The Role of Arachidonic Acid Metabolites in Mononuclear Phagocytic Cell Interactions

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The elucidation of the reactions leading to both the release of arachidonic acid from membrane-bound phospholipids and its subsequent metabolic conversion into potent, biologically active lipids are landmark discoveries in the areas of physiology and inflammation. Historically, early investigations in this field were directed at isolating and characterizing the diverse metabolites of the cyclooxygenation of arachidonic acid. Kurzock and Lieb,[1] Goldblatt,[2] and von Euler[3] contributed seminal observations regarding the biologic activity of an acidic lipid believed to be synthesized by the prostate gland, hence the term prostaglandin. Later, Bergstrom and co-workers[4,5] demonstrated that prostaglandins represent a spectrum of related lipids with a similar chemical structure. The major impetus to study the biochemical role and pharmacologic manipulation of arachidonic acid metabolism, with regard to inflammation, was provided by Vane,[6] with the observation that aspirin and aspirin-like drugs could suppress prostaglandin synthesis and regulate inflammatory reactions. The foundation for subsequent work concerning products of the lipoxygenase pathway was laid by Feldberg and Kellaway[7] in 1938. In these early experiments, they demonstrated that the perfusate of cobra venom-treated lungs contained both a lysolecithin-like compound and a compound that generated a smooth muscle contracting factor termed "slow reacting substance" (SRS). Nearly 30 years later, these same SRS-type compounds were found to play a key role in immediate hypersensitivity reactions, especially asthma.[8] SRS of anaphylaxis (SRS-A) is usually referred to as an immunologically released SRS and now is known to consist of leukotriene C_4, D_4, and E_4. The structural work and complete chemical characterization of SRS-A was reported in 1979.[9] At the same time that the structure of SRS-A was reported, Borgeat and Samuelsson[10] isolated a dihydroxy metabolite of arachidonic acid formed by rabbit leukocytes and subsequently named this compound leukotriene B_4. The importance of arachidonic acid metabolites in diverse systems and the contribution of key scientists was recognized in 1982 with Nobel prizes being awarded to Drs. Bergstrom, Samuelsson, and Vane.

In addition to the studies by these Nobel laureates, numerous investigators have demonstrated the ability of arachidonic acid metabolites to participate in the regulation of diverse physiologic systems. This is truly exemplified by the key role these ubiquitous fatty acids play in dictating the function of cells that are involved in acute and chronic immune reactions. Products from both the cyclooxygenase and lipoxygenase pathway (Fig. 1) are known to be synthesized during immune-inflammatory responses and can influence the outcome of various phlogistic episodes. There is little doubt that LTB_4 and many of the hydroxylated eicosatetraenoic acids (HETEs) are important in acute-neutrophil-mediated reactions. These lipoxygenase products appear to play a central role in the initiation and maintenance of acute inflammation by causing leukocyte chemotaxis,[11] aggregation,[12] lysosomal enzyme release,[13] and the production of oxygen metabolites.[14] Conversely, specific cyclooxygenase-derived metabolites (PGE_2 and PGI_2) have been shown to suppress many of the above leukocytic functions.[15-17] Thus, the products of the two major pathways of arachidonic acid metabolism have been hypothesized to function in a yin–yang manner as the inflammatory reaction is initiated and eventually resolved. Although the current

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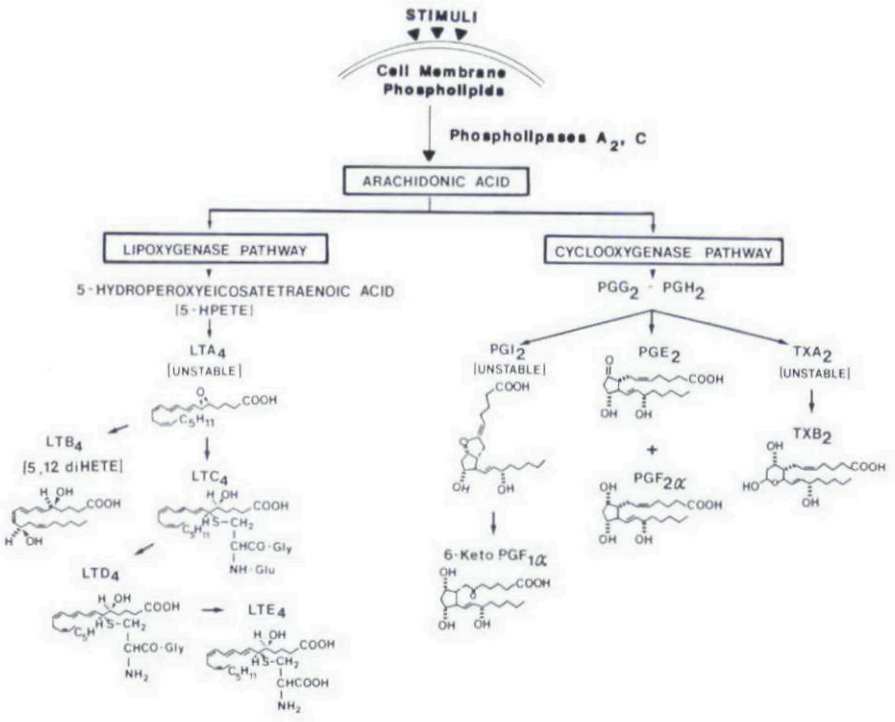

