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Macrophage response to bacteria and bacterial products: modulation of Fcγ receptors and secretory and cellular activities

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SUMMARY

The ability of bacteria and bacterial products to modulate the expression of Fcγ receptors and major histocompatibility complex (MHC) class II molecules in resting rat bone marrow-derived mononuclear phagocytes (BMMϕ) was determined by means of flow cytometry (FCM). Binding of IgG via Fcγ receptors was considerably enhanced by most microbial agents; bacterial lipopolysaccharide, lipoteichoic acid and some intact bacteria proved to be as active as interferon-γ (IFN-γ) and augmented binding of IgG via high- and low-affinity Fcγ receptors. In contrast, expression of MHC class II molecules by BMMϕ was only slightly affected by the microbial agents. Additional findings attest that resting unprimed rat BMMϕ are able to respond directly to Gram-negative and Gram-positive bacteria and to some of their products with the expression of marked secretory [in particular tumour necrosis factor-α (TNF-α) and nitrite] and cellular activities (TNF-α-independent tumoricidal activity). This extensive, direct type of macrophage activation may substantially amplify the capability of these cells to cope with these infectious agents in first-line, non-specific host defence.

INTRODUCTION

For various reasons, macrophages are uniquely qualified to play a pivotal role in first-line host defence.[1] The work of Mackaness and co-workers[2,3] has laid the foundations for the concept that the enhanced antimicrobial resistance generated in the course of the specific immune response is associated with intrinsic adaptive changes in macrophages, the so-called macrophage activation.[4] More recent findings suggested that direct interaction of microbial agents and macrophages may also trigger some secretory and cellular activities.[5–14] In this study, the ability of microbial agents to modulate in a pure population of resting unprimed rat bone marrow-derived mononuclear phagocytes (BMMϕ) the expression of major histocompatibility complex (MHC) class II molecules and Fcγ receptors was assessed in parallel with various other macrophage parameters. To ensure that BMMϕ were not contaminated with other cells, in particular lymphocytes and natural killer (NK) cells, various experimental attempts, that had been utilized on different occasions during the past decade, were made here in parallel on the same cell populations.

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Abbreviations: BMMϕ, bone marrow-derived mononuclear phagocytes; FCM, flow cytometry; FCS, fetal calf serum; IFN-γ, interferon-γ; IgG, immunoglobulin G; IMDM, Iscove's modified Dulbecco's medium; LPS, lipopolysaccharide; LTA, lipoteichoic acid; NU, neutralizing units; mAb, monoclonal antibody; PE, phycoerythrin; PGMC, peptidoglycan from *Moraxella catarrhalis*; SN, supernatant; TNF-α, tumour necrosis factor-α.

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MATERIALS AND METHODS

Reagents

Rat myeloma protein IgG2bκ (IR 863) was from Dr H. Bazin (Brussels, Belgium); purified human IgG was from Sigma Chemical Co. (St Louis, MO). For binding studies, rat myeloma protein IgG2b was spun at 30,000 *g* to remove insoluble aggregates and the supernatant (SN) used for the experiments. Monoclonal antibody (mAb) to rat MHC class II antigen (MRC OX6) and affinity-purified phycoerythrin (PE)-conjugated $F(ab')_2$ anti-mouse (Star 12), anti-rat (Star 30) and anti-human IgG (Star 31) were from Serotec (Blackthorn, Bicester, U.K.). Recombinant rat interferon-γ (IFN-γ) (1·7 U ~0·25 ng) and polyclonal antiserum against rat IFN-γ (~100,000 NU/ml) were from Dr P. H. van der Meide (Rijswijk, The Netherlands). Murine tumour necrosis factor-α (TNF-α) (specific activity $1{\cdot}2 \times 10^7$ U/ml protein) was from Dr G. R. Adolf (Vienna, Austria), conventional sheep anti-mouse TNF-α (neutralizing activity ~100,000 NU/ml) was from Dr R. M. Zinkernagel (Zurich, Switzerland).

