Functional heterogeneity in liver and lung macrophages

Debra L. Laskin,* Barry Weinberger,† and Jeffrey D. Laskin†

*Rutgers University and †University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, Piscataway, New Jersey

Abstract: Although initially considered merely "scavenger cells" that participate in immunologic responses only after B and T lymphocytes have performed their biological tasks, more recent evidence suggests that macrophages play a key role in host defense as well as in the maintenance of normal tissue structure and function. For macrophages to perform their biological functions, they must be activated. This involves up-regulation of an array of signaling pathways resulting in altered gene expression and increased biochemical and functional activity. Macrophages have been identified in almost all tissues of the body. However, the basal activity of these cells, as well as their ability to respond to inflammatory mediators, varies considerably with their location. In addition, even within a particular tissue, there is evidence of macrophage heterogeneity. The largest populations of macrophages in the body are located in the liver and lung. Because of the unique attributes of these tissues, hepatic and pulmonary macrophages play essential roles not only in nonspecific host defense but also in the homeostatic responses of these tissues. In this review, the functional and biochemical activities of macrophages localized in the liver and lungs are compared. Evidence suggests that these represent distinct cell populations with unique functions and responsiveness to inflammatory agents. *J. Leukoc. Biol.* 70: 163–170; 2001.

Key Words: *mononuclear phagocytes · Kupffer cells · alveolar macrophages · subpopulations*

INTRODUCTION

Macrophages are derived from bone marrow precursors and blood monocytes. Mature macrophages localize in tissues and constitute the mononuclear-phagocyte or reticuloendothelial system. They are present in connective tissue and around the basement membrane of small blood vessels and are particularly concentrated in the liver (Kupffer cells), alveolar spaces of the lung (alveolar macrophages), and linings of splenic and lymph node medullary sinusoids, where they are strategically localized to filter foreign material. Other examples of macrophages are Langerhan's cells in the skin, mesangial cells in the kidney glomerulus, brain microglia, and osteoclasts in bone. In general, macrophages are characterized morphologically by an enlarged horseshoe-shaped nucleus, significant rough-surfaced endoplasmic reticulum, and large numbers of mitochondria and cytoplasmic vacuoles, although these characteristics vary depending on the tissue origin of the cell. Macrophages are motile cells that typically appear at inflammatory sites within 24–48 h. They are relatively long-lived cells that exhibit continuous secretory activity during inflammatory processes, enabling them to destroy a range of cells, antigens, and pathogens [1, 2]. Macrophages are also highly phagocytic cells, readily engulfing and digesting a variety of substances including viruses, bacteria, effete red blood cells, tissue and cellular debris, and some tumor cells [3]. Despite their origin from a common bone marrow progenitor population [4], macrophages display considerable tissue heterogeneity. Moreover, even within tissues, there appear to be subpopulations of macrophages that exhibit unique characteristics. These findings suggest that the microenvironment of a tissue regulates the phenotype of these cells. This is most clearly evident in macrophages localized in the liver and the lungs, and these macrophages are the focus of this review.

LIVER MACROPHAGES

Macrophages were first identified in the liver histologically in the late nineteenth century by the German pathologist, von Kupffer. These cells, later referred to as Kupffer cells, are the most abundant mononuclear phagocytes in the body. They are predominantly localized in the lumen of hepatic sinusoids and are anchored to the endothelium by long cytoplasmic processes [5]. The major function of Kupffer cells is to clear particulate and foreign materials from the portal circulation, primarily through the process of phagocytosis. Kupffer cells possess both Fc and C3 receptors and are known to phagocytize a wide variety of both opsonized and nonopsonized particles [6]. Kupffer cells play a central role in the uptake and detoxification of endotoxin from the portal circulation [7]. Like other mononuclear phagocytes, they have the capacity to act as antigen-presenting cells for the induction of T-lymphocyte responses [8]. When activated by antigens or inflammatory stimuli, Kupffer cells release superoxide anions, hydrogen peroxide, nitric oxide, hydrolytic enzymes, and eicosanoids, each of which can aid in antigen destruction [9–11]. Kupffer

Correspondence: Dr. Debra Laskin, Rutgers University, Department of Pharmacology and Toxicology, 160 Frelinghuysen Rd., Piscataway, New Jersey. E-mail: laskin@eohsi.rutgers.edu

Received November 14, 2000; revised March 31, 2001; accepted April 3, 2001.

cells also release a number of different immunoregulatory and inflammatory cytokines, including interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, platelet-activating factor, transforming growth factor-β and interferon (IFN)-γ [9–11].

