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Secretory Products of Macrophages

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Introduction

Phagocytosis by macrophages¹ is essential to metazoan life. Without it, organs would go unmodelled, wounds unattended. Senescent cells would stagnate in the vessels, invading microbes flourish in the tissues. Recent research, however, has focussed more on macrophage secretion than on endocytosis. There is cogent cause for this intense interest in macrophage products. Macrophages in large numbers (1) line submucosae, pulmonary alveoli, juxtaglomerular and other perivascular spaces, bony trabeculae, and renal tubules (2). They congregate in most subacute or chronic inflammatory reactions, including exudates, granulomas, fatty streaks, and atheromas (3). In culture, they provide monotypic, monodisperse, differentiating cell populations that react dramatically to soluble and particulate stimuli of mammalian and microbial origin and of physiologic and pharmacologic interest. Their responses include the secretion of some 100 substances, ranging in molecular mass from 32 (superoxide anion) to 440,000 (fibronectin), and in biologic activity from induction of cell growth to cell death. This rich an array of products has been demonstrated for few if any other cells. Thus, through their abundance, distribution, motility, responsivity, and versatility, macrophages can influence almost every aspect of the immune and inflammatory responses, from acute to delayed hypersensitivity, from the first breach of epithelium to its eventual repair.

Constraints on space confine this review to a catalog with commentary. Worthy topics that cannot be covered include control of secretion at the intercellular, cell surface, and intracellular levels, and the heterogeneity of secretion by macrophages of different species, anatomic sources, and states of differentiation.

Multiple macrophage products

Paradoxically, the list of macrophage secretory products (Table I) has not grown much longer in the last few years, despite continual entries. The explanation is the increased molecular definition of entities previously known only as activities. This has permitted two insights: that a single macrophage product can have diverse activities, and that a single activity can reflect the action of many macrophage products. Thus, while earlier reviews

(51, 102, 103) listed many activities, Table I can now be restricted mostly to molecules. A few activities are included whose preliminary characterization supports their distinction. A third generalization has also emerged: few if any of the products in Table I arise solely from macrophages. Evaluation of the importance of macrophages as their source requires consideration of the anatomic and pathophysiologic circumstances pertaining in each instance. These three points are illustrated below.

Multiple activities of individual products

The remarkable polypeptide hormones interleukin 1- α and interleukin 1- β , and TNF- α or cachectin,² vividly illustrate this point. Each was discovered in one of the few bioassays which, in retrospect, could distinguish it from the other. Thus, IL-1 (104-106), but not TNF (107), promotes the expression of interleukin 2 receptors and mitogenic response of T cells, while TNF (7), but not IL-1 (Paliadino, M. A., Jr., personal communication) causes hemorrhagic necrosis of certain tumor implants in mice. The purification and cloning (4-11) of these molecules has allowed them to lay claim to a wide range of bioactivities of major importance to the pathogenesis of inflammatory responses, both acute (fever, shock, altered levels of hormones, coagulopathies, adherence of leukocytes to endothelium), subacute (tumor cell injury, muscle breakdown, development of humoral and cell-mediated immunity), and chronic (wound healing, fibrosis, erosion of cartilage, remodelling of bone) (Table II). Whether pure IL-1 or TNF induces cachexia awaits demonstration. The diversity of actions of these hormones on a single cell type, combined with the numerous types of cells that are their targets, is reminiscent of the action of glucocorticoids—which IL-1 induces (183, 184) and which in turn suppress IL-1 release (192).

Why does the macrophage transcribe at least three different genes (IL-1- α and - β , TNF- α) encoding potent pleiotropins with largely but incompletely shared functions? We know too little about inflammation to appreciate the implications. Part of the functional overlap may be more apparent than real, since IL-1 and TNF can induce each other's release by some cells (107, 118, 139, 156a), notably macrophages themselves. Thus, some of the actions attributed to one of these monokines may be due to the unsuspected presence of the other. However, in at least one instance where this possibility was considered, IL-1 and TNF exerted a shared action independently (139).

Even the macrophage secretory products of lowest molecular weight have diverse effects. The reactive oxygen intermediates

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1. "Macrophage" is used here to refer to all cells of the mononuclear phagocyte lineage, including monocytes.