The bacteria were selected, grown, harvested and inactivated as previously described; wet weight was taken as a quantitative measure of bacteria.[7–9] Lipopolysaccharide (LPS) from *Escherichia coli* 0128:B12 (L2755) and lipoteichoic acid (LTA) from *Enterococcus faecalis* (L4015) were from Sigma. Peptidoglycan from *Moraxella catarrhalis* (PGMC) was isolated as described previously.[9]

BMMϕ

Bone marrow cells were obtained and cultured as previously described.[6,15] In short, bone marrow cells from femurs of male DA rats suspended in Iscove's modified Dulbecco's medium (IMDM) supplemented with 10% fetal calf serum (FCS) and conditioned with SN (final concentration 10%) from strain L clone 929 cells (ATCC CCL1; ATCC, Rockville, MD) were cultured in bacteriologic glass Petri dishes (diameter 96 mm; Greiner, Nürtingen, Germany). On day 6, the cells remaining adherent after repeated washing were cultured for the time indicated in medium alone or in medium supplemented with one of the agents under examination before the secretory and cellular activities were determined.

To characterize adherent bone marrow-derived effector cells, their light and electron microscopic appearance,[5,13] the cytochemical staining for esterase and their capacities to bind IgG-coated sheep erythrocytes and to ingest particles such as latex or *Listeria monocytogenes* organisms were regularly assessed.[5,15]

Secretory activities

TNF-α activity was checked by measuring the cytolytic activity of macrophage culture supernatants in the absence of actinomycin D, utilizing the TNF-α-sensitive WEHI-164/13 cells as a target and murine TNF-α and sheep anti-mouse TNF-α as a reference.[9] IL-1[11,16] and IL-6 activity[12,17] were quantified by means of their ability to induce a proliferative cell response. Prostaglandin E_2 (PGE_2) concentration was determined in a ^{125}I radioimmunoassay (RIA) kit as previously described.[12] For the measurement of NO_2^-, cell-free culture SN were mixed with Griess reagent and absorbance at 550 nm determined after 10 min at room temperature.[6]

Cellular activities

Expression of MHC class II molecules and binding of monomeric IgG by BMMϕ was measured by flow cytometry (FCM).[18] Briefly, BMMϕ were first incubated for 60 min at 4° in medium containing 2% FCS and anti-MHC class II mAb or IgG, washed twice, fixed with paraformaldehyde (1%, 20 min, 4°), washed twice, and incubated for a further 60 min at 4° with the corresponding PE-conjugated anti-IgG $F(ab')_2$ before analysis in a fluorescence-activated cell system (FACS Analyzer IFA, Becton Dickinson, Sunnyvale, CA). Electrical cell volume, 90° light scatter, log fluorescence 1 and log fluorescence 2 of each cell was determined. Data were collected in a list mode with a Hewlett Packard 9217 (Fort Collins, CO) computer with hard disk data acquisition. Analysis of the flow histogram data was performed utilizing the Multi 2D software (Phoenix Flow Systems, San Diego, CA) with the histogram subtraction technique described by Overton.[19] A minimum of 10^4 cells/sample was measured. For each type of experiment, three to six determinations were performed. Units employed were per cent of total cells exceeding the fluorescence of the control sample in log mode.

Reductive capacity

The reductive capacity of the cells (5×10^4 cells/well) was determined in a MTT tetrazolium assay by measuring absorbance at 570 nm in a microplate reader.[6]

TNF-α-independent tumoricidal activity

Resting day 6 BMMϕ were first incubated for 24 hr in medium supplemented with one of the agents to be tested. The medium was then replaced by new medium supplemented with the same agent and pre-labelled TNF-α-resistant P-815 mastocytoma tumour targets (initial ratio of effectors and targets 1:1 or 2·5:1), and tumoricidal activity determined in a 36 hr [^{14}C]thymidine release assay.[5]

RESULTS

Adherent cells harvested on day 6 after initiation of the culture of bone marrow cells were identified as mononuclear phagocytes by various criteria (e.g. light and electron microscopic appearance, esterase activity, phagocytosis, reductive capacity, autofluorescence, FCM characteristics, lack of positive signals using anti-lymphocyte antisera.[6,8,9,11,18] These cells were homogeneous with respect to cell lineage and in particular, were free of lymphocytes; they secreted no or only minor amounts of TNF-α, IL-1, IL-6, NO_2^-, and PGE_2 and did not express spontaneous tumoricidal activity against TNF-α-resistant tumour targets. On incubation with IFN-γ and microbial agents, these BMMϕ were able to modulate the expression of some surface molecules and to enhance their secretory and cell-mediated activities.

