PRODUCTION OF CYCLOOXYGENASE PRODUCTS AND SUPEROXIDE ANION BY MACROPHAGES IN RESPONSE TO CHEMOTACTIC FACTORS

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Abstract

Mononuclear phagocytes are known to play a key role in various phlogistic reactions by synthesizing and releasing products that may potentiate or inhibit inflammatory processes. The expression of these products appears to be dependent on the source of the macrophage population as well as the stimulus employed. We have studied superoxide anion (O_2^-) production as well as the generation of PGE_2, $PGF_{2\alpha}$, and TXB_2 from resident, oil-elicited and thioglycollate-induced peritoneal macrophages in mice in the presence and absence of chemotactic peptides. Production of O_2^-, occurred only in elicited macrophages stimulated with high concentrations of FMLP or C5a; resident cells stimulated with either of the chemotactic peptides were completely unresponsive. Although resident peritoneal macrophages incubated with chemotactic peptides did not generate O_2^-, these cells did secrete significant levels of PGE_2, $PGF_{2\alpha}$, and TXB_2 in response to C5a. FMLP had no stimulatory effect. Elicited macrophages generated increased levels of PGE_2 and $PGF_{2\alpha}$ when incubated with C5a. However, production of TXB_2 was not stimulated. FMLP was inactive in stimulating PGE_2, $PGF_{2\alpha}$, and TXB_2 in all types of macrophages studied. These studies indicate a heterogeneity in the production of inflammatory mediators from various macrophage populations in response to chemotactic factors.

Introduction

Recent experimental evidence has demonstrated that mononuclear phagocytes can synthesize and release a variety of inflammatory mediators including lysosomal enzymes (1,2,3), plasminogen activator (4), oxygen metabolic products (5,6,7), and arachidonic acid metabolites (8,9,10). The expression of any of these phlogistic mediators is not only dependent upon the nature of the inflammatory stimulus but also on the source of the mononuclear phagocytes (11,12). This is especially true concerning the ability of two potent chemotactic stimuli, C5a and N-formylmethionyl leucyl phenylalanine (FMLP), to stimulate the synthesis and release from various peritoneal macrophage populations, of superoxide anion (O_2^-) and cyclooxygenase products (Prostaglandin E_2, PGE_2, Prostaglandin $F_{2\alpha}$, $PGF_{2\alpha}$, and thromboxane B_2, TXB_2). Our studies demonstrate that the chemotactic peptides C5a and FMLP produce only slight increases in O_2^- levels from elicited mouse peritoneal macrophages, while resident peritoneal macrophages are totally unresponsive. C5a, but not FMLP, is effective in stimulating the release of cyclooxygenase products from the various macrophage populations. These data suggest that there are important differences between various macrophage cell populations with respect to their ability to be stimulated by chemotactic peptides resulting in mediator release.

Methods

Animals. Female, CBA/J mice (Jackson laboratories, Bar Harbor, ME) were used in all experiments. Mice were maintained under standard care and given food and water ad libitum.

Macrophage cultivation. Peritoneal macrophages from CBA-J mice were elicited by the intraperitoneal injection of 2 ml thioglcollate medium

(Becton Dickinson, Cockeysville, MD) or 2 ml of Marcol light oil (Mobil Oil Co.). Four days after injection, peritoneal macrophages were harvested, washed in RPMI-1640 medium (Gibco, Grand Island Biological Co., Grand Island, NY) and resuspended at 5 x 10^5/ml in RPMI-10% fetal calf serum containing 100 units/ml penicillin and 100 µg/ml of streptomycin. Resident macrophages were harvested from the peritoneum, washed and resuspended in the medium. Cells (5 x 10^5) were added to plastic dishes (35mm diameter; Costar, Cambridge, MA). The cells were allowed to adhere for 16 hrs at 37°C in 5% CO_2/95% air prior to the addition of chemotactic peptides. The numbers of macrophages adherent to the surface of the culture dishes were determined by direct counting of adherent cells, as described elsewhere (13). This methodology has been confirmed by the use of biochemical parameters (14). Typically, 3 x 10^5 macrophages were found to adhere to individual plates.