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2. Abbreviations used in this paper: CSF-G/M, colony-stimulating factor for granulocytes and macrophages; IL-1, interleukin 1- α and 1- β , collectively; PGE₂, prostaglandin E₂; TNF, tumor necrosis factor- α (cachectin).

Table I. Secretory Products of Mononuclear Phagocytes*

<p>Polypeptide hormones</p> <p>Interleukin 1-α and 1-β (collectively, IL-1) (4–6)</p> <p>Tumor necrosis factor-α (cachectin) (TNF) (7–11)</p> <p>Interferons-α (12, 13)</p> <p>Interferon-γ (confirmation needed) (14, 15)</p> <p>Platelet-derived growth factor(s) (16, 17)</p> <p>Fibroblast growth factors (18, 19)</p> <p>Fibroblast activating factors (20)</p> <p>Transforming growth factor-β (21)</p> <p>Insulinlike activity (22)</p> <p>Thymosin B4 (23)</p> <p>Erythropoietin (24)</p> <p>Colony-stimulating factor for granulocytes and macrophages (CSF-G/M) (25; but see 25a and 139a)</p> <p>Colony-stimulating factor for granulocytes (CSF-G) (25a)</p> <p>Erythroid colony-potentiating factor (26)</p> <p>Factor-inducing monocytopoiesis (27)</p> <p>β-Endorphin (28)</p> <p>Adrenocorticotrophic hormone (28)</p> <p>Plasmacytoma growth factor (29)</p> <p>Neutrophil-activating factor (30)</p> <p>Complement (C) components (31–35)</p> <p>Classical path: C1, C4, C2, C3, C5</p> <p>Alternative path: factor B, factor D, properdin</p> <p>Inhibitors: C3b inactivator, β-1H</p> <p>Active fragments generated by macrophage proteases: C3a, C3b, C5a, Bb</p> <p>Coagulation factors</p> <p>Intrinsic path: IX, X, V, prothrombin (36, 37)</p> <p>Extrinsic path: VII (38)</p> <p>Surface activities: tissue factor, prothrombinase (39, 40)</p> <p>Prothrombolytic activity: plasminogen activator (41, 42)</p> <p>Antithrombolytic activities: plasminogen activator inhibitors (42, 43), plasmin inhibitors (44)</p> <p>Other enzymes</p> <p>Neutral proteases: plasminogen activator (41), elastase (45), collagenases (46–49), angiotensin convertase (50), others (51)</p> <p>Lipases: lipoprotein lipase (52, 53), phospholipase A2 (54)</p> <p>Glucosaminidase: lysozyme (55)</p> <p>Lysosomal acid hydrolases: proteases, lipases (deoxy)ribonucleases, phosphatases, glycosidases, sulfatases (56–58)</p> <p>Deaminase: arginase (59)</p>	<p>Inhibitors of enzymes and cytokines</p> <p>Protease inhibitors: α-2-macroglobulin (60, 61), α-1-antiprotease (62, 63), plasminogen activator inhibitors (42, 43), plasmin inhibitors (44), collagenase inhibitor (49)</p> <p>Phospholipase inhibitor: lipomodulin (macrocortin) (64)</p> <p>IL-1 inhibitors (65–67)</p> <p>Proteins of extracellular matrix or cell adhesion</p> <p>Fibronectin (68–71)</p> <p>Gelatin-binding protein of 95 kD (72)</p> <p>Thrombospondin (73)</p> <p>Chondroitin sulfate proteoglycans (74)</p> <p>Other binding proteins</p> <p>For metals: transferrin (75), acidic isoferritins (76), transcobalamin II (77)</p> <p>For lipids apolipoprotein E (78), lipid transfer protein (79)</p> <p>For biotin: avidin (80)</p> <p>Bioactive oligopeptides</p> <p>Glutathione (81)</p> <p>Bioactive lipids</p> <p>Cyclooxygenase products: prostaglandin E₂ (PGE₂), prostaglandin F_{2α}, prostacyclin, thromboxane (82–85)</p> <p>Lipoxygenase products: monohydroxyeicosatetraenoic acids, dihydroxyeicosatetraenoic acids, leukotrienes B₄, C, D, E (86–89)</p> <p>Platelet-activating factors (1-O-alkyl-2-acetyl-<i>sn</i>-glyceryl-3-phosphorylcholine) (90)</p> <p>Sterol hormones</p> <p>1α,25-Dihydroxyvitamin D3 (91)</p> <p>Purine and pyrimidine products</p> <p>Thymidine (92, 93), uracil (93), uric acid (93), deoxycytidine (94)</p> <p>Neopterin (2-amino-4-oxo-6-trihydroxypropylpteridine) (95, 96)</p> <p>Reactive oxygen intermediates</p> <p>Superoxide (97), hydrogen peroxide (98), hydroxyl radical (99), hypohalous acids (100)</p> <p>Reactive nitrogen intermediates</p> <p>Nitrites, nitrates (101)</p>
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* Numbers in parentheses are selected references.