FIG. 1. Cascade of arachidonic acid metabolites synthesized via the cyclooxygenase and lipoxygenase pathways.

literature concerning arachidonate metabolites in neutrophil-mediated reaction is voluminous, an exhaustive review examining the participation of these various lipids in acute inflammation is beyond the scope of this article. The goal of this review is to summarize and expand our current understanding of the biochemical, biologic and clinical aspects of arachidonic acid metabolic products in macrophage- and lymphocyte-mediated reactions.

Metabolism of Arachidonic Acid by Mononuclear Phagocytic Cells

The importance of arachidonic acid metabolites synthesized by mononuclear phagocytes is suggested by the high percentage of this fatty acid found esterified in the number two position of membrane phospholipids. Arachidonic acid was found to constitute approximately 25% of all esterified membrane fatty acids in various mononuclear phagocytic cell preparations,[18,19] while neutrophil membranes contained less than 3% esterified arachidonic acid.[20] Phospholipid analysis of macrophage membranes indicates that the majority of arachidonic acid is found at position two of phosphatidylcholine.[21] The functional importance of this particular phospholipid as a reservoir of macrophage arachidonic acid is shown clearly by the reduction in arachidonic acid metabolites by macrophages treated with inhibitors of phosphatidylcholine synthesis,[22] and the dramatic loss of arachidonic acid from phosphatidylcholine with a concomitant appearance of metabolites by stimulated macrophages. It is important to note that the mobilization of arachidonic acid is dependent upon the activation of phospholipases by specific receptor–ligand interactions.[23] This concept is critical, since investigations have demonstrated that phospholipases may be maintained as separate pools within the macrophage.[24] One pool appears to be associated with intracellular lysosomes and triggered by a phagocytic stimulus and an additional pool appears to be associated with the plasmalemma and activated by membrane perturbation. In additional studies,[25] the activation of phospholipase and the mobilization of different pools of substrate arachidonic acid have been shown to result in different types of metabolic products. Membrane perturbants, such as phorbol esters[20] and lipopolysaccharide,[26] selectively stimulated the cyclooxygenation of arachidonic acid, while zymosan triggered both metabolic pathways.

As detailed above, the metabolism of arachidonic acid occurs by two major routes. The major metabolites synthesized by macrophages via the cyclo-oxygenase pathway are prostaglandin E_2 (PGE_2) and prostacyclin (PGI_2), while thromboxane TXA_2 (and its stable metabolite, TXB_2) and prostaglandin $F_{2\alpha}$) have also been identified.[27] Macrophages have a significant ability to metabolize arachidonic acid through the lipoxygenase pathway with the concomitant synthesis of mono-

TABLE 1. *Comparison of the State of Macrophage Activation and Effect of Various Stimulus on Arachidonic Acid Metabolic Products*

Macrophage Population	Stimulus	NG PGE_2/5 × 10^5 Cells	NG 6-KETO-$PGF_{1\alpha}$/5 × 10^5 Cells	NG LTC_4/5 × 10^5 Cells
Resident peritoneal	—	2.14 ± 0.28	0.30 ± 0.09	>0.05
BCG-elicited peritoneal	—	5.42 ± 0.48	1.05 ± 0.16	>0.05
Thioglycollate peritoneal	—	2.54 ± 0.31	0.87 ± 0.11	>0.05
Resident peritoneal	Zymosan (250 μg/ml)	36.62 ± 2.74	42.32 ± 3.03	38.1 ± 2.90
BCG-elicited peritoneal	Zymosan (250 μg/ml)	17.65 ± 1.39	15.20 ± 2.81	8.3 ± 1.09
Thioglycollate peritoneal	Zymosan (250 μg/ml)	10.14 ± 3.04	9.98 ± 4.02	2.3 ± 0.97
Resident peritoneal	Arachidonic acid (10 μM)	69.31 ± 6.11	46.01 ± 4.98	29.7 ± 2.77
BCG-elicited peritoneal	Arachidonic acid (10 μM)	21.63 ± 3.19	9.4 ± 1.34	5.1 ± 0.98
Thioglycollate peritoneal	Arachidonic acid (10 μM)	14.30 ± 1.97	7.1 ± 1.02	4.9 ± 0.75
Resident peritoneal	Lipopolysaccharide (10 μg/ml)	73.90 ± 8.31	54.15 ± 7.59	>0.05
BCG-elicited peritoneal	Lipopolysaccharide (10 μg/ml)	7.99 ± 2.01	10.05 ± 1.98	>0.05
Thioglycollate peritoneal	Lipopolysaccharide (10 μg/ml)	3.14 ± 1.09	11.23 ± 2.71	>0.05