Expression of MHC class II molecules

In the majority of experiments, only a minor portion of resting BMMϕ expressed MHC class II molecules; in a few experiments (three out of 11) up to 40% of resting BMMϕ expressed MHC class II molecules. In both populations, expression of MHC class II molecules was not or only slightly affected by their interaction with microbial agents (Table 1); only *E. faecalis* organisms and lipoteichoic acid (Fig. 1) slightly increased the percentage of MHC class II-positive cells. On the other hand, incubation with IFN-γ in low concentration resulted in a high proportion of BMMϕ expressing MHC class II molecules (Fig. 1).

Expression of Fcγ receptors

A considerable percentage of rat BMMϕ was able even in resting state to bind rat monomeric IgG2b via high-affinity

Table 1. Effect of bacteria and bacterial agents on the expression of MHC class II molecules by BMMϕ

BMMϕ had been incubated for 24 hr with the following agents	% positive cells (range)
None, resting BMMϕ (control)	12–18
C. parvum (10, 50 μg/ml)	10–16
E. faecalis (5, 10, 50 μg/ml)	18–24*
M. catarrhalis (1, 2·5, 5, 10 μg/ml)	12–20
P. aeruginosa (5, 10, 50 μg/ml)	10–20
LPS *E. coli* (1–100 ng/ml)	15–20
LTA *E. faecalis* (1–10 μg/ml)	18–22*
PGMC (1–10 μg/ml)	10–16
IFN-γ (1 U/ml; positive control)	91–98**

Values represent the range from three to five experiments.

Values are statistically significantly different from resting BMMϕ control: * $P < 0.01$; ** $P < 0.001$; Mann-Whitney *U*-test.

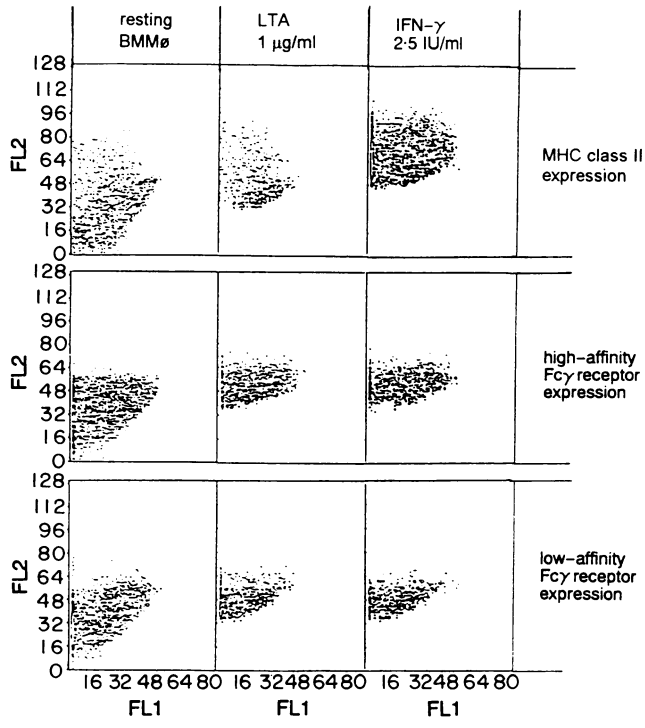

Figure 1. Flow cytometric analysis of the changes induced in resting rat BMMϕ in the expression of MHC class II molecules and high- and low-affinity Fcγ receptors by lipoteichoic acid (1 μg/ml) or IFN-γ (2·5 U/ml).

