopetrosis or macrophage deficiency (24). Op/op mice were fed powdered Purina chow, whereas the +/? mice received conventional Purina chow. All the experiments were approved by McMaster Animal Care Committee and the Canadian Council on the Use of Laboratory Animals.

DNBS-induced colitis. DNBS colitis was induced by intrarectal instillation of a 0.1-m solution containing 3 mg of DNBS (ICN Biomedicals, Aurora, OH) dissolved in 50% ethanol or 50% ethanol alone as a control. The magnitude of colitis was evaluated at day 1 and day 3 after induction, by assessing macroscopic damage score, histological damage, and myeloperoxidase (MPO) activity. Macroscopic damage was assessed by using a score described by Chin and Barrett (7). Histological damage was evaluated on full-thickness specimens processed and stained with hematoxylin and eosin (H&E), by using a described score (5). An unaware observer assessed both macroscopic and histological damages. MPO activity, as index of granulocytic infiltrate, was measured on full-thickness samples by the method described by Bradley et al. (6). Samples were also taken to measure proinflammatory cytokine and chemokine macrophage inflammatory protein-1α (MIP-1α) levels by ELISA and to evaluate the presence of macrophages by immunohistochemistry for the marker F4/80, a surface antigen expressed by mature murine macrophages.

DSS-induced colitis. Mice received 5% DSS (Sigma, St. Louis, MO) in their drinking water, whereas control mice received water alone as drinking fluid. After 5 or 7 days of treatment mice were euthanized by cervical dislocation. Severity of colitis was assessed by evaluating the histological damage, MPO activity, proinflammatory cytokine, and chemokine MIP-1α levels. Full-thickness specimens were taken, fixed in 10% formalin, routinely processed, and stained with H&E for histological analysis. Histological damage was assessed by using a described score (8). MPO activity and presence of macrophages were evaluated on full-thickness sections, as described below. The disease activity index, was evaluated in mice receiving 5% DSS for seven consecutively days.

Assessment of the severity of colitis: DAI. Disease activity index (DAI) scores have historically correlated well with the pathological findings in a DSS-induced model of IBD (8). DAI is the combined score of weight loss, stool consistency, and bleeding. Scores were defined as follows: weight: 0, no loss; 1, 5–10%; 2, 10–15%; 3, 15–20%; and 4, 20% weight loss; stool: 0, normal; 2, loose stool; and 4, diarrhea; and bleeding: 0, no blood; 2, presence; and 4, gross blood.

MPO activity. MPO activity was determined by following an established protocol (6). Briefly, MPO activity, used to detect eosinophils peroxidase, was measured by a modified version of the method described by Bradley et al. (6). Tissue samples were homogenized (50 mg/ml) in ice-cold 50 mM potassium phosphate buffer (pH 6.0) containing 0.5% hexadecyl trimethyl ammonium bromide (Sigma, St Louis, MO). The homogenate was freeze-thawed three times, briefly sonicated, and then centrifuged at 12,000 rpm for 12 min at 4°C. The supernatant was then added to a solution of o-dianisidine (Sigma, St Louis, MO) and hydrogen peroxide. The absorbance of the colorimetric reaction was measured by a spectrophotometer. MPO is expressed in units per milligram of wet tissue, 1 unit being the quantity of enzyme able to convert 1 μmol of hydrogen peroxide to water in 1 min at room temperature.

Immunohistochemistry for macrophages. Immunohistochemistry was performed on cryopreserved sections 4 μm thick using a biotin-streptavidin indirect technique as follows: sections were fixed in cold acetone and washed in Tris-phosphate buffer (TBS) three times. Slides were then incubated in 3% hydrogen peroxide for 30 min, washed three times in TBS, and incubated in 1% BSA for 60 min. After a wash the primary antibody (clone CI:A3–1 Serotec, Oxford, UK) was added at a dilution of 1:50 and incubated overnight at room temperature. Sections were then washed and a secondary antibody (goat anti-rat, Cedarlane Laboratories, Hornby, Ontario, Canada, dilution 1:200) was added for 60 min. After wash, the streptavidin (GIBCO-BRL Life Technologies, Burlington, Ontario, Canada, dilution 1:300) was added for 60 min. Slides were then washed and incubated for 15 min in acetate buffer solution containing the chromogen 3-amino-9-ethylcarbazole (Sigma, St Louis, MO) and hydrogen peroxide. Slides were then counterstained with Mayer’s hematoxylin, covered, and examined under a light microscope by a blinded observer.