HETEs and leukotrienes. Although mono-HETEs (predominantly 12-HETE) appear to be the most abundant of the macrophage-derived lipoxygenase products, the leukotrienes are the best understood. Various cultured macrophage preparations have been shown to synthesize a number of biologically active lipids, including conjugated trienes.[28-30] While speculations abound concerning the clinical role these leukotrienes play in human disease, save for certain types of asthma, the exact role of these lipoxygenase products remains enigmatic.

There is little doubt that mononuclear phagocytic cells possess a unique capability to metabolize arachidonic acid to numerous metabolic end points. This prolific metabolic capacity of macrophages has lead numerous investigators to study those factors that dictate the various facets of macrophage arachidonic acid metabolism. The quantitative and qualitative aspects of metabolite formation clearly is a function of both the exogenous stimulus and the state of macrophage activation. The latter is defined by a variety of biochemical and physiologic criteria. Much of the current understanding of macrophage arachidonate metabolism stems from studies using different populations of murine peritoneal macrophages. These populations include both resident or resting macrophages and macrophages elicited by either an irritant, such as thioglycollate, or an immunologic challenge, such as heat-killed organisms of *Corynebacterium* or *Mycobacterium*. The diverse nature of the different cell populations is reflected in the different arachidonic acid metabolites these cells synthesize. Investigations using resting peritoneal macrophage have demonstrated that, in the unstimulated state, these cells release minimal metabolic products. If these resident macrophages are given an exogenous source of arachidonic acid in the absence of other stimuli, approximately 40% of the arachidonic acid is incorporated into phospholipids, while the remainder is metabolized to mono-HETEs and the stable analogue of PGI_2, 6-Keto-$PGF_{1\alpha}$. The metabolism of endogenous arachidonic acid (phospholipid bound) following a phagocytic challenge of zymosan or immune complexes was found to result in the formation of PGE_2, 6-Keto-$PGF_{1\alpha}$, and LTC_4.[31] In contrast, elicited peritoneal macrophages have a diminished capability to synthesize arachidonic acid metabolites. Macrophages elicited with either an irritant or immunologic challenge incorporate more exogenous arachidonic acid and release significantly less metabolites. In addition, zymosan-treated-elicited macrophages convert endogenous arachidonic acid to only 10% of the metabolites formed by similarly treated resting cells.[32] A possible mechanism for the above observations may be due to an increase in the acylation of arachidonic acid or decrease in the deacylation by the activated macrophage populations. The absolute amounts of arachidonic acid metabolites released by various resting and elicited peritoneal macrophage populations in the presence and absence of a stimulus are shown in Table 1.

In addition to the state of macrophage activation, the amount and variety of metabolites are dependent upon the particular stimulus under study. As discussed above, synthesis of arachidonic acid metabolites by both the cyclooxygenase and lipoxygenase pathways can be observed when macrophages or monocytes are given a zymosan phagocytic challenge. Interestingly, phagocytosis itself does not appear to be directly responsible for product generation, since latex bead phagocytosis did not cause prostaglandin synthesis.[23] The most important step in phagocytosis-induced arachidonate metabolism appears to be receptor–ligand