Assay for superoxide anion. A modification of the procedure of Johnston et al. (13) was used to quantitate the production of O_2^-. Briefly, adherent monolayers of macrophages were washed three times with Hanks buffer. One ml of 80 µM ferricytochrome C in Hanks buffer was added alone or in the presence of one of the following reagents: C5a, opsonized zymosan, N-formyl methionyl leucyl phenylalanine, or phorbol myristate acetate (PMA). The cell cultures were allowed to incubate for 120 minutes at 37C in 5% CO_2 95% air. The reaction mixtures were then removed by decantation, the fluids cleared of cells by centrifugation, and the optical density of the supernatants determined spectrophotometrically at 550 nm. Superoxide anion concentration was calculated as the superoxide dismutase inhibitable reduction of ferricytochrome C and expressed as nMoles $O_2^-/10^6$ cells/2 hr. (13). Each sample was examined in triplicate.

Assay for cyclooxygenase products. Radioimmunoassays (RIA) using antibodies and methods developed by Fitzpatrick et al. (15,16,17) were used to quantitate prostaglandin E_2 (PGE_2), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and thromboxane B_2 (TXB_2) in macrophage culture fluids. Prior to assay, sample were extracted to remove protein and free fatty acids. Bound ligand was separated from free ligand by the use of dextran-coated charcoal. The limits of sensitivity for PGE_2, $PGF_{2\alpha}$, and TXB_2 were 8 picograms, 4 picograms, and 2 picograms, respectively. Levels of the above cyclooxygenase products were expressed as ng/10^6 cells/2 hr. All samples were examined in triplicate.

Reagents. C5a was isolated and purified according to the procedure of Fernandez and Hugli (18). Ferricytochrome C (Horse heart, type II), PMA, zymosan, superoxide dismutase (bovine blood, type I), indomethacin and FMLP were all obtained from Sigma Chemical Co. (St. Louis, MO).

Results

Comparison of C5a and FMLP-induced release of O_2^- from resident and elicited peritoneal macrophages. Superoxide anion levels, measured as the superoxide dismutase inhibitable reduction of ferricytochrome C, were examined in both resident and elicited peritoneal mouse macrophages stimulated with either C5a or FMLP. Cultured resident and oil elicited macrophages obtained from the peritoneum of normal mice released minimal

O_2^- when challenged with either C5a or FMLP. Over a 6 log range of FMLP concentrations, (10^{-5} - 10^{-10}M), levels of O_2^- in resident macrophage cultures were not elevated significancantly above the levels found in fluids in which cells had been incubated in Hank's buffer (Figure 1). Cultured macrophages elicited by thioglycollate exhibited an increase in O_2^- production above control values only at extremely high concentrations of FMLP (10^{-7}, 10^{-6}, and 10^{-5}M; Figure 1). At 10^{-5}M FMLP, an approximate 2-fold increase above control values of O_2^- production was observed.

As with FMLP, the chemotactic peptide C5a failed to stimulate significant release of O_2^- in cultured resident and oil elicited macrophages (Figure 2). Over a concentration range from 50 ng/ml to 4 µg/ml, C5a failed to stimulate O_2^- production from these cells (Figure 2). Thioglycollate elicited macrophages did respond to C5a with production of O_2^-, but only at high concentrations (above 1 µg/ml). The higher concentrations of C5a were shown to induce a 2-4 fold increase in O_2^- production above control values.

In order to compare superoxide production from resident and elicited macrophage in the presence of other stimuli, opsonized zymosan and PMA were used as the stimulus. As shown in Figure 3, peritoneal macrophages, regardless of source, respond to opsonized zymosan and PMA with O_2^- generation. Both the particulate and soluble stimuli were active over a wide range of concentrations. In each case thioglycollate induced macrophages were the most responsive. These data are consistent with previously reported experiments that demonstrate the ability of thioglycollate-elicited macrophages to generate high levels of O_2^- in response to opsonized zymosan and PMA (13).