Cytokine levels. Cytokine levels were analyzed 5 or 3 days after the beginning of the DSS or DNBS treatment, respectively. Colonic sample was homogenized in 700 μl of Tris·HCl buffer containing protease inhibitors (Sigma, St Louis, MO). Samples were centrifuged for 30 min, and the supernatant was frozen at −80°C until assay. Cytokine levels (IL-1β, IL-6, IL-10, and TNF-α) were determined using ELISA commercial kit (Quantikine M murine; R&D Systems, Minneapolis, MN).

Determination of colonic MIP-1α. MIP-1α levels were analyzed 5 or 3 days after the beginning of the DSS or DNBS treatment, respectively. Full-thickness specimens were taken from the colon, weighted, and homogenized in phosphate-buffered saline. MIP-1α content of the tissues were determined using an ELISA technique, MIP-1α levels are expressed as picograms of protein per milligram of tissue (36).

Reconstitution with human-recombinant M-CSF. In different experiments, op/op mice were treated with human recombinant macrophage colony-stimulating factor (hr-M-CSF, kindly donated by Chiron, Emeryville, CA). Mice received 50 μg of hr-M-CSF intraperitoneally twice a day, starting 2 days prior to colitis induction and daily until the euthanasia.

Data analysis. All the experiments, excluding the reconstitution with hr-M-CSF, which involved six animals, involved at least eight animals per group. Data are expressed as means ± SE. Statistical analysis was performed by Kruskal-Wallis, ANOVA, and Bonferroni’s tests. Statistical significance was inferred for P values < 0.05.

RESULTS

In the absence of colitis, no macroscopic nor histological differences were noticed in the colon in op/op compared with +/+ mice. Similarly, MPO activity was similar between the two groups of mice (0.3 ± 0.1 compared with 0.1 ± 0.08 U/mg of protein in +/+ mice, P > 0.05).

Increased severity of DNBS colitis in op/op mice. DNBS colitis was associated with a massive transmural infiltrate of F4/80 positive macrophages in +/+ mice. As shown in Fig. 1A, F4/80 positive cells were evident in mucosa, submucosa, and muscle layers. In contrast, F4/80 macrophages were almost

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absent in op/op mice with DNBS-induced colitis (Fig. 1B). These findings suggest a role for M-CSF-derived macrophages in DNBS colitis and validate the use of the op/op mouse to examine their role. The severity of colitis was substantially greater in op/op mice compared with the M-CSF-expressing +/-? mice. Indeed, DNBS-induced colitis caused a 55% spontaneous mortality in the M-CSF-deficient op/op mice within 3 days after the induction, whereas all the M-CSF-expressing +/-? mice survived at day 3 postcolitis. As illustrated in Fig. 2A, the increased severity of colitis in op/op mice was evident in the macroscopic score, which increased by 64% at day 1, and by 121% by day 3 post-DNBS compared with values seen in

![Image](https://via.placeholder.com/150)

**Fig. 1.** Macrophage infiltration in the colon 3 days after induction of dinitrobenzene sulfonic acid (DNBS)-induced colitis evaluated by immunohistochemistry for F4/80. A: cryopreserved cross section of colon from colitic +/-? mouse. Note the presence of transmural infiltrate of a large number of F4/80-positive cells (arrow). B: cryopreserved cross section of colon from colitic M-CSF-deficient op/op mouse. C: cryopreserved cross section of colon from colitic M-CSF-deficient op/op mouse mice after treatment with exogenous human recombinant M-CSF (hr-M-CSF). Note that only a few scattered positive cells are present.

![Image](https://via.placeholder.com/150)

**Fig. 2.** A: magnitude of DNBS-induced colitis expressed as macroscopic score of the damage at day 1 and day 3 postinduction. B: histological score of the damage at day 1 and day 3 postinduction. C: myeloperoxidase (MPO) activity in full-thickness colonic tissue at day 1 and day 3 after DNBS-induced colitis. D: cytokine level in full-thickness colonic tissue at day 3 after DNBS-induced colitis. Open bars represent +/-? mice and solid bars represent op/op mice. Values are means ± SE from n = 8 experiments. *P < 0.05.
and +/− mice. Similarly, the scores for histological damage during colitis were significantly higher in op/op mice compared with +/− mice (see Fig. 2B). In addition, the increases in MPO activity postcolitis were significantly greater in op/op mice compared with +/− mice; values were 121% greater at day 1 and 171% greater at day 3 post-DNBS in op/op mice (see Fig. 2C).