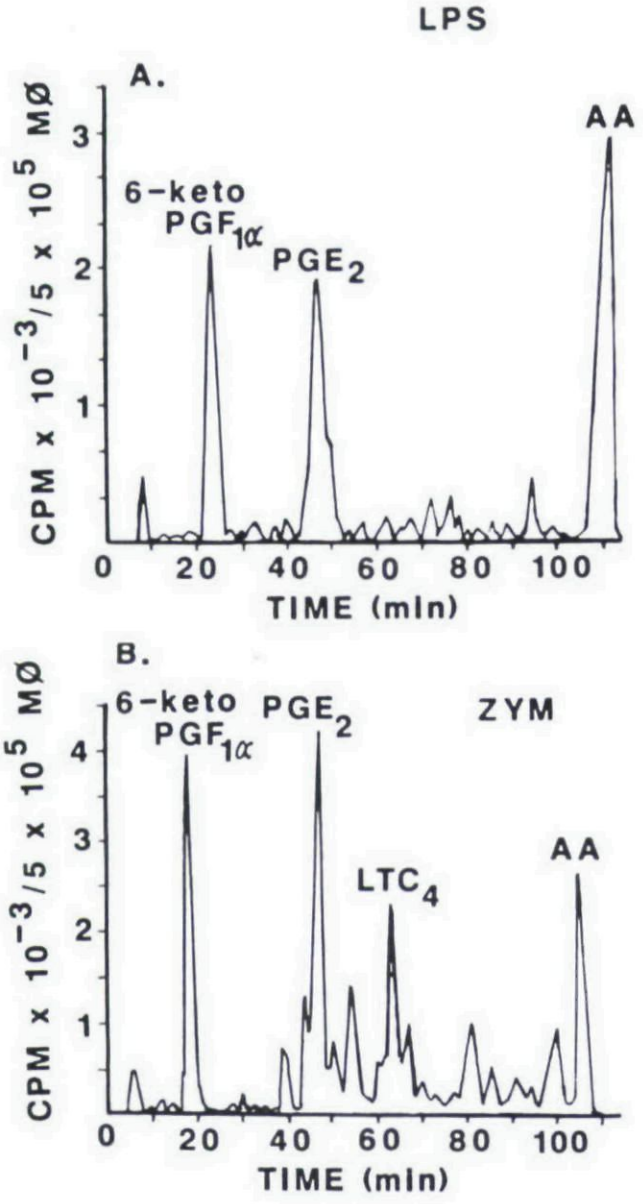

FIG. 2. HPLC analysis of ^{3}H-arachidonic acid metabolites synthesized by resident murine peritoneal macrophages stimulated with either 10 μg/ml LPS (A) or 250 μg/ml zymosan (B).

interaction involving specific receptors.[33] Macrophages treated with compounds that suppress lysosome–phagosome fusion and block phagocytosis still produced normal levels of PGE_2 when challenged with zymosan. A number of soluble stimuli that can induce membrane perturbation, independent of specific receptor interaction, also have been shown to stimulate arachidonic acid metabolism, including lipopolysaccharide (LPS), phorbol esters, and colchicine. As shown in Figure 2, the selectivity of metabolite formation varies dramatically with the stimulus under study. The membrane perturbant LPS resulted in the synthesis of only cyclooxygenase products, while zymosan induced the synthesis of both cyclooxygenase and lipoxygenase-derived metabolites. It is important to reiterate that the metabolism of arachidonic acid by mononuclear phagocytic cells is dependent upon a multitude of independent factors: (1) the anatomic location of the macrophage, (2) the state of macrophage activation, (3) the stimulus under study, (4) whether the cells are adherent, and (5) the presence of free or membrane-bound arachidonic acid.

Regulation of Immune Cell Function by Metabolites of Arachidonic Acid

Experimental evidence supports the view that various metabolites of arachidonic acid can exert profound modulatory effects on cells involved in immune–inflammatory responses. The robust ability of certain macrophage populations to synthesize diverse arachidonic acid metabolites implicates these cells in the immunoregulation of immune reactions.[34] It is well established that macrophages can synthesize rather large quantities of PGE_2. The ability of PGE to promote local vasodilitation and edema[35] has led many clinicians to presume this prostaglandin to be proinflammatory; however, current experimental evidence suggests that PGE_2 and PGI_2 possess dramatic suppressive activity in macrophage- and lymphocyte-mediated reactions. *In vitro,* PGE_2 has been shown to suppress a number of critical lymphocyte functions including B and T cell proliferation,[36,37] natural killer cell activity,[38] and cell-mediated cytotoxicity.[39] With regard to the production of lymphocyte-derived soluble mediators, Gordon et al.[40] and Bray et al.[41] have demonstrated that PGE_2 can suppress lymphokine production, as monitored by macrophage migration inhibition. In addition, Baker and co-workers[42] and Rappaport and Dodge[43] have shown that PGE_2 is efficacious in suppressing the production of interleukin-2 (IL-2). In the latter study, treatment of preparations with cyclooxygenase inhibitors was shown to augment the production of IL-2, thus providing support that endogenous PGE_2 is involved in regulating the production of lymphocyte mediators. Prostaglandins also may exert an immunosuppressive effect by inducing the activity of suppressor T cells.[44] A supporting study suggests that PGE_2 inhibits mitogen-induced proliferation by inducing a short-lived radiosensitive suppressor T cell;[45] upon activation with PGE_2, this lymphocyte population may suppress the proliferative response of the remaining lymphocytes.