Production of prostaglandins by macrophages treated with C5a and FMLP. The production of PGE_2, $PGF_{2\alpha}$, and TXB_2 were examined in elicited and in resident macrophages following contact with chemotactic peptides. An interesting dichotomy between the effect of FMLP and C5a was observed (Figure 4 and 5). Over a wide concentration range (10^{-5} to 10^{-9}M), FMLP did not significantly stimulate the synthesis of PGE_2, $PGF_{2\alpha}$, or TXB_2 above control values (cells incubated in the absence of chemotactic peptide). This observation was independent of the source of macrophage. After contact with human C5a, both elicited and resident macrophages demonstrated an increase in the synthesis of PGE_2, $PGF_{2\alpha}$ and TXB_2 (Figure 5). When compared to their respective control values resident macrophages had an increased capacity for the synthesis and release of PGE_2, $PGF_{2\alpha}$, and TXB_2; as compared to the elicited (thioglycollate and oil) macrophage populations. Production of PGE_2 in response to a wide range of concentration of C5a is shown in Figure 5a. Although an increase of approximately 2-fold in levels of PGE_2 from resident macrophages levels was observed when the C5a concentration was 100 ng/ml, there was a plateau effect in the levels of PGE_2 when the dose of C5a was 1 µg/ml, resulting in a 6-fold increase in PGE_2 levels above control values. The synthesis of $PGF_{2\alpha}$ and TXB_2 by C5a stimulated resident macrophages were increased 3 and 2 fold, respectively (Figure 5b and 5c). When thioglycollate or oil-elicited macrophages were similarly studied, C5a induced lower levels of PGE_2, $PGF_{2\alpha}$ and TXB_2. With these cells, the highest doses of C5a produced a two fold increase in level of PGE_2 and $PGF_{2\alpha}$ levels, whereas little generation of TXB_2 occurred.

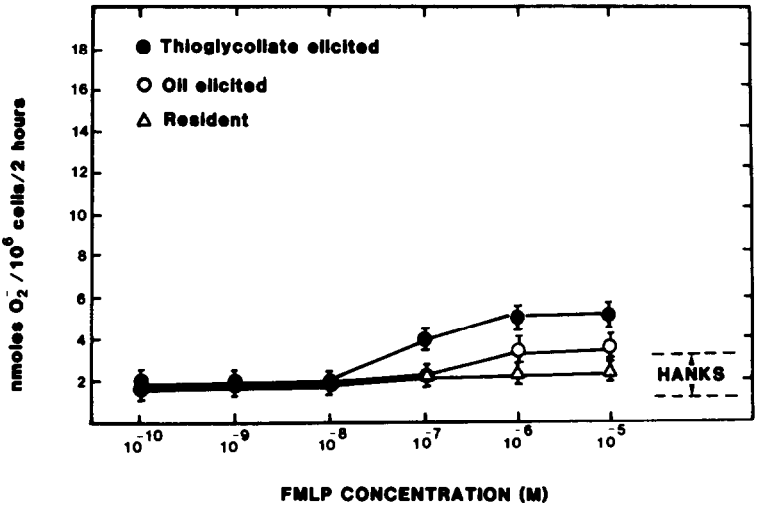

Fig. 1: Effect of FMLP on superoxide anion generation by elicited and resident peritoneal macrophages.

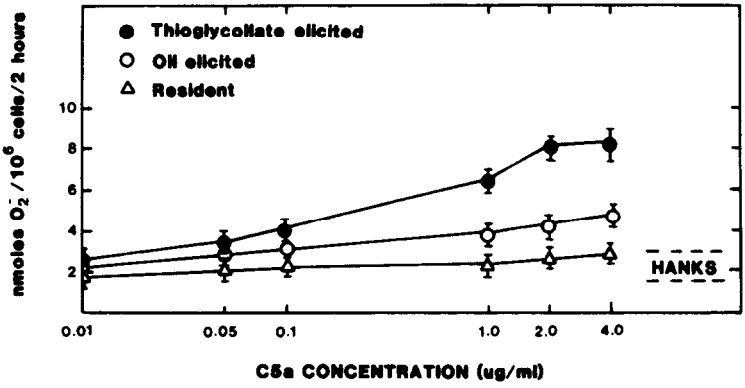

Fig. 2: Generation of superoxide anion by elicited and resident peritoneal macrophages in response to C5a.

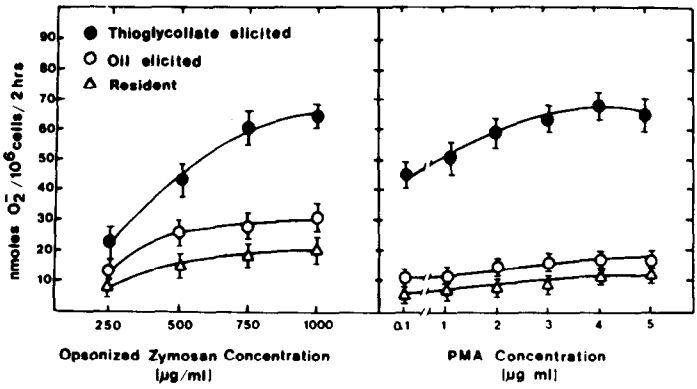

Fig. 3: Superoxide anion generation by elicited and resident peritoneal macrophages in response to particular (zymosan) and soluble (PMA) stimulus.