Although the liver tissue is uniform at the level of histology, it is heterogeneous with respect to morphometry and histochemistry. This heterogeneity appears to be related to the blood supply. Thus cells located in the upstream or periportal regions of the liver lobule differ from those in the downstream or centrilobular (perivenous) regions in several key enzymes, receptors, and subcellular structures and therefore have different functional capacities [12, 13]. Kupffer cells have been reported to be about twofold more abundant in periportal than centrilobular regions of the liver lobule [13, 14]. Moreover, in situ experiments have demonstrated that Kupffer cells in periportal regions are larger, possess greater lysosomal enzyme activities, and are more phagocytic than cells in centrilobular regions but generate less superoxide anion [5, 14, 15]. These data suggest that Kupffer cell functional heterogeneity and size are related to the location of these cells within the liver acinus [14]. Subpopulations of Kupffer cells that differ in size have also been isolated from the livers of rodents and characterized. Whereas the majority of Kupffer cells of all sizes display an endogenous peroxidase pattern characteristic of resident tissue macrophages and show positive staining for macrophage markers such as nonspecific esterase (NSE), ED1, and ED2, heterogeneity in intensity of staining has been observed [16]. In general, the intensity of staining for these markers decreases with decreasing cell size, suggesting that these cells display a more immature phenotype [14]. Phenotypic heterogeneity of human liver macrophages has also been observed histologically, using monoclonal antibodies that recognize the macrophage antigens CD68 and 25-F9. Whereas most macrophages in normal human liver are positive for CD68, fewer mature macrophages express the macrophage differentiation antigen 25-F9 [17, 18]. Moreover, although some cells are doubly positive for these antigens, others are only CD68 positive. Quantitative analysis has confirmed these differences, suggesting that liver macrophage maturation is heterogeneous.

Functional heterogeneity has also been described in macrophages of different sizes isolated from rat livers. Thus large macrophages are more phagocytic and generate increased quantities of lysosomal enzymes, TNF-α, IL-1, and prostaglandin E (PGE), when compared with small liver macrophages [5, 13, 14, 19–25]. In contrast, the smaller macrophages express greater quantities of Ia antigen, release more nitric oxide and superoxide anion, and exhibit increased cytotoxic activity towards tumor cells [14, 15, 19, 25–28]. These cells also appear to be more susceptible to activation [20, 23, 29]. These observations suggest that there is a relationship between Kupffer cell functionality, maturation, and size. The findings that large liver macrophages located in periportal regions appear to provide more scavenger functions and are less active in inflammatory reactions may in part explain the relative immunological tolerance of the liver for immunogens entering from the portal vein [19]. **Figure 1** is a schematic summarizing the relationship between size, maturation, function, and location of macrophages in the liver.

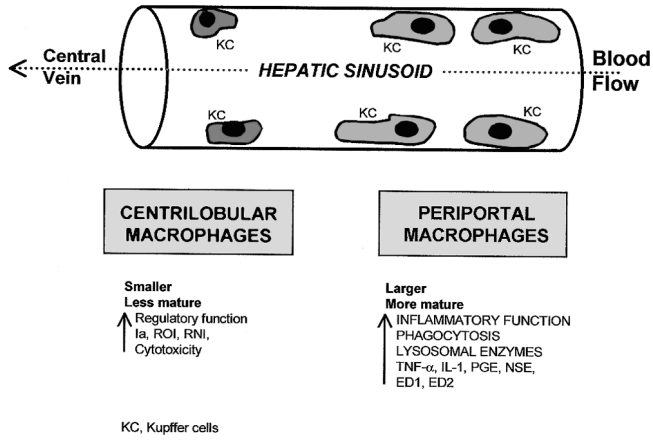

Fig. 1. Schematic diagram illustrating liver macrophage heterogeneity. Phenotypic and functional characteristics of liver macrophages (Kupffer cells) are related to their location within the hepatic sinusoid.