FcγR. This capacity was further enhanced by the microbial agents, in particular LPS and LTA, as well as by IFN-γ (Figs 1 and 2). In contrast, only a minor portion of resting BMMϕ was able to bind human IgG via low-affinity FcγR. This capability was considerably amplified by various bacterial agents, especially by *E. faecalis* and *M. catarrhalis* organisms and by LPS and LTA; on the other hand, *P. aeruginosa* organisms and IFN-γ only had a modest effect on low-affinity FcγR expression (Figs 1 and 2).

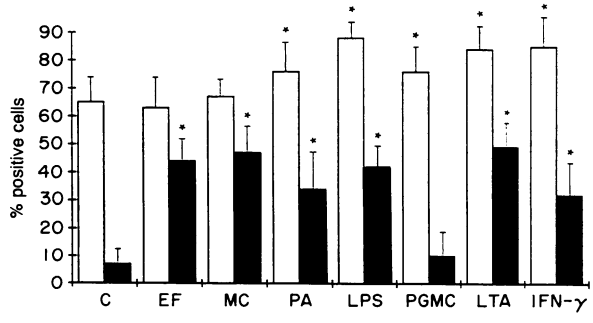

Figure 2. Ability of bacteria and bacterial products to affect binding of immunoglobulins via high (monomeric rat IgG2b, 5 μg/ml; □) and low-affinity Fcγ receptors (human IgG, 100 μg/ml; ■) by rat BMMϕ. Concentrations of agents were as specified in Table 1. Values represent the means ± SD of per cent positive cells from four to six experiments. Values are statistically significantly different from resting BMMϕ controls: * $P < 0.001$; Mann–Whitney *U*-test.

Other macrophage parameters

In parallel to the changes induced in the expression of MHC class II molecules and high- and low-affinity Fcγ receptors, the effects of the microbial agents on some secretory and cellular macrophage activities were also determined. The results of these experiments, summarized in Table 2, show that in keeping with earlier data, Gram-positive organisms triggered primarily the secretion of TNF-α and PGE_2 and tumoricidal activity. Gram-negative bacteria were mostly potent in eliciting the secretion of TNF-α and nitrite and in enhancing expression of low-affinity FcγR but rather poor in inducing tumoricidal activity; at variance, *M. catarrhalis* organisms promoted each of the measured secretory and cellular macrophage activities. PGMC triggered the secretion of TNF-α and NO_2^- and tumoricidal activity and increased binding of IgG via high-affinity FcγR without affecting expression of MHC class II molecules and low-affinity FcγR. LTA and IFN-γ enhanced almost all molecules and low-affinity FcγR. LTA and LTN-γ enhanced almost all of the macrophage parameters measured (Table 2).

DISCUSSION

Mononuclear phagocytes have long been considered major effectors of host defence against microbial infection.[1,3,20] Resting macrophages express only limited functional activity but can cope with infectious agents upon functional activation. Contemporary interest in macrophages began in the 1960s with the evidence provided by Mackaness *et al.* that interaction of sensitized lymphocytes and antigen was accompanied by macrophage activation.[2] Subsequently, IFN-γ was identified as an important macrophage-activating lymphokine, thus establishing a major pathway of paracrine macrophage activation.[21,22] Further observations revealed that macrophages activated for non-specific resistance to infectious agents selectively destroyed neoplastic cells in culture.[23-26] Other evidence, predominantly derived from experiments with purified macrophages and monocytes and in particular BMMϕ, suggested that the mere interaction with micro-organisms might also trigger some macrophage activity.[5,10,14,27] For example, virtually pure populations of resting rat and human BMMϕ were found to be able to respond to bacterial agents with marked amplification of their secretory and cellular activity.[6-9,13] To ensure that the induction of macrophage activity was not due to contamination with other cells and/or their products, various tests were performed in parallel with the following results: (1) all cells were strongly esterase-positive; (2) electron microscopic analyses did not reveal the presence of other cell types; (3) the activities triggered in BMMϕ by bacteria and their products were not affected by anti-IFN-γ while the activities induced by IFN-γ were abolished by anti-IFN-γ; (4) incubation of BMMϕ with viruses known to induce IFN-γ in T cells was not associated with induction of secretory or cellular macrophage activities (R. Keller, R. Keist and P.W. Joller, manuscript in preparation); (5) interaction of BMMϕ with bacteria or their products was not associated with an increase in the expression of MHC class II molecules; in contrast, incubation with even small amounts of IFN-γ (0·1–1 U) resulted in a high proportion of BMMϕ expressing MHC class II molecules[28] (Table 1); and (6) FCM analyses showed that the bone marrow-derived cell population was devoid of other cells.[18,28] These experiments were repeated many times with similar results.