Increases in proinflammatory cytokines TNF-α, IL-1β, and IL-6 were seen in both +/− and op/op mice with colitis. Concentration of TNF-α, IL-1β, IL-6, and IL-10 found in noninflamed control op/op were 2.13 ± 0.1, 26.75 ± 3.1, 7.85 ± 1.15, and 2.25 ± 0.2 mg/mg of protein, respectively, and in +/− mice 2.45 ± 0.25, 24.79 ± 0.47, 7.15 ± 1.2, and 3.15 ± 0.4 mg/mg of protein. As shown in Fig. 2D, the fold increases over noninflamed controls were 6.34 ± 0.8 for TNF-α in op/op mice compared with 4.1 ± 0.14 in +/− mice. Corresponding values for IL-1β were 5.44 ± 0.2 vs. 3.5 ± 0.26, for IL-6 2.5 ± 0.13 vs. 1.38 ± 0.4. The fold increases over noninflamed controls were 3.25 ± 0.7 for the anti-inflammatory cytokine IL-10 in op/op mice compared with 7.3 ± 0.2 in +/− mice. Each of these increases was statistically significant (Fig. 2D).

Effect of treatment with hr-M-CSF on DNBS colitis in op/op mice. To confirm the role of M-CSF in the susceptibility of op/op mice to DNBS colitis, studies were performed on op/op mice reconstituted with hr-M-CSF. Treatment with hr-M-CSF was accompanied by the presence of a large infiltrate of macrophages in the colon of op/op mice following DNBS administration (Fig. 1C). M-CSF-treated mice also exhibited a reduction in mortality from 55 to 25%. This was associated with a reduction in the severity of colitis. As shown in Fig. 3A, M-CSF-treated op/op mice demonstrated a significant reduction in the macroscopic injury score on day 3 post-DNBS. Similarly, there was a significant reduction in the histological damage score in M-CSF-treated op/op mice at day 3 after DNBS (Fig. 3B). As shown in Fig. 3C, there was a significant 48% reduction in MPO activity in M-CSF-treated mice evident at day 1 post-DNBS and a decrease of 55% at day 3 post-DNBS.

DSS-induced colitis. To determine whether the protective role of M-CSF-dependent macrophages was specific for the hapten-induced colitis, we next examined DSS-induced colitis in op/op mice. DSS induced a significant colitis in both op/op and +/− mice. In contrast to studies in DNBS colitis, DSS colitis appeared more severe in M-CSF-expressing +/− mice, as reflected by the DAI. As shown in Fig. 4, the differences in severity became evident at days 4 and 5 post-DSS. The DAI was 61% lower in op/op mice compared with +/− mice at day 4 post-DSS and 39% at day 5 (Fig. 4). To determine whether there was a delay in the influx of inflammatory cells from the circulation, we extended our protocol by 2 more days (to a total of 7 days), and found that the DAI was also significantly lower in op/op mice compared with +/− mice. This unexpected reduction in disease severity seen in op/op mice post-DSS was also reflected in the parameters of inflammation, as shown in Fig. 5. At day 5, DSS increased significantly the macroscopic score from 0.45 ± 0.12 to 3.25 ± 0.25 in +/− mice and from 0.44 ± 0.10 to 1.25 ± 0.37 in op/op mice and the difference between these responses was statistically significant (see Fig. 5A). Similarly, the fold increase in histological damage scores was significantly less in op/op mice compared with +/− mice (Fig. 5B). This pattern was also seen with MPO activity. DSS 5% significantly increased MPO activity from 0.2 ± 0.1 to 2.04 ± 0.5 U/mg in +/− mice compared with an increase from 0.2 ± 0.15 to only 1.2 ± 0.2 U/mg in op/op mice (Fig. 5C).

Concentration of TNF-α, IL-1β, IL-6, and IL-10 found in control op/op were 2.75 ± 1.27, 15.85 ± 2.2, 4.79 ± 0.19, and 4.2 ± 0.4 pg/mg of protein, respectively, and in +/− mice 2.15 ± 0.21, 14.56 ± 0.189, 4.35 ± 0.21, and 3.9 ± 0.29 pg/mg of protein. We found significantly smaller increases in proinflammatory cytokines in the colon of op/op mice with DSS colitis (Fig. 5D). The fold increases over noninflamed controls were 1.8 ± 0.2 for TNF-α in op/op mice compared with 3.7 ± 0.15 in +/− mice. Corresponding values for IL-1β were 1.25 ± 0.1 vs. 1.8 ± 0.2 and for IL-6 were 1.2 ± 0.2 vs. 2.1 ± 0.8. No differences were seen for IL-10; corresponding values were 1.2 ± 0.17 pg/mg for the op/op and 1.4 ± 0.2 pg/mg for the +/− mice.