LUNG MACROPHAGES

Like Kupffer cells in the liver, pulmonary macrophages play an important role in nonspecific host defense, as well as in specific immune responses in the lung. This is mediated through their phagocytic, microbicidal, and secretory functions [30]. At least two different subpopulations of macrophages, alveolar macrophages and interstitial macrophages, are localized in distinct anatomical compartments in the lung, including the air spaces and lung connective tissue, respectively [31, 32]. Alveolar macrophages reside within the alveolus and are often seen protruding from the alveolar epithelial walls into the lumen of the lungs. They occupy a relatively unique position within the body because they are exposed directly to a relatively hyperoxic environment and are in intimate contact with both air- and blood-borne materials. Alveolar macrophages are strategically located to function as a primary defense of the lung against inhaled particulate matter, microorganisms, and environmental toxins [30, 33, 34]. Damage to these cells is an important factor in increased host susceptibility to airborne bacterial infection and toxicants [31]. Interstitial macrophages are also quite prominent in the lung, constituting approximately 40% of the total macrophages in tissue [35]. Morphometric studies show that the number of macrophages within the interstitium of normal lung approximates or exceeds the number of alveolar macrophages [30, 32]. Moreover, because interstitial macrophages are in direct contact with matrix and other pulmonary connective-tissue components, the release of mediators or enzymes by these cells may have greater biological and/or pathological effects than those released by macrophages in the alveolar compartment.

In normal lung tissue, alveolar macrophages are considered the end stage of development of blood monocytes. A number of studies have suggested that interstitial macrophages are actually an intermediary stage in the maturation of alveolar macrophages [36, 37]. Morphologic studies have shown that alveolar macrophages are large, mature cells, with an increased cytoplasm/nucleus ratio which resembles other tissue macrophages, whereas interstitial macrophages are smaller, more

uniform in size, have blunt pseudopodia, contain few intracytoplasmic lamellar inclusions or lysosomes, and in general more closely resemble peripheral blood monocytes [38–44]. Based on these observations, it has been suggested that the pulmonary interstitium provides an environment for late-stage maturation or preconditioning of blood monocytes prior to their entrance into the air space [36]. Nevertheless, there is considerable evidence to support the concept that alveolar and interstitial macrophages represent distinct cell populations with unique functional attributes and that each population has the capacity to contribute to pulmonary inflammatory and immune responses [45]. Thus, although alveolar macrophages exhibit greater functional activity related to inflammation and antimicrobial defense including increased chemotaxis, phagocytosis, cytotoxicity, and release of reactive oxygen and nitrogen intermediates, PGE, TNF-α, and IFN, interstitial macrophages express greater quantities of C3 receptor and intercellular adhesion molecule 1, are more active in secreting IL-1 and IL-6 and exhibit greater Ia antigen expression along with a stronger accessory function [36, 40, 45–56]. These capabilities demonstrate that interstitial macrophages display pronounced immunoregulatory capacity and suggest that they are more involved in specific immune responses. Interstitial macrophages have also been reported to exhibit a significantly greater proliferative capacity when compared with alveolar macrophages [40], and this capacity is thought to play a role in maintaining the lung macrophage pool under homeostatic and pathologic conditions [57]. **Figure 2** summarizes the differences between alveolar and interstitial macrophages.

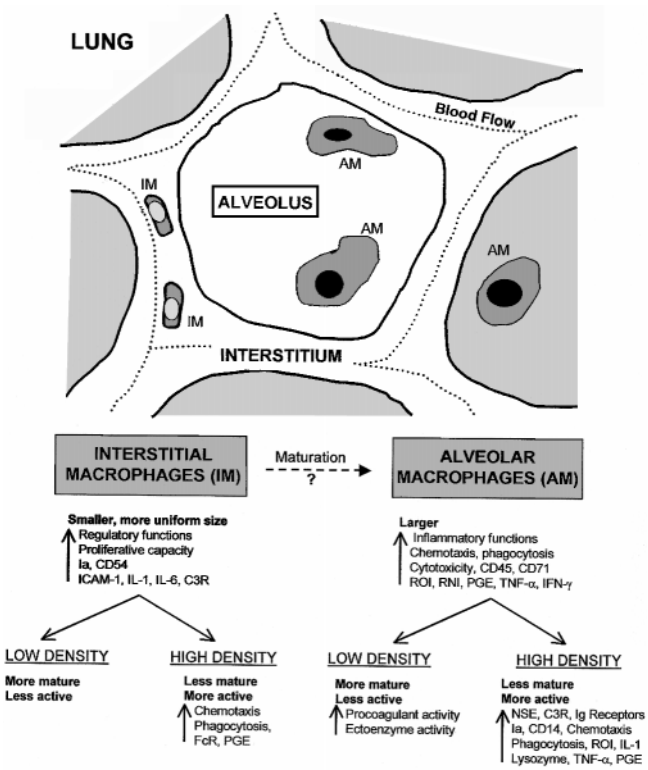

Fig. 2. Schematic diagram illustrating lung macrophage heterogeneity. Phenotypic and functional characteristics of lung macrophages are related to their location within the alveolus or interstitium.