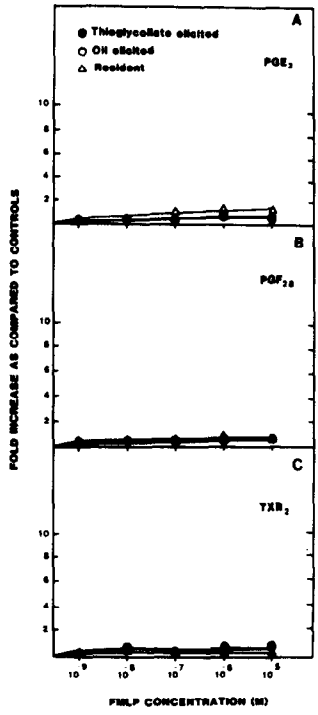

Fig. 4: Synthesis of prostaglandin E_2, prostaglandin $F_{2\alpha}$ and thromboxane B_2 by elicited and resident peritoneal macrophages in response to various concentrations of FMLP.

The production of arachidonate metabolites by either resident or elicited populations could be completely suppressed by the presence of 10^{-7}M indomethacin. As shown in Table 1, resident macrophages in the presence of this inhibitor did not respond with production of PGE_2, $PGF_{2\alpha}$ and TXB_2 in the presence of chemotactic peptides. Furthermore, resident macrophages treated with this drug also showed markedly reduced amount of PGE_2, $PGF_{2\alpha}$ and TXB_2 when the cells were suspended in Hank's medium; as compared to similarly treated cells in the absence of indomethacin.

Discussion

The interaction between cellular and humoral mediator systems represents two major components of all phlogistic processes. This is exemplified by the interaction between granulocytes and chemoattractants during an inflammatory event. Although the response of neutrophils to chemotactic factors has been well characterized (19,20,21), specific responses of mononuclear phagocytes to chemoattractants remains less well defined. This is especially true with regard to C5a-induced macrophage stimulation and secretion (3).

Recent investigations have demonstrated that various N-formyl peptides are potent chemotactic agents for many macrophage populations (22,23), but these same peptides are both species and population dependent with regard to their ability to cause generation of phlogistic products from these cells (11,12,24). For example, guinea pig and rabbit peritoneal macrophages stimulated with N-formyl peptides respond with a rapid increase in O_2 consumption and a concommitant rise in the production of superoxide anion and hydrogen peroxide (12). However, guinea pig, but not rabbit pulmonary macrophages synthesize and release O_2^- after contact with N-formyl peptides (11,12,24,25). Earlier studies have demonstrated that O_2^- generation may vary within a population of macrophages depending upon the method used to elicit the cells (13). Thus, thioglycollate or lipopolysaccharide-elicited mouse peritoneal macrophages generate significant levels of O_2^- in response to either a soluble, (PMA), or particulate, (opsonized zymosan), stimulus, while resident mouse peritoneal macrophages are much less responsive (5,13).

Various macrophage populations have also been examined for the ability to synthesize and release arachidonate metabolites in response to specific stimuli (8,26,27). These studies have centered around the production of PGE_2 from elicited and resident mouse peritoneal macrophage in response to PMA (28), opsonized zymosan (27) and, more recently, immune complexes (29). As with the production of O_2^-, the synthesis and release of arachidonic acid products in response to an inflammatory stimulus appear to be dependent on the source of the macrophages.

Since synthesis and release of inflammatory mediators may be dependent upon the stimulus as well as the species and population of macrophages under investigation, we were interested in examining the effects of two diverse chemotactic factors, FMLP and C5a, on the production of O_2^- and generation of metabolites of arachidonic acid, specifically PGE_2, $PGF_{2\alpha}$, and TXB_2. Resident and elicited mouse peritoneal macrophages were quantitatively and qualitatively compared. Resident peritoneal macrophages stimulated with either C5a or FMLP over a wide concentration range failed