damage a wide variety of cells. At lower concentrations, they elicit noncytotoxic secretory responses, and modify the products of the cells of origin as well as of neighboring cells. The consequences are both pro- and anti-inflammatory (Table III).

Multiple products with similar activities

There are many examples, besides IL-1 and TNF, of this phenomenon (Table IV). As yet, there has been little study of potential interactions among such products (195). As with IL-1 and TNF, we do not yet appreciate the strengths or subtleties of control that apparent redundancy can afford, such as synergy through affecting a pathway at different points; selectivity through

engaging receptors represented differentially on potential targets; or temporal modulation through dissimilar kinetics of product release, product decay, and target cell response.

Multiple cell sources

A few of the products in Table I have not yet been shown to come from cells other than macrophages. Examples are neopterin (95, 96) and the reactive intermediates in the oxidation of nitrogen (101). This may change when a wider spectrum of cell types is tested. Most of the factors in Table I can be released by cells other than macrophages. For example, molecules with serologic, physicochemical, receptor-binding, and bioactive sim-

Table II. Multiplicity of Actions of IL-1 and TNF

Target	Action	IL-1	TNF
T lymphocytes	Co-mitogenesis;	104-106*	NO [‡] ; 107
	Chemotaxis	108	— [§]
B lymphocytes	Co-mitogenesis; Ia antigen expression;	109, 110	
	Chemotaxis	108	—
Natural killer cells	Increased cytotoxicity,	111	—
	Interleukin 2 receptors	112	—
Mononuclear phagocytes	Differentiation of precursors;	—	113, 114
	Induction of cytotoxic,	115	—
	Antimicrobial, and	—	116
	ROI secretory capacity;	NO: 117	117
	Secretion of IL-1,	—	107
	TNF	118	—
	Thromboxane	119	—
Neutrophils	Inhibition of precursors;	—	120, 121
	Degranulation, lysosomal enzyme release;	122, 123	124
	Secretion of ROI,	125	124, 126
	Thromboxane;	119	—
	Enhancement of phagocytosis, ADCC, [§]	—	124, 127
	Adhesion to endothelium,**	—	128
	Surface display of C3bi receptors	—	128
Eosinophils	Toxicity to schistosomes	—	129
Endothelium	Enhanced proliferation;**	130	—
	Induction of procoagulant activity,		
	Decreased synthesis of plasminogen activator,		
	Decreased activation of protein C,		
	Increased synthesis of plasminogen activator inhibitor,	131-134	134, 135
	Platelet-activating factor, PGE ₂ , prostacyclin,	136-138	—
	IL-1,	—	139
	CSF-G/M;	139a	140, 141
	Induction of HLA A, B antigens,	—	142
	p100,120 antigen;	143	143
	Adhesion of neutrophils, monocytes,	144, 145	128, 145
	Lymphocytes	146	—
Fibroblasts,	Increased proliferation;	106, 147	148, 149
Synoviocytes	Synthesis of PGE ₂ , collagenase,	106, 150	151
	Interferons including interferon β-1 and/or β-2,	152, 152a	153
	Protease inhibitor,	154	—
	Hyaluronate,	155	—
	CSF-G/M,	156	140
	IL-1;	—	156a
	Expression of HLA A, B antigens,	—	142
	Antiviral activity	—	156b, 156c
Chondrocytes	Decreased synthesis of proteoglycans,**		
	Increased proteoglycanase, collagenase,	157, 158	159
	PGE ₂	160	—
Osteoclasts,	Increased proliferation and bone resorption,		
Osteoblasts	Decreased bone synthesis	161-163	164
Adipocytes	Decreased synthesis of lipoprotein lipase	165	166
Skeletal myocytes	Protein breakdown, PGE ₂ release,	167	—
	Membrane depolarization	—	168
Hepatocytes	Induction of serum amyloid A and P, complement factor B, haptoglobin,	169-173**	—
	α-2-macroglobin; inhibition of albumin synthesis		
Astroglia	Increased proliferation	174	—
Mesangial cells	Increased proliferation	175	—
	Neutral protease secretion	176	—
Pancreatic islets	Cytotoxicity	177	—
Tumor cells	Cytotoxicity	178-181	7, 148, 182
	Antiviral activity	—	156b, 156c
In vivo, loci of action	Hemorrhagic necrosis of some tumors;	NO [‡]	7, 8
not certain	Increased plasma ACTH, corticosteroids;	183, 184	NO:183
	Increased turnover of plasma amino acids;	185	—
	Increased plasma iron, fibrinogen,		
	Decreased plasma glucose;	184, 186, 187	—
	Accumulation of neutrophils;	186, 188, 189	190
	Epidermal hyperplasia; fibrosis;	188	—
	Decreased lethality from radiation	191	—