Alveolar macrophages are the best studied of the lung macrophages, in part because of their ease of isolation by bronchoalveolar lavage. A number of studies have demonstrated that these cells are not homogeneous and can be separated into subpopulations with distinct morphologic and functional properties on the basis of adherence to the alveolar walls, flow-cytometric parameters, expression of surface receptors, and density [36, 38, 43, 58–67]. Most studies have focused on cells grouped by density. In general, alveolar macrophages of higher density are smaller and appear less mature when compared with lower-density cells [64]. However, these cells are more functionally active. Thus, high-density alveolar macrophages exhibit increased NSE staining and express greater numbers of C3 and immunoglobulin (Ig) receptors, as well as Ia antigen [54, 58]. They are also more phagocytic and chemotactic, and they generate increased amounts of superoxide anion, lysozyme, IL-1, TNF-α, neutrophil chemotactic factor, and PGE when compared with low-density alveolar macrophages [43, 45, 50, 59, 65–77]. High-density alveolar macrophages also exhibit greater cytotoxicity towards neoplastic cells and more effectively support T-cell proliferation [43, 66, 77, 78]. In contrast, low-density alveolar macrophages, which have been characterized cytochemically as more mature cells [78], display increased procoagulant activity and ectoenzyme function [64, 79–82]. Several investigators have suggested that morphologic and cytochemical maturation is associated with decreasing cell density and increasing cell size [59, 60, 64, 79, 83]; thus, density centrifugation has been proposed as a method to separate alveolar macrophages at different stages of maturation. However, it is also possible that heterogeneity in alveolar macrophages reflects the existence of macrophage subpopulations with functionally distinct roles in airway immunity and is derived from distinct bone marrow precursors [84].

As observed in alveolar macrophages, considerable heterogeneity with respect to size, morphology, function, and antigen expression has also been observed within the interstitial macrophage population [32, 39]. Separation of interstitial macrophages by density has yielded results similar to those reported for alveolar macrophages. Thus, higher-density interstitial macrophages exhibit increased chemotaxis, phagocytosis, and Fc receptor expression, as well as increased prostaglandin biosynthesis, when compared with lower-density fractions [45, 46, 54]. As suggested for alveolar macrophages, these differences may reflect distinct maturational stages of these cells, although differences could also be related to the anatomical location of cells within the tissue.

ARE LIVER AND LUNG MACROPHAGES DIFFERENT?

Although only a few studies have directly compared liver and lung macrophages, these clearly indicate that significant heterogeneity exists between these two populations. Thus, whereas normal Kupffer cells are highly phagocytic, alveolar macrophages produce significantly greater quantities of reactive-oxygen species and reactive-nitrogen intermediates (**Table 1**). This difference most likely reflects the nature of the mediators

TABLE 1. Comparison of Kupffer Cells, Alveolar Macrophages, and Peritoneal Macrophages

	Kupffer cells	Alveolar macrophages	Peritoneal macrophages	References
Antigen Expression				
MHC II	+	++	++++	47, 56, 89
ICAM-1	+++	++	+++	90, 91
β2-Integrin	+++	++++	+++	91–93
CR3	+++	++	++++	6, 34, 49, 54, 92, 94, 95
Fc Receptor	++	++	+++	17, 34, 73, 94, 96, 97
ED1	+++	+++	++++	16, 92, 98–100
ED2	+++	ND	++	99–101
CD68	++++	++++	+++	17, 89, 102–105
25-F9	+++	+++	+++	17, 18, 49, 106–111
CD14	+	++	++	17, 94, 112, 113
Immunohistochemistry				
NSE	++	++++	++	16, 41, 58, 114
Peroxidase	+++	+	+	5, 114
Functional Responses				
Phagocytosis	++++	++	+++	5, 6, 91, 115
Chemotaxis	++++	+++	++++	73, 91, 115
Ag Presentation	++	+	++++	8, 13, 77, 92
Tumor Cytotoxicity	+++	++	+++	47, 56, 73, 108, 116
Bactericidal	+++	+	++++	34, 49, 92, 117, 118
Fungicidal	++++	++++	+	49, 92, 119
Mediator Production				
RNI	++	++++	+++	23, 47, 49, 52, 91, 120
Superoxide anion	+	++++	++++	9, 15, 115, 119, 121
Prostaglandins	++++	+++	+	9, 23, 45, 49, 75, 114, 122
IFN-γ	++	++	+++	123–129
IL-10	+	ND	++++	123, 130–134
TNF-α	++	+++	+++	9–11, 20, 24, 135
IL-1	++	++	++++	47, 72, 74, 135–137
PAF	+++	+++	+++	9–11, 138–140
IL-6	++	++	+++	47, 56, 72, 135
MIP-1	++	++++	++	141–144
MCP-1	++	++	+++	115, 141, 142, 145