MIP-1α levels in DNBS- and DSS-induced colitis. We next examined the tissue concentrations of MIP-1α, a chemokine that plays a key role in the recruitment of macrophages and other inflammatory cells. Both DNBS- and DSS-induced colitis were associated with increased levels of MIP-1α. MIP-1α levels were higher in op/op mice compared with +/− mice in the absence of colitis. As shown in Fig. 6A, following the

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**Fig. 3.** Effect of hr-M-CSF on DNBS colitis. A: magnitude of DNBS-induced colitis expressed as macroscopic score of the damage at day 1 and day 3 postinduction. B: histological score of the damage at day 1 and day 3 postinduction. C: MPO activity in full-thickness colonic tissue at day 1 and day 3 after DNBS-induced colitis. Solid bars represent op/op mice and hatched bars represent op/op mice-treated. Values are means ± SE from n = 6 experiments. *P < 0.05.
induction of colitis by DNBS, there was no significant increase in this chemokine in +/? mice. In contrast, there was a sevenfold and a ninefold increase in MIP-1α in op/op mice at days 1 and 3 post-DNBS. In contrast, no difference was seen in MIP-1α between op/op and +/? mice with DSS colitis (Fig. 6B).

DISCUSSION

In this study, we investigated the role of M-CSF-dependent macrophages in intestinal inflammation. Using two different experimental models of colitis in M-CSF-deficient mice, we have shown that this cell type plays a complex role in acute colonic inflammation, being protective in hapten-induced DNBS colitis but proinflammatory in DSS-induced colitis. In our previous work in the model of nematode-induced enteritis, we observed similar histological damage and MPO activity in M-CSF-deficient and M-CSF-expressing mice, suggesting that this subset of macrophages did not contribute to the mucosal inflammatory response to the parasite (16). Taken together with recent studies (21), these findings suggest that the role of macrophages differs depending on the nature of the inflammatory milieu and the stimulus used to induce the inflammatory response.

The results of this study also add to the growing body of literature demonstrating the functional diversity of macrophages during inflammation. Recently, it has been shown that GM-CSF and M-CSF can polarize the differentiation of bone marrow CD11b+ cells in two different macrophage populations releasing pro- and counterinflammatory cytokines, respectively (21). The exact role in vivo of GM-CSF and M-CSF in relation to each other has been difficult to define, particularly in view of their overlapping functional activities, GM-CSF acting earlier and M-CSF acting later in the course of macrophage differentiation and activation (20). These observations underscore the importance of M-CSF in the functional diversity of macrophages and rationalize the use of the M-CSF-deficient op/op mouse (42) in this study. In absence of M-CSF-dependent macrophages DNBS colitis was associated with high mortality rate and greater macroscopic histological damage, MPO activity, and TNF-α, IL-1β, IL-6 production but was also associated with a decrease in IL-10 production indicating a protective role of M-CSF-dependent macrophages in this model of intestinal inflammation. The differentiation of macrophages into a counterinflammatory phenotype requires IL-10, and previous work has shown that IL-10 is increased in the colon of mice with TNBS-induced colitis (22). This is confirmed by our results showing an increase of IL-10 vs. control
mice in both phenotype. However, in absence of M-CSF this increase is significantly reduced compared with the heterozygote group. The remaining increase of IL-10 in M-CSF-deficient mice likely originates from other immune cells including T lymphocytes, as the DNBS hapten model colitis is triggered via a T cell-mediated mechanism. We speculate that this small amount of IL-10 is sufficient to induce the differentiation of macrophages into a counterinflammatory phenotype releasing more IL-10 in the heterozygote mice. In our study the increased severity of colitis in op/op mice is likely due to the absence of these counterinflammatory macrophages.

We observed a compensatory increase in MIP-1α in op/op mice with DNBS colitis. A recent study by von Stebut et al. (40) has shown that, in a model of cutaneous granuloma, the influx of macrophages depends on the release of MIP-1α by neutrophils. We have shown a greater increase in MPO activity in colitic M-CSF-deficient mice compared with their M-CSF-expressing littermates. Therefore our finding might indicate that, in absence of the principal target cell, MIP-1α is overproduced as a compensatory mechanism by granulocyte, as indicated by MPO activity. This is supported by the fact that when the macrophagic infiltrate was restored with hr-M-CSF, MPO levels dropped to values similar to those seen in +/? colitic mice. Although this MIP-1α is mainly involved in the recruitment of monocytes, is also involved in the recruitment of other cells such as lymphocytes and neutrophils (36). Moreover it has been shown that systemic administration of MIP-1α worsened experimental colitis in mice by boosting the T cell responses in the gut wall (1, 31). Thus is possible that this chemokine contributes indirectly to the enhancement of the inflammatory process induced by DNBS in op/op mice.