It is becoming increasingly apparent that not only is the function and activity of lymphocytes regulated by prostaglandins, but the macrophage itself appears to

be modulated by various arachidonic acid metabolites. Prostaglandin E_2 has been shown to regulate macrophage oxygen metabolite production,[46] tumoricidal activity,[47] and macrophage proliferation.[48] Of particular interest is the suppressive effect of PGE_2 on the production of macrophage- and monocyte-derived signals necessary to activate lymphocytes. These studies include the inhibition of macrophage interleukin-1 (IL-1) production,[26] as well as the suppression of lymphokine-induced macrophage membrane I-region associated (Ia) antigens.[49,50] The suppressive effect of PGE_2 on macrophage Ia antigen expression appeared to possess a high degree of specificity since neither Fc receptor expression nor H-2K expression was altered. The *in vivo* suppression of Ia antigen expression would dramatically alter the antigen-presenting capability of macrophages and inhibit lymphocyte activation. We recently have demonstrated that IL-1, an important macrophage-derived signal with profound effects on lymphocyte-mediated reactions, can be regulated by a self-induced inhibitor, PGE_2.[26] As shown in Table 2, PGE_2 can suppress IL-1 production by LPS-stimulated macrophages in a dose-dependent manner. Furthermore, the cyclooxygenase inhibitor, indomethacin, demonstrated a dose-dependent augmentation in IL-1 production by LPS-stimulated macrophages. These studies suggest that endogenous PGE_2 can serve as a mechanism to regulate the production of an important lymphocyte-activating factor.

TABLE 2. *Dose-dependent Suppression of IL-1 Production by LPS-stimulated Murine Peritoneal Macrophage by PGE_2 and Dose-dependent Augment of IL-1 Production by LPS-stimulated Macrophages**

Sample	IL-1 Activity (CPM)
LPS 10 μg/ml	4,421 ± 492
LPS + 1 μM PGE_2	948 ± 52
LPS + 0.1 μM PGE_2	1,589 ± 109
LPS + 0.01 μM PGE_2	2,719 ± 294
LPS + 0.001 μM PGE_2	3,801 ± 345
LPS + 1 μM indomethacin	28,941 ± 1,001
LPS + 0.1 μM indomethacin	25,050 ± 843
LPS + 0.01 μM indomethacin	10,133 ± 641

* IL-1 was assayed using a thymocyte proliferation assay in the presence of dialyzed macrophage supernatant and suboptimal doses of PHA.

Regulation of *In Vivo* Macrophage- and Lymphocyte-dependent Reactions by Metabolites of Arachidonic Acid

Considering the large body of evidence showing that both macrophages and lymphocytes are targets for the regulatory effects of arachidonic acid metabolites, it is not surprising that numerous *in vivo* models have demonstrated that the development of chronic inflammation can be altered by these metabolites. Animal models of adjuvant-induced arthritis,[51] pulmonary hypersensitivity granulomas,[52] and autoimmune nephritis[53] all have been demonstrated to be susceptible to PGE-mediated suppression. The initial impetus to study the therapeutic effect of prostaglandins stemmed from the observation that these biologically active lipids, with *in vitro* suppressive activity, commonly were found in inflammatory exudates. Prostaglandin E_2 treatment first was shown to be effective in suppressing the macrophage- and lymphocyte-mediated reactions that result in the development of the polyarthritic response. In an extension of these early studies, investigations have shown that the polyarthritic response can be suppressed by the oral administration of a stable PGE_1 analogue, 15-methyl-PGE_1.[54] The oral activity of this compound most likely resides in its stability due to the protection of the 15-hydroxyl group from the action of the 15-hydroxy-prostaglandin dehydrogenase. The stable analogue of PGE_1 also was found to be efficacious in the treatment of murine systemic lupus erythematosus-like syndrome.[53] Both NZB/NZW mice and MRL/1 mice responded to prostaglandin therapy with a decrease in clinical nephritis and mortality. The therapeutic activity of PGE compounds in these animals is most likely due to the preservation of cell-mediated immunity by dictating the appropriate number of T and B cells, since diminished T-lymphocyte populations and increased B-lymphocyte functions are an early index of this disease. Additional studies have demonstrated the ability of PGE to suppress the normal progression of the nephritic response in animal whose disease was established at the onset of treatment.[55] Recent studies have examined the *in vivo* activity of prostaglandins on the development of foreign-body- and delayed-type hypersensitivity granulomatous inflammation. The delayed-type hypersensitivity granuloma involves a highly active T-lymphocyte-mediated lesion, whose development and regulation is controlled by macrophage–lymphocyte interactions, while the foreign body reaction is less vigorous and does not involve T cell sensitization. Investigations have demonstrated that prostaglandins can alter the delayed-type hypersensitivity, but not the foreign-body response.[52] In this study, PGE treatment was shown to suppress the elicitation of the granulomatous response and inhibit the induction of sensitized lymphocytes, whereas $PGF_{2\alpha}$ augmented the elicitation phase of the response. To further elucidate the mode of PGE-induced suppression of the delayed-