Quantitative comparisons of phenotypic and functional characteristics of Kupffer cells, alveolar macrophages and peritoneal macrophages were made using an arbitrary scale of + (minimal) to ++++ (maximal). Relative values were obtained by comparing data presented in the cited references or by contrast with a common standard (e.g., blood monocytes). Most data are derived from rodent models; data from human cells are cited when available. ND, not detected.

and pathogens to which these cells are exposed in vivo, as well as the needs of the tissue. For example, the liver is the major site for clearance of gut-derived endotoxin. Thus, Kupffer cells localized in hepatic sinusoids have developed a highly efficient phagocytic capacity to remove endotoxin from the portal circulation. Moreover, since Kupffer cells are continuously exposed to endotoxin, they are in a chronic state of low-level activation. In this regard, resident Kupffer cells have been reported to constitutively express enzymes such as cyclooxygenase-2 and nitric oxide synthase-2, which mediate the formation of inflammatory prostaglandins and reactive-nitrogen intermediates, respectively [85]. In contrast to interstitial macrophages, alveolar macrophages are primed by exposure to inhaled pathogens and particulates to generate increased quantities of cytotoxic mediators that aid in their destruction. The relative functional capacities and antigenic differences between alveolar macrophages and Kupffer cells are shown in Table 1. For comparison purposes, we also included peritoneal macrophages. Although all three macrophage populations exhibit characteristic features of mononuclear phagocytes, levels of these activities vary considerably, demonstrating clearly that functional, antigenic, and morphologic heterogeneity exists both within and between tissues. A question arises, however, as to whether heterogeneity observed within the macrophage family stems from differences in the stage of differentiation or activation state of a single highly dynamic macrophage/monocyte lineage or the existence of multiple distinct macrophage/monocyte lineages. Whereas animals studies have supported the concept that macrophage subpopulations arise from distinct bone marrow precursors [4], in humans, this remains to be determined [86].

SUMMARY AND CONCLUSIONS

The role of macrophages in host defense and tissue injury is now well established, not just in the liver and lungs but also in almost all other tissues of the body [1, 2, 87, 88]. Although there is considerable evidence demonstrating macrophage heterogeneity between tissues, accumulated data suggest that there is also heterogeneity within each tissue. A question arises about the relationship among cell size, density, and function. Based on the literature surveyed, it appears that smaller, denser macrophages might play a more prominent role in

immune regulation while larger, less dense cells are engaged in anti-inflammatory/antimicrobial activity. Whether this is true for tissues other than the liver and lung remains to be determined. For the future, a focus on understanding the functional importance of macrophage subpopulation heterogeneity will be important in designing new and potentially more effective approaches to limiting inflammation and cytotoxicity.

ACKNOWLEDGMENTS

This work was supported by NIH grants ES04738, ES06897, and GM34310 and by a Career Development Award from the Burroughs Wellcome Fund awarded to D. L. L.