* Numbers refer to selected reports of the indicated action. ‡ NO, reportedly not observed. § —, No observations reported, to my knowledge.
^{||} ROI, reactive oxygen intermediates. [†]ADCC, antibody-dependent, cell-mediated cytotoxicity. ** There are also nonconfirmatory reports.

Table III. Multiplicity of Actions of Reactive Oxygen Intermediates*

On cells
Killing of viruses, bacteria, fungi, protozoa, nematodes, trematodes
Injury of tumor cells, erythrocytes, lymphocytes, leukocytes, platelets, endothelial cells, fibroblasts, lung cells, spermatozoa
Inhibition of leukocyte lysosomal enzyme release
Stimulation of secretion by platelets, mast cells, endothelial cells, glomerular cells
Noncytotoxic suppression of function of lymphocytes directly or through activation of soluble immune response suppressor
Mutagenesis of bacteria and mammalian cells
Tumor promotion and carcinogenesis
On extracellular products
Generation of chemotactic lipids from arachidonate
Activation of leukocyte collagenase, gelatinase
Inactivation of chemotactic leukotrienes, chemotactic peptides, α -1-antiprotease, met-enkephalin, leukocyte hydrolases, bacterial toxins

* Adapted from reference 193.

ilarities to TNF are produced by natural killer cells (120) and some transformed fibroblasts (196), while IL-1-like factors are released by B cells, natural killer cells, polymorphonuclear leukocytes, endothelial cells, epidermal cells, astroglia, and some hepatomas (197). Likewise, reactive oxygen intermediates are released not only by macrophages (198) and polymorphonuclear leukocytes (199), but also by mast cells (200), mesangial cells (201), smooth muscle cells (202), thyroid follicle cells (203), and the ova of some species upon fertilization (204).

Quantitatively, the contribution of macrophages to a given pool of product varies from major (serum lysozyme) to minor

Table IV. Multiple Macrophage Products with Similar Activities

Bioactivity	Products
Inhibition of cell proliferation	Reactive oxygen intermediates, TNF- α , IL-1- α , IL-1- β , transforming growth factor- β , interferons- α , interferon- γ , oxidized soluble immune response suppressor, CSF-G/M (action on leukemic cells), arginase; PGE ₂ , thymidine, reactive nitrogen intermediates? (speculative)
Promotion of cell proliferation	TNF- α , IL-1- α , IL-1- β , fibroblast growth factors, platelet-derived growth factor, CSF-G/M, erythropoietin, erythroid colony-stimulating factor, plasmacytoma growth factor, leukotriene B ₄ (for keratinocytes)
Chemotactic attraction	Leukotrienes B ₄ and C, IL-1- α , IL-1- β , platelet-derived growth factor, platelet-activating factor, β -endorphin, γ -induced protein 10? (speculative) (194), fragments of fibronectin and elastin
Induction of fever	IL-1- α , IL-1- β , TNF- α , interferons- α , interferon- γ

(serum complement). However, quantities alone say little about the physiologic importance of secretion of a given product by macrophages, relative to its secretion by other cells.