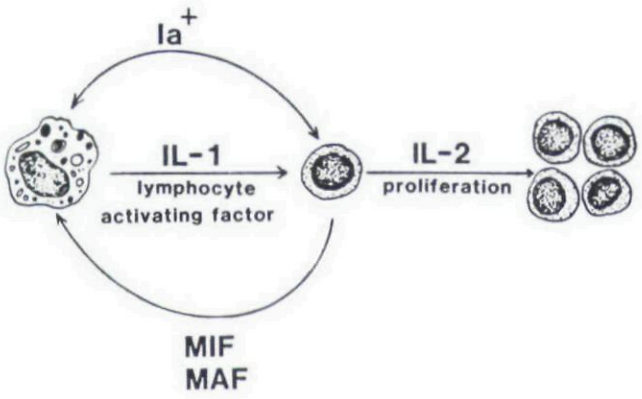

FIG. 3. Synopsis of the molecular signals that are responsible for the normal communications that occur between macrophages and lymphocytes. Each of the chemical signals are potential targets for the potentiation or suppression of chronic immune responses by specific metabolites of arachidonic acid.

type hypersensitivity lesion, the kinetics of the appearance of Ia-positive macrophages in developing lesions was studied. Prostaglandin E treatment dramatically suppressed granuloma macrophage Ia expression throughout the study period,[50] at times by as much as 60%. On the contrary, $PGF_{2\alpha}$, was shown to enhance granuloma macrophage Ia antigen expression during the early phase of granuloma development. The alteration in the percentage of Ia positive granuloma macrophages was shown to parallel the degree of cellular infiltrate. Neither $PGF_{2\alpha}$ nor PGE had an effect on the low levels of Ia antigen being expressed on the macrophages recovered from the foreign-body lesions. These observations may prove to be very important in the control of noninfectious granulomatous inflammation, since Ia antigen expression by macrophages is a critical signal for antigen presentation and T-lymphocyte proliferation.

Summary

Numerous investigations support the theory that arachidonic acid metabolites play a critical role in dictating the progression of chronic immune reactions. With regard to macrophage-mediated inflammatory responses, enzymatic oxygenation of arachidonic acid via the lipoxygenase or cyclooxygenase pathway can result in the production of compounds that may potentiate or suppress the inflammatory lesion. We recently have presented data demonstrating that lipoxygenase derived leukotriene B_4 and C_4 can induce the release of IL-1 by macrophages, while PGE_2 and PGI_2 can suppress the production of IL-1.[26] Macrophages are central to the induction of immune responses and the progression of chronic inflammatory reactions. Therefore, an understanding of the role that macrophage-derived arachidonic acid metabolites play in the initiation, maintenance, and resolution of chronic immune responses is essential. As shown in Figure 3, there are a number of chemical signals that occur between macrophages and lymphocytes that are critical for immune cell communication. The investigations described above have demonstrated that the macrophage may regulate the production and expression of any or all of these signals, such that the inflammatory response is potentiated, sustained, suppressed, or resolved. A better comprehension of the activity of these potent arachidonate derivatives will undoubtedly aid in the therapeutic manipulation of inflammatory disease.