REFERENCES

1. Nathan, C. F. (1987) Secretory products of macrophages. J. Clin. Invest. 79, 319–326.
2. Laskin, D. L., Laskin, J. D. (1997) Phagocytes. In *Comprehensive Toxicology, vol. 5, Toxicology of the Immune System* (D. A. Lawrence, ed.), New York, Pergamon, 97–112.
3. Johnson, R. B. (1988) Current concepts: immunology. Monocytes and macrophages. N. Engl. J. Med. 318, 747–752.
4. Van Furth, R. (1982) Current view on the mononuclear phagocyte system. Immunobiology 161, 178–185.
5. Bouwens, L., Baekeland, M., De Zanger, R., Wisse, E. (1986) Quantitation, tissue distribution and proliferation kinetics of Kupffer cells in normal liver. Hepatology 6, 718–722.
6. Pilaro, A., Laskin, D. L. (1986). Accumulation of activated mononuclear phagocytes in the liver following lipopolysaccharide treatment of rats. J. Leukoc. Biol. 40, 29–41.
7. Mathison, J. C., Ulevitch, R. J. (1979). The clearance, tissue distribution, and cellular localization of intravenously injected lipopolysaccharide in rabbits. J. Immunol. 123, 2133–2143.
8. Rogoff, T. M., Lipsky, P. E. (1980) Antigen presentation by isolated guinea pig Kupffer cells. J. Immunol. 124, 1740–1744.
9. Decker, K. (1990) Biologically active products of stimulated liver macrophages (Kupffer cells). Eur. J. Biochem. 192, 245–261.
10. Laskin, D. L. (1990). Nonparenchymal cells and hepatotoxicity. Semin. Liver Dis. 10, 293–304.
11. Laskin, D. L. (1997) Xenobiotic-induced inflammation and injury in the liver. In *Comprehensive Toxicology, vol. 9, Hepatic and Gastrointestinal Toxicology* (R. S. McCuskey and D. L. Earnst, eds.), New York, Pergamon, 151–164.
12. Jungermann, K., Kietzmann, T. (1996) Zonation of parenchymal and nonparenchymal metabolism in liver. Annu. Rev. Nutr. 16, 179–203.
13. Bouwens, L., De Bleser, P., Vanderkerken, K., Geerts, B., Wisse, E. (1992) Liver cell heterogeneity: functions of non-parenchymal cells. Enzyme 46, 155–168.
14. Sleyster, E. C., Knook, D. L. (1982) Relation between localization and function of rat liver Kupffer cells. Lab. Invest. 47, 484–490.
15. Mochida, S., Ogata, I., Ohta, Y., Yamada, S., Fujiwara, K. (1989) In situ evaluation of the stimulatory state of hepatic macrophages based on their ability to produce superoxide anion in rats. J. Pathol. 158, 67–71.
16. Hoedemakers, R. M., Atmosoerodjo-Briggs, J. E., Morselt, H. W., Daemen, T., Scherphof, G. L., Hardonk, M. J. (1995) Histochemical and electron microscopic characterization of hepatic macrophage subfractions isolated from normal and liposomal muramyl dipeptide treated rats. Liver 15, 113–120.
17. Tomita, M., Yamamoto, K., Kobashi, H., Ohmoto, M., Tsuji, T. (1994) Immunohistochemical phenotyping of liver macrophages in normal and diseased human liver. Hepatology 20, 317–325.
18. Zwadlo, G., Brocker, E. B., von Bassewitz, D. B., Feige, U., Sorg, C. (1985) A monoclonal antibody to a differentiation antigen present on mature human macrophages and absent from monocytes. J. Immunol. 134, 1487–1492.
19. Itoh, Y., Okanoue, T., Morimoto, M., Nagao, Y., Mori, T., Hori, N., Kagawa, K., Kashima, K. (1992) Functional heterogeneity of rat liver macrophages: interleukin-1 secretion and Ia antigen expression in contrast with phagocytic activity. Liver 12, 26–33.
20. ten Hagen, T. L. M., van Vianen, W., Heremans, H., Bakker-Woudenberg, I. A. J. M. (1998) Differential nitric oxide and TNF-α production of murine Kupffer cell subfractions upon priming with IFN-γ and TNF-α. Liver 18, 299–305.
21. Doolittle, M., Bohman, R., Durstenfeld, A., Cascarano, J. (1987) Identification and characterization of liver nonparenchymal cells by flow cytometry. Hepatology 7, 696–703.
22. Derksen, J. T., Morselt, H. W., Scherphof, G. L. (1988) Uptake and processing of immunoglobulin-coated liposomes by subpopulations of rat liver macrophages. Biochim. Biophys. Acta 971, 127–136.
23. Hoedemakers, R. M. J., Morselt, H. W. M., Scherphof, G. L., Daemen, T. (1995) Heterogeneity in secretory responses of rat liver macrophages of different size. Liver 15, 313–319.