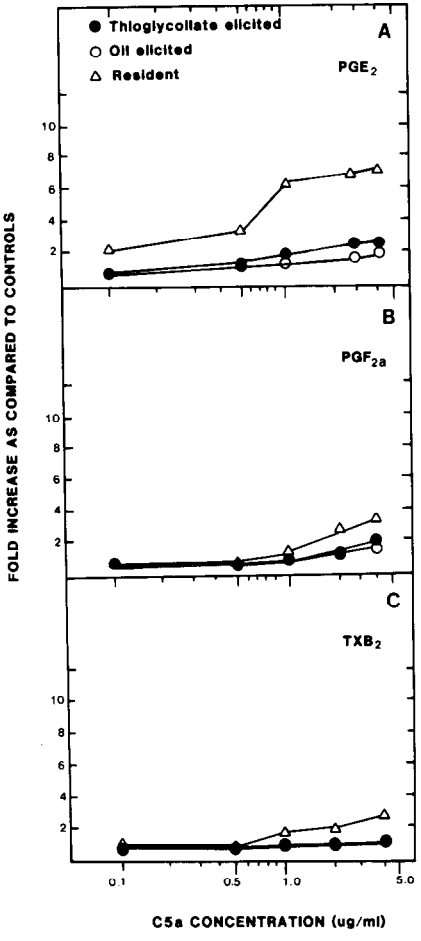

Fig. 5: Synthesis of prostaglandin E_2, prostaglandin $F_{2\alpha}$, and thromboxane B_2 by elicited and resident peritoneal macrophages in response to various concentration of C5a.

Production of PGE_2, $PGF_{2\alpha}$ and TXB_2 by Different Populations of Macrophages

A	Resident			Oil Elicited			Thioglycollate Elicited		
	ng/10^6 cells/2 hr.								
	PGE_2	$PGF_{2\alpha}$	TXB_2	PGE_2	$PGF_{2\alpha}$	TXB_2	PGE_2	$PGF_{2\alpha}$	TXB_2
2μg/ml C5a	2.7±.17*	.67±.05*	.29±.05*	.98±.10	.25±.03	.17±.06	1.2±.11	.85±.07	.41±.01
10^{-6}M FMLP	.39±.03	.24±.07	.19±.03	.39±.09	.21±.01	.18±.01	.49±.09	.44±.06	.29±.04
Hank's buffer	.35±.06	.21±.02	.13±.02	.43±.19	.19±.02	.14±.01	.59±.07	.40±.07	.32±.03

B	PGE	$PGF_{2\alpha}$	TXB_2
2μg/ml C5a**	.11±.012	.045±.014	.030±.011
10^{-6}FMLP**	.09±.011	.041±.013	.026±.007
Hank's buffer**	.075±.009	.039±.011	.021±.009

Table 1. A, chemotactic factor induced release of PGE_2, $PGF_{2\alpha}$, and TXB_2 from resident and elicited peritoneal macrophages and B, resident peritoneal macrophages treated with C5a, FMLP, or control buffer in the presence of 10^{-7}M indomethacin.

*Data expressed as nanograms/10^6 cells/2 hrs.

**All macrophage cultures in part B were pretreated with 10^{-7}M indomethacin.

to induce a significant production of O_2^-, as determined by the superoxide-dismutase inhibitable reduction of ferricytochrome C. Only thioglycollate recruited peritoneal macrophages, stimulated with high concentrations of either FMLP or C5a, demonstrated an elevation in O_2^- levels. As shown in Figures 1 and 2, 10^{-6}M FMLP or greater than 1 µg/ml C5a was needed to observe an increase in O_2^- levels above controls. Johnston et al. (13) previously reported a similar observation with PMA stimulated resident and elicited peritoneal macrophages. In the latter study, thioglycollate elicited peritoneal macrophages responded to PMA challenge (2-4 µg/ml) with a large increase in O_2^- production, while resident macrophages were much less responsive.