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References

1. Kurzock R, Lieb CC. Biochemical studies of human semen: II. The action of semen on the human uterus. Proc Soc Exp Biol Med. 1930;28:268–271.
2. Goldblatt MW. A depressor substance in seminal fluid. J Soc Chem Ind. 1933;52:1056–1059.
3. von Euler US. On the specific vasodilitating and plain muscle stimulating substances from accessory genital glands in man and certain animals (prostaglandin and vesiglandin). J Physiol (London). 1936;88:213–219.
4. Bergstrom S, Sjovall J. Studies on prostaglandins: occurrence, formation, and biological actions. Acta Physiol Scand. 1959;158:1–52.
5. Bergstrom S, Ryhage R, Samuelsson B. The structure of prostaglandins E_1, F_1 and F_2. Acta Chem Scand [B]. 1962;16:501–511.
6. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature. 1971;231:232–235.
7. Feldberg W, Kellaway CN. Liberation of histamine and formation of lysolecithin-like substances by cobra venom. J Physiol. 1938;94:187–192.
8. Orange RR, Austin KF. Slow-reacting substances of anaphylaxis. Adv Immunol. 1969;10:105–111.
9. Murphy RC, Hammarstrom S, Samuelsson B. Leukotriene C: a slow-reacting substance from murine mastocytoma cells. Proc Natl Acad Sci USA. 1979;79:4275–4281.
10. Borgeat P, Samuelsson B. Transformation of arachidonic acid by rabbit polymorphonuclear leukocytes. J Biol Chem 1979;254:2643–2646.
11. Goetzl EJ, Pickett WC. The human PMN leukocyte chemotactic activity of complex hydroxy-eicosatetraenoic acids (HETEs) J Immunol. 1980;125:1789–1791.
12. Ford-Hutchinson AW, Bray MA, Doig MU, et al. Leukotriene B_4: a potent chemokinetic and aggregating substance released from polymorphonuclear leukocytes. Nature. 1980;286:264–265.
13. Showell HJ, Naccache PH, Borgeat P, et al. Characterization of the secretory activity of leukotriene B_4 for rabbit neutrophils. J Immunol. 1982:128:811–816.
14. Sherhan CN, Radin A, Smolen JE, et al. Leukotriene B_4 is a complete secretogogue for human neutrophils: a kinetic analysis. Biochem Biophys Res Commun. 1982;107:1006–1012.
15. O'Flaherty JT, Kreutzer DL, Ward PA. Effects of PGE_1, PGE_2, and $PGF_{2\alpha}$ on neutrophil activation. Prostaglandins. 1979;17:201–208.
16. Rivkin I, Rosenblatt J, Becker EL. The role of cyclic AMP in the chemotactic responsiveness and spontaneous motility of rabbit peritoneal neutrophils. J Immunol. 1975;115:1126–1134.