24. Hoedemakers, R. M., Morselt, H. W., Scherphof, G. L., Daemen, T. (1994) Secretion pattern of the rat liver macrophage population following activation with liposomal muramyl dipeptide in vivo and in vitro. J. Immunother. Emphasis Tumor Immunol. 15, 265–272.
25. ten Hagen, T. L. M., van Vianen, W., Bakker-Woudenberg, I. A. J. M. (1996) Isolation and characterization of murine Kupffer cells and splenic macrophages. J. Immunol. Methods 193, 81–91.
26. Sugihara, S., Martin, S. R., Hsuing, C. K., Maruiwa, M., Bloch, K. J., Moscicki, R. A., Bhan, A. K. (1990) Monoclonal antibodies to rat Kupffer cells: anti-KCA-1 distinguishes Kupffer cells from other macrophages. Am. J. Pathol. 136, 345–355.
27. Hoedemakers, R. M., Vossebeld, P. J., Daemen, T., Scherphof, G. L. (1993) Functional characteristics of the rat liver macrophage population after a single intravenous injection of liposome-encapsulated muramyl peptides. J. Immunother. 13, 252–260.
28. Daemen, T., Veninga, A., Roerdink, F. H., Scherphof, G. L. (1989) Endocytic and tumoricidal heterogeneity of rat liver macrophage populations. Sel. Cancer Ther. 5, 157–167.
29. Daemen, T., Veninga, A., Regts, J., Scherphof, G. L. (1991) Maintenance of tumoricidal activity and susceptibility to reactivation of subpopulations of rat liver macrophages. J. Immunother. 10, 200–206.
30. Nicod, L. P. (1999) Pulmonary defence mechanisms. Respiration 66, 2–11.
31. Brain, J. D. (1992) Mechanisms, measurement, and significance of lung macrophage function. Environ. Health Perspect. 97, 5–10.
32. Lehnert, B. E. (1992) Pulmonary and thoracic macrophage subpopulations and clearance of particles from the lung. Environ. Health Perspect. 97, 17–46.
33. Zhang, P., Summer, W. R., Bagby, G. J., Nelson, S. (2000) Innate immunity and pulmonary host defense. Immunol. Rev. 173, 39–51.
34. Crystal, R. G. (1991) Alveolar macrophages. In *The Lung: Scientific Foundations* (R. G. Crystal and J. B. West, eds.), New York, Raven Press, 527–535.
35. Crowell, R. E., Heaphy, E., Valdez, Y. E., Mold, C., Lehnert, B. E. (1992) Alveolar and interstitial macrophage populations in the murine lung. Exp. Lung Res. 18, 435–446.
36. Holt, P. G., Warner, L. A., Papadimitriou, J. M. (1982) Alveolar macrophages: functional heterogeneity within macrophage populations from rat lung. Aust. J. Exp. Biol. Med. Sci. 60, 607–618.
37. Blas van Oud Alblas, A., Van Furth, R. (1982) The origin of pulmonary macrophages. Immunobiology 161, 186–192.
38. Lavnikova, N., Prokhorova, S., Helyar, L., Laskin, D. L. (1993) Isolation and partial characterization of subpopulations of alveolar macrophages, granulocytes, and highly enriched interstitial macrophages from rat lung. Am. J. Respir. Cell Mol. Biol. 8, 384–392.
39. Kobzik, L., Godleski, J. J., Barry, B. E., Brain, J. D. (1988). Isolation and antigenic identification of hamster lung interstitial macrophages. Am. Rev. Respir. Dis. 138, 908–914.
40. Johansson, A., Lundborg, M., Skold, C. M., Lundahl, J., Tornling, G., Eklund, A., Camner, P. (1997) Functional, morphological, and phenotypical differences between rat alveolar and interstitial macrophages. Am. J. Respir. Cell Mol. Biol. 16, 582–588.
41. Warren, J. S., Kunkel, R. G., Johnson, K. J., Ward, P. A. (1987) Comparative O_2^- responses of lung macrophages and blood phagocytic cells in the rat: possible relevance to IgA immune complex lung formation. Lab. Invest. 57, 311–320.
42. Sebring, R. J., Lehnert, B. E. (1991) Morphometric comparisons of rat alveolar macrophages, pulmonary interstitial macrophages, and blood monocytes. Exp. Lung Res. 18, 479–496.
43. Zwilling, B. S., Campolito, L. B., Reiches, N. A. (1982) Alveolar macrophage subpopulations identified by differential centrifugation on a discontinuous albumin density gradient. Am. Rev. Respir. Dis. 125, 448–452.
44. Bowden, D. H. (1987) Macrophages, dust and pulmonary disease. Exp. Lung Res. 12, 89–107.