Although C5a and FMLP-induced O_2^- generation from various populations of peritoneal macrophages was similar, the ability of the two chemotactic factors to stimulate arachidonic acid metabolism was significantly different. There was no significant increase in the synthesis and release of PGE_2, $PGF_{2\alpha}$, or TXB_2 from either resident or elicited peritoneal macrophages when stimulated over a wide range of FMLP concentrations. On the other hand, stimulation with C5a of resident and elicited macrophages resulted in an increase in the production of arachidonate metabolites. Resident peritoneal macrophages stimulated with C5a were shown to possess an increased capacity to generate PGE_2, $PGF_{2\alpha}$, and TXB_2, as compared to thioglycollate and oil recruited macrophages. A 6-fold increase in PGE_2 levels was observed in C5a stimulated resident macrophages, while a 2-3 fold increase in PGE_2 was observed in the C5a treated elicited macrophage populations. In previous studies, Humes et al. (27) demonstrated that resident mouse macrophages challenged with opsonized zymosan release significantly more PGE_2 as compared to elicited macrophage populations. A pausible explanation for the decrease in the PGE_2 levels from stimulated, elicited macrophages may be due to a decrease in their cyclooxygenase activity (30) or to a decrease in the rate of arachidonic acid release from membrane phospholipids (31). An additional explanation for the differences observed in chemotactic factor-induced mediator release from the various macrophage population may be associated with the chemotactic receptors found on these cells. Although specific membrane receptors for the chemotactic peptides have been identified on macrophage membranes (23,32), the density of these receptors on the various macrophage populations may vary dramatically. Thus, dictating the responsiveness of the various macrophages to each chemotactic stimulus.

It had become increasingly clear that macrophages derived from various tissues in several species can synthesize and release a number of phlogistic products in response to various stimuli. We have demonstrated that different populations of mouse peritoneal macrophage vary in their ability to generate superoxide anion and arachidonic acid metabolites in response to two potent chemotactic peptides, C5a and FMLP. While resident peritoneal macrophages did secrete significant levels of PGE_2, $PGF_{2\alpha}$, and TXB_2 in response to C5a, elicited cells are much less responsive. Both resident and elicited peritoneal macrophages are unresponsive to FMLP-induced stimulation of arachidonic acid metabolism. Interestingly, neither C5a nor FMLP was an effective stimulator for the synthesis of O_2^- from either resident or elicited peritoneal macrophages. Further knowledge concerning the capability of various macrophage populations to synthesize and release various mediators will undoubtedly aid in understanding the interaction between cellular and humoral systems involved in inflammatory processes.

References

1. Davies, P., and A.C. Allison. In: Immunobiology of the macrophage. (D.S. Nelson, ed.) Academic Press, Inc., New York. 1976 P. 427.
2. Schorlemmer, H.U., and A.C. Allison. Effects of activated complement components on enzyme secretion by macrophages. Immunology 31:781, 1976.
3. McCarthy, K., and P.M. Henson. Induction of lysosomal enzyme secretion by alveolar macrophages in response to the purified complement fragments C5a and C5a des arg. J. Immunol. 123:2516, 1979.
4. UnKeless, J., S. Gordon, and E. Reich. Secretion of plasminogen activator by stimulated macrophages. J. Exp. Med. 139:834, 1974.
5. Karnovsky, M.D., J. Lazdins, and S.R. Simmons. In Mononuclear phagocytes in immunity infection, and pathology. (R. Van Furth, ed) Blackwell Scientific Publication, Oxford. 1975 p. 423.
6. Klebanoff, S.J. In: Mononuclear phagocytes Edited by R. Van Furth. Martinus Nijhoff Publishers Boston. 1980 p. 1105.
7. Johnson, R.B., J.E. Lehmeyer, and L.A. Guthrie. Generation of superoxide anion and chemiluminescence by human monocytes during phagocytosis and on contact with surface-bound immunoglobulin G. J. Exp. Med. 143:1551, 1976.
8. Davies, P., R.J. Bonney, J.L. Humes and and F.A. Kuehl. Synthesis and release of oxygenation products of arachidonic acid by mononuclear phagocytes in response to inflammatory stimuli. Inflammation 2:335, 1977..
9. Kurland, J.I. and R. Bockman. Prostaglandin E production by human blood monocytes and mouse peritoneal macrophages. J. Exp. Med. 147:952, 1978..
10. Morley, J., M.A. Bray, R.W. Jones, D.H. Nugteren, and D.A. Van Dorp. Prostaglandin and thromboxane production by human and guinea-pig macrophages and leukocytes. Prostaglandins. 17:729, 1979.
11. DeChatelet, L.R., D. Mullikin, and C.E. McCall. The generation of superoxide anion by various types of phagocyte. J. Infect. Dis. 131:44, 1975.
12. Hatch, G.E., D.E. Gardner, and D.B. Menzel. Chemiluminescence of phagocytic cells caused by N-formyl-methionyl peptides. J. Exp. Med. 147:182, 1978.
13. Johnston, R.B., C.A. Godzik, and Z.A. Cohn. Increased superoxide anion production by immunologically activated and chemically elicited macrophages. J. Exp. Med. 148:115, 1978.
14. Nathan, C.F., R. Asofsky, and W.D. Terry. Characterization of the nonphagocytic adherent cell from the peritoneal cavity of normal and BCG-treated mice. J. Immunol. 118:1612, 1977.
15. Fitzpatrick, F.A. and G.L. Bundy. Hapten mimic elicits antibodies recognizing prostaglandin E_2. Proc. Natl. Acad. Sci. 75:2689, 1978.
16. Fitzpatrick, F.A. and W.A. Wynalda. A rapid, solid phase radioimmunoassay for prostaglandin F_2 and its main circulating metabolites. Analytical Biochem. 73:198, 1976.
17. Fitzpatrick, F.A., R.R. Gorman, J.C. McGuire, R.C. Kelly, M.A. Wynalds, and F.F. Sun. A radioimmunoassay for thromboxane B_2. Analytical Biochem. 82:1, 1977.
18. Fernandez, H.N. and T.E. Hugli. Primary structure analysis of the polypeptide portion of C5a. J. Biol. Chem. 253:6955, 1978.