17. Fantone JC, Kinnes DA. Prostaglandin E_1 and prostaglandin I_2 modulation of superoxide production by human neutrophils. Biochem Biophys Res Commun. 1983;113:506–512.
18. Scott WA, Zrike JM, Hamill AL, et al. Regulation of arachidonic acid metabolites in macrophages. J Exp Med. 1980;152:324–335.
19. Stossel TP, Mason RJ, Smith AL. Lipid peroxidation by human blood phagocytes. J Clin Invest. 1974;54:638–645.
20. Mason RJ, Stossel TP, Vaughn M. Lipids of alveolar macrophages, polymorphonuclear leukocytes, and their phagocytic vesicles. J Clin Invest. 1972;51:2399–2407.
21. Sahn S, Lin WS. Lipid composition of human alveolar macrophages. Inflammation. 1977;2:83–96.
22. Bonney RJ, Wightman PD, Davies P. Selective inhibitors of lecithin biosynthesis in mouse peritoneal macrophages. Biochem Pharmacol. 1979;28:2471–2478.
23. Rouzer CA, Scott WA, Kempe J, et al. Prostaglandin synthesis by macrophages requires a specific receptor-ligand interaction. Proc Natl Acad Sci USA. 1980;77:4279–4282.
24. Hsueh W, Desai U, Gonzaley-Crussi J. Two phospholipase pools for prostaglandin synthesis in macrophages. Nature. 1981;290:710–713.
25. Humes JL, Sadowski S, Galavage M. Evidence for two sources of arachidonic acid for oxidative metabolism by mouse peritoneal macrophages. J Biol Chem. 1982;257:1591–1594.
26. Kunkel SL, Chensue SW, Spengler M, et al. Effects of arachidonic acid metabolites and their metabolic inhibitors of interleukin-1 production. In: Kluger MJ, Oppenheim JJ, Powanda MC, eds. The physiologic, metabolic, and immunologic actions of interleukin-1. New York: Alan R Liss, 1985:297–307.
27. Kurland JI, Bockman R. Prostaglandin E production by human blood monocytes and mouse peritoneal macrophages. J Exp Med. 1978;147:952–957.
28. Boch MK, Brashler JR, Hammerstrom S. Identification of leukotriene C-1 as a major component of slow-reacting substance from rat mononuclear cells. J Immunol. 1980;125:115–117.
29. Roubin R, Benveniste J. Release of leukotriene C (LTC) and D (LTD) from inflammatory macrophages during phagocytosis of zymosan and bacteria. Agents Actions. 1981;11:578–579.
30. Kunkel SL, Chensue SW, Mouton C, et al. Role of lipoxygenase products in murine pulmonary granuloma formation. J Clin Invest. 1984;74:514–524.
31. Scott WA, Pawlowski NA, Andreach M, et al. Resting macrophages produce distinct metabolites from exogenous arachidonic acid. J Exp Med. 1982;155:535–547.
32. Scott WA, Pawlowski NA, Murray HW, et al. Regulation of arachidonic acid metabolism by macrophage activation. J Exp Med. 1982;155:1148–1160.
33. Hsueh W, Kuhn C, Needleman P. Relationship of prostaglandin secretion by rabbit alveolar macrophages to phagocytosis and lysosomal enzyme release. Biochem J. 1979;184:345–354.
34. Kunkel SL, Chensue SW. Prostaglandins and the regulation of immune responses. Adv Inflam Res. 1984;7:93–109.
35. Williams TJ, Morley J. Prostaglandins as potentiators of increased vascular permeability in inflammation. Nature. 1973;246:215–217.
36. Kurland JI, Kincade PW, Moore MAS. Regulation of B cell clonal proliferation by stimulatory and inhibitory macrophage-derived factors. J Exp Med. 1977;146:1420–1435.
37. Stobo JD, Kennedy MS, Goldyne MC. Prostaglandin E modulation of the mitogenic response of human T cells. J Clin Invest. 1979;64:1188–1195.
38. Korn HS, Anderson SJ, Fischer DG. Regulation of human natural killing: I. The role of monocytes, interferon, and prostaglandins. J Immunol. 1981;127:2007–2013.
39. Henney CS, Bourne HR, Lichtenstein LM. The role of cyclic AMP in the specific cytolytic activity of lymphocytes. J Immunol. 1971;108:1526–1534.
40. Gordon D, Bray MA, Morley J. Control of lymphokine secretion by prostaglandins. Nature. 1976;262:401–402.
41. Bray MA, Gordon D, Morley J. Prostaglandins as regulators in cellular immunity. Prostaglandin Med. 1978;1:183–190.
42. Baker PE, Fahey JV, Munck A. Prostaglandin inhibition of T cell proliferation is mediated at two levels. Cell Immunol. 1981:61:52–60.
43. Rappaport RS, Dodge GR. Prostaglandin E inhibits the production of human interleukin 2. J Exp Med. 1982;155:943–948.
44. Fulton AM, Levy JG. The possible role of prostaglandins in mediating immune suppression by nonspecific T suppressor cells. Cell Immunol. 1980;52:29–37.
45. Goodwin JS, Webb DR. Regulation of the immune response by prostaglandins. Clin Immunol Immunopathol. 1980;15:106–113.
46. Smith RL, Weidemann MJ. Reactive oxygen production associated with arachidonic acid metabolism by peritoneal macrophages. Biochem Biophys Res Commun. 1980;97:973–980.
47. Snider ME, Fertel RN, Zwilling BS. Prostaglandin regulation of macrophage function: effect of endogenous and exogenous prostaglandins. Cell Immunol. 1982;74:234–242.
48. Pelus LM, Broxmeyer HE, Kurland JL. Regulation of macrophage and granulocyte proliferation. J Exp Med. 1979;150:277–292.
49. Snyder DS, Beller DI, Unanue ER. Prostaglandin modulate macrophage Ia expression. Nature. 1982;299:163–165.
50. Kunkel SL, Chensue SW, Plewa MC, et al. Macrophage function in the *Schistosoma mansoni* egg-induced pulmonary granuloma: role of arachidonic acid metabolites in macrophage Ia antigen expression. Am J Pathol. 1984;114:240–249.
51. Zurier RB, Quagliata F. Effects of prostaglandin E_1 on adjuvant arthritis. Nature. 1971;234:304–305.
52. Chensue SW, Kunkel SL, Ward PA, et al. Exogenously administered prostaglandins modulate pulmonary granulomas induced by *Schistosoma mansoni* eggs. Am J Pathol. 1983;111:78–87.
53. Zurier RB, Damajanov I, Miller PL. Prostaglandin E_1 treatment prevents progression of nephritis in murine lupus erythematosus. J Clin Lab Immunol. 1978;1:95–106.
54. Kunkel SL, Ogawa H, Conran PB, et al. Suppression of acute and chronic inflammation by orally administered prostaglandins. Arthritis Rheum. 1981;24:1151–1158.
55. Zurier RB, Gionfriddo M, Miller P. Treatment of NZB/W ("lupus") mice with 15(S)-15-methyl PGE_1. Prostaglandin Med. 1980;4:281–284.

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