Table 2. Comparative ability of bacteria and bacterial products to induce secretory and cellular activities directly in resting rat BMMϕ

Type of bacteria and bacterial product	Parameters of macrophage functional activity								
	TNF-α ng/ml/10^6 BMMϕ/4 hr	IL-1 pg/ml/10^6 BMMϕ/24 hr	IL-6 ng/ml/10^6 BMMϕ/24 hr	NO_2^- μM/10^6 BMMϕ/24 hr	PGE_2 pg/10^6 BMMϕ/36 hr	MHC class II molecules	High-affinity FcγR	Low-affinity FcγR	Tumor cell lysis (net thymidine release/36 hr)
						% positive cells (24 hr)			
None (resting BMMϕ)	0–0·5	0–0·25	0	0–1·5	0–3	10–18	62–75	5–13	0
Gram-positive organisms (CP, LM, EF, SE, 5–25 μg/ml)	3–8*	0–0·5	5–9*	1–12*	750–1500*	12–25	60–82	4–16	45–81*
Gram-negative organisms									
P. aeruginosa, *E. coli*, 5–25 μg/ml	2–10*	ND	ND	40–86*	ND	10–17	60–84	40–68*	12–35*
M. catarrhalis, 1–2·5 μg/ml	3–10*	1–2·5*	ND	50–115*	ND	12–20	60–73	38–63*	52–84*
LPS 1–100 ng/ml	2–10*	1–2·5*	ND	45–140*	ND	13–20	75–93*	35–43*	0–3
PGMC 1–10 μg/ml	3–7*	ND	ND	45–84*	ND	10–16	68–83*	7–18	30–64*
LTA *E. faecalis* 1–10 μg/ml	2·5–9*	ND	ND	15–130*	ND	18–22*	75–94*	41–52*	20–62*
IFN-γ 0·5–2·5 IU/ml	0·5–1·5*	1·5–2·5*	0·5–2·0*	0–15*	1–9	90–99*	73–92*	21–33*	41–62*

Values represent the range from three to seven experiments.
Values are statistically significantly different from the values obtained for resting BMMϕ; *$P < 0{\cdot}001$; Mann–Whitney U-test.
CP, *C. parvum*; LM, *L. monocytogenes*; EF, *E. faecalis*; SE, *S. epidermidis*.

In addition to triggering a series of secretory (in particular TNF-α and NO_2^-) and cellular activities (reductive capacity, TNF-α-independent tumoricidal activity; Table 2), interaction of microbial agents and BMMϕ was also accompanied by a modulation of the expression of some cell-surface molecules. While expression of MHC class II molecules was only slightly affected, the binding of rat monomeric IgG2b via high-affinity FcγR[18,29] and human IgG via low-affinity FcγR was markedly increased by a series of microbial agents (Table 2). This increase in the expression of Fcγ receptors may considerably amplify the functional capabilities of macrophages. Actually, many of the essential roles of macrophages are mediated via their Fcγ receptors.[30-32]

From comparison of these and earlier results,[6-9,11,12] it appears on the whole, that: (1) each bacterial agent reproducibly triggers in BMMϕ its characteristic response; (2) induction of the secretion of TNF-α, IL-1, and NO/NO_2^-, and expression of MHC class II molecules, high- and low-affinity Fcγ receptors and the generation of TNF-α-independent tumoricidal activity by macrophages are not closely related processes. The data moreover show that apart from intact bacteria and LPS/lipid A, derivatives from Gram-positive organisms, such as peptidoglycan and lipoteichoic acid, in concentrations readily achieved during infection have the potential to enhance various secretory and cellular activities of macrophages.

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