19. Becker, E.L. Some interrelations of neutrophil chemotaxis, lysosomal enzyme secretion, and phagocytosis as revealed by synthetic peptides. Am. J. Pathol. 85:385, 1976.
20. Kunkel, S.L., J.C. Fantone, and P.A. Ward. Complement mediated inflammatory reactions. Pathobiol. Ann. 11:127, 1981.
21. Showell, H.J., R.J. Freer, S.H. Zigmond, E. Schiffmann, S. Aswanikumar, B. Corcoran, and E.L. Becker. The structure-activity relations of synthetic peptides as chemotactic factors and inducers of lysosomal enzyme secretion for neutrophils. J. Exp. Med. 143:1154, 1976.
22. Dauber, J.H., and R.P. Daniele. Chemotactic activity of guinea pig alveolar macrophages. Am. Rev. Respir. Dis. 117:1390, 1978.
23. Schiffman, E., B.A. Corcoran, and S.M. Wahl. N-formyl-methionyl peptides as chemoattractants for leukocytes. Proc. Natl. Acad. Sci. 72:1059, 1975.
23. Holian, A. and R.P. Daniele. Release of oxygen products from lung macrophages by N-formyl peptides. J. Appl. Physiol. 50:736, 1981.
25. Yamaguchi, T., K. Kakinuma, M. Kaneda, and K. Shimada. Comparative study on alveolar macrophages and polymorphonuclear leukocytes. H_2O_2 and O_2^- generation by rabbit alveolar macrophages. J. Biochem. 87:1449, 1980.
26. Brune, K., M. Glatt, H. Kalin, and H.H. Peskar. Pharmacological control of prostaglandin and thromboxane release from macrophages. Nature 274:261, 1978.
27. Humes, J.L., R.J. Bonney, L. Pelus, M.E. Dahlgren, S. Sadowski, F.A. Kuehl, and P. Davies. Macrophages synthesize and release prostaglandins in response to inflammatory stimuli. Nature 269:149, 1977.
28. Humes, J.L., P. Davies, R.J. Bonney, and F.A. Kuehl. Phorbol myristate acetate stimulates the release of arachidonic acid and its cyclooxygenation products by macrophages. Fed. Proc. 37:1318, 1978.
29. Bonney, R.J., P. Narums, P. Davies, and J.L. Humes. Antigen-Antibody complexes stimulate the synthesis and release of prostaglandins by mouse peritoneal macrophages. Prostaglandins 18:605, 1979.
30. Bonney, R.J., I. Bery, T.Y. Lin, M.F. Meyenhafer, W. Acenedo, and P. Davies. Mononuclear phagocytes from carrageenin-induced granulomas. Isolation, cultivation, and characterization. J. Exp. Med. 148:261, 1978.
31. Humes, J.L., S. Burger, M. Galavage, F.A. Kuehl, P.D. Wightman, M.E. Dahlgren, P. Davies, and R.J. Bonney. The diminished production of arachidonic acid oxygenation products by elicited mouse peritoneal macrophages: Possible mechanisms. J. Immunol. 124:2110, 1980.
32. Snyderman, R. and E.J. Feedman. Demonstration of a chemotactic factor receptor on macrophages. J. Immunol. 124:2754, 1980.

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