Macrophage scavenger receptor (MSR-A) is a family of membrane receptors involved in the phagocytosis and binding of macrophages to the bacterial wall, and its expression is enhanced by M-CSF (9). Therefore, another possible explanation for our finding of an enhanced inflammatory response to DNBS in op/op mice is an impairment of MSR-A-mediated phagocytosis with a consequent aggravation of colitis due to overimposed systemic bacterial infection. Thomas et al. (39) have shown that MSR-A-deficient mice are more sensitive to gram-positive-induced peritonitis and de Villiers et al. (10) reported increased severity of TNBS colitis in MSR-A-deficient mice. However, our mice were kept in specific pathogen-free conditions and previous studies have demonstrated that M-CSF-deficient mice are not more susceptible to bacterial peritonitis than their normal littermates (14). In addition, studies in the respiratory tract have shown that op/op mice are susceptible to Mycobacterium tuberculosis infection, suggesting a preserved phagocytic function, but they present a higher mortality, indicating a failure in the immune response (38).

In contrast to our findings with DNBS, colitis induced by DSS improved in the absence of M-CSF as mentioned by Marshall et al. (25) using anti-MCSF antibody, suggesting a proinflammatory role of M-CSF-dependent macrophages in this model. This improvement was reflected in all parameters including DAI, macroscopic and histological scores, MPO activity, and proinflammatory cytokine levels, but no changes were seen for the IL-10 production. The histological improvement was characterized by a reduced cellular infiltrate, probably due to the absence of M-CSF in DSS colitis in op/op mice, but this was not associated with a greater increase in MPO activity, as was observed in the DNBS model. As we also found a smaller increase in MIP-1α in op/op and +/? mice with DSS colitis as reported by Selmecky et al. (35), but no differences were seen between these two groups. The reduction in the inflammatory response to DSS in op/op mice suggests a critical role for M-CSF-derived macrophages in the accompanying colitis. This is supported by the observation that DSS colitis is expressed in SCID mice (11) reflecting a reduced role of T cells in this model. Increases in IL-10 were smaller in this model than in DNBS-induced colitis as reported by Selmeczy et al. (35), but no differences were seen for the IL-10 production. The histological improvement was characterized by a reduced cellular infiltrate, probably due to the absence of M-CSF in DSS colitis in op/op mice, but this was not associated with a greater increase in MPO activity, as was observed in the DNBS model. As we also found a smaller increase in MIP-1α in op/op and +/? mice with DSS colitis as reported by Selmecky et al. (35), but no differences were seen between these two groups. The reduction in the inflammatory response to DSS in op/op mice suggests a critical role for M-CSF-derived macrophages in the accompanying colitis. This is supported by the observation that DSS colitis is expressed in SCID mice (11) reflecting a reduced role of T cells in this model. Increases in IL-10 were smaller in this model than in DNBS-induced colitis and were not affected by the presence or the absence of M-CSF-derived macrophages, suggesting that this subset plays a proinflammatory role of this model. In op/op mice, the population of resident tissues macrophages that secrete the chemotactic cytokines causing neutrophil influx is depleted but compensatory mechanisms could have come into play. We excluded a delayed influx of neutrophils and other inflammatory cells from the circulation by extending our protocol by 2 days and we found no additional inflammatory changes.

A recent study showed that intraperitoneal injection of recombinant yeast-derived pegylated murine GM-CSF down-regulated the inflammation induced by DSS (15). It is possible,
The role of M-CSF, GM-CSF via the plasmacytoid dendritic cells can contribute directly to further suppress the inflammatory response (34) to DSS in op/op mice.

In conclusion, we have shown that M-CSF-dependent macrophages play a complex role in intestinal inflammatory processes and that their role depends on the stimulus used to induce inflammation. Under certain conditions, reflected by our results in DNBS colitis, M-CSF can induce a counterinflammatory response through a subset of macrophages. Because M-CSF as well as macrophages are increased in IBD, a better understanding of the factors that determine the differentiation of macrophages into a counter inflammatory phenotype may lead to novel therapeutic strategies.

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