For example, the presence of macrophages at foci of inflammation magnifies the importance of their contribution of C2. C2 is probably rate limiting in complement fixation at extravascular sites in the early phases of inflammation, before transudate becomes exudate (205). Minute quantities of macrophage-derived C3 may be responsible for opsonizing yeasts (206) and leishmania (207) so that they bind better to macrophages and acquire the capacity to trigger a respiratory burst in neighboring neutrophils (208).

As noted by Shimokado et al. (16), many cells secrete mitogenic proteins resembling platelet-derived growth factor. Other than platelets, however, monocytes are the only blood cells that do so. In the earliest phases of atheroma formation, invasion by monocytes precedes adhesion of platelets (3). In the later phases, macrophages are embedded in the intima, in direct contact with myocytes and fibrocytes. In contrast, the platelet thrombus caps the plaque at a greater distance from these target cells in a swift-flowing stream that may dilute and wash away platelet products. In other conditions that eventuate in fibrosis, platelets are virtually absent and macrophages abundant (16). Thus, although platelets outnumber macrophages by about a hundredfold, macrophages are likely to be an important source of platelet-derived growth factor (16).

Product interactions

Another source of complexity in the macrophage secretory repertoire is the propensity of the products to affect each other. Only four of many types of interaction will be illustrated.

First, the products may affect each other's release. For example, TNF enhances macrophage capacity to release reactive oxygen intermediates (117), which share antitumor activity with TNF (198). Another cytokine whose antiproliferative action synergizes with that of TNF, interferon- γ , enhances macrophage release of TNF (209), and like TNF, enhances macrophage capacity to secrete reactive oxygen intermediates (210). Leukotrienes (211) and C5a (212) trigger the release of IL-1, C3b the release of PGE₂ (213), and C3a the release of thromboxane (214). On the other hand, macrophage-derived interferon- α can block the induction by interferon- γ of macrophage H₂O₂ secretion (215), and α -2-macroglobulin-protease complexes can also suppress superoxide release by macrophages (216).

Second, macrophage products may affect each other's actions. Examples are synergy in killing bacteria by complement components and lysozyme (217), and in degrading matrix by elastase and plasminogen activator (218). On the negative side, macrophage elastase can cleave α -1-protease inhibitor (219), and macrophage-derived oxidants can inactivate it (220). Other inhibitory factors secreted by macrophages, along with the substances whose actions they block, are plasminogen activator inhibitors (42, 43), collagenase inhibitor (49), and IL-1 inhibitors (65-67).

Third, the macrophage products may affect the secretion by other cells of products macrophages also make. For example, TNF stimulates endothelial cells to release IL-1 (139). IL-1 (106, 147, 156) and TNF (140, 151) stimulate fibroblasts to release PGE₂, collagenase, and CSF-G/M, and suppress adipocyte production of lipoprotein lipase (165, 166).

Fourth, macrophage products like TNF may induce target

cells to release cytokines that mediate (142, 153) or antagonize (120, 121, 140, 141) some of the actions attributed to the monokines.

Next steps

To move from catalog to comprehension, we must turn in two directions. First, into the cell: How are these products actually formed? What is the import of monokines without signal sequences, bound to the plasma membrane, like IL-1? Are such agents secreted in the strict sense, shed, or released from dying cells? How are signals transduced for secretion? How do macrophages respond to higher order signals that regulate secretory capacity? Second, in vivo, the really tough questions: How do macrophage secretory products actually function? Which effects are important, which figments of our assays? When do the multiple products work in concert, when in conflict? What sets the tempo? Answers will require monoclonal antibodies, complementary DNAs, recombinant proteins, transfected genes, receptor antagonists, enzyme inhibitors, and the judicious choice of animal models and human diseases for detection, deletion, and reconstitution.

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