45. Chandler, D. B., Bayles, G., Fuller, W. C. (1988) Prostaglandin synthesis and release by subpopulations of rat interstitial macrophages. Am. Rev. Respir. Dis. 138, 901–907.
46. Chandler, D. B., Brannen, A. L. (1990) Interstitial macrophage subpopulations: responsiveness to chemotactic stimuli. Tissue Cell 22, 427–434.
47. Steinmuller, C., Franke-Ullmann, G., Lohmann-Matthes, M. L., Emmendorffer, A. (2000) Local activation of nonspecific defense against a respiratory model infection by application of interferon-γ: comparison between rat alveolar and interstitial lung macrophages. Am. J. Respir. Cell Mol. Biol. 22, 481–490.
48. Bilyk, N., MacKenzie, J. S., Papadimitriou, J. M., Holt, P. G. (1988) Functional studies on macrophage populations in the airways and the lung wall of SPF mice in the steady-state and during respiratory virus infection. Immunology 65, 417–425.
49. Lohmann-Matthes, M. L., Steinmuller, C., Franke-Ullmann, G. (1994) Pulmonary macrophages. Eur. Respir. J. 7, 1678–1689.
50. Prokhorova, S., Lavnikova, N., Laskin, D. L. (1994) Functional characterization of interstitial macrophages and subpopulations of alveolar macrophages from rat lung. J. Leukoc. Biol. 55, 141–146.
51. Wizemann, T. M., Laskin, D. L. (1994) Enhanced phagocytosis, chemotaxis, and production of reactive oxygen intermediates by interstitial lung macrophages following acute endotoxemia. Am. J. Respir. Cell Mol. Biol. 11, 358–365.
52. Wizemann, T. M., Gardner, C. R., Laskin, J. D., Quinones, S., Durham, S. K., Goller, N. L., Ohnishi, S. T., Laskin, D. L. (1994) Production of nitric oxide and peroxynitrite in the lung during acute endotoxemia. J. Leukoc. Biol. 56, 759–767.
53. Liu, H. W., Anand, A., Bloch, K., Christiani, D., Kradin, R. (1997) Expression of inducible nitric oxide synthase by macrophages in rat lung. Am. J. Respir. Crit. Care Med. 156, 223–228.
54. Chandler, D. B., Kennedy, J. I., Fulmer, J. D. (1986) Studies of membrane receptors, phagocytosis, and morphology of subpopulations of rat lung interstitial macrophages. Am. Rev. Respir. Dis. 134, 542–547.
55. van Oud Alblas, A. B., van Furth, R. (1979) Origin, kinetics, and characteristics of pulmonary macrophages in the normal steady state. J. Exp. Med. 149, 1504–1518.
56. Franke-Ullmann, G., Pfortner, C., Walter, P., Steinmuller, C., Lohmann-Matthes, M. L., Kobzik, L. (1996) Characterization of murine lung interstitial macrophages in comparison with alveolar macrophages in vitro. J. Immunol. 157, 3097–3104.
57. Adamson, I., Bowden, D. (1981) Dose response of the pulmonary macrophagic system to various particulates and its relationship to transepithelial passage of free particles. Exp. Lung Res. 2, 165–175.
58. Dauber, J. H., Holian, A., Rosemiller, M. E., Daniele, R. P. (1983) Separation of bronchoalveolar cells from the guinea pig on continuous density gradients of Percoll: morphology and cytochemical properties of fractionated lung macrophages. J. Reticuloendothel. Soc. 33, 119–126.
59. Chandler, D. B., Fuller, W. C., Jackson, R. M., Fulmer, J. D. (1986) Fractionation of rat alveolar macrophages by isopycnic centrifugation: morphologic, cytochemical, biochemical, and functional properties. J. Leukoc. Biol. 39, 371–383.
60. Holian, A., Dauber, J. H., Diamond, M. S., Daniele, R. P. (1983) Separation of bronchoalveolar cells from the guinea pig on continuous gradients of Percoll: functional properties of fractionated lung macrophages. J. Reticuloenothel. Soc. 33, 157–164.
61. Drath D., Davies, P., Shorey, J., Bibran, N., Simpson, P., Huber, G. (1982) Characterization of postlavage, in situ pulmonary macrophage population. J. Cell Physiol. 111, 97–103.
62. Lehnert, B. E., Valdez, Y. E., Fillak, D. A., Steinkamp, J. A., Stewart, C. C. (1986) Flow cytometric characterization of alveolar macrophages. J. Leukoc. Biol. 39, 285–298.
63. Saunders, G. C., Steinkamp, J. A., Lehnert, B. E. (1987) Flow cytometric analyses of lectin binding to rat alveolar macrophages. Cytometry 8, 602–611.
64. Calhoun, W. J., Salisbury, S. M. (1989) Heterogeneity in cell recovery and superoxide production in buoyant, density-defined subpopulations of human alveolar macrophages from healthy volunteers and sarcoidosis patients. J. Lab. Clin. Med. 114, 682–690.
65. Shellito, J., Kaltreider, H. B. (1985) Heterogeneity of immunologic function among subfractions of normal rat alveolar macrophages. II. Activation as a determinant of functional activity. Am. Rev. Respir. Dis. 131, 678–683.
66. Shellito, J., Kaltreider, H. B. (1984) Heterogeneity of immunologic function among subfractions of normal rat alveolar macrophages. Am. Rev. Respir. Dis. 129, 747–753.
67. Spiteri, M. A., Clarke, S. W., Poulter, L. W. (1992) Isolation of phenotypically and functionally distinct macrophage subpopulations from human bronchoalveolar lavage. Eur. Resp. J. 5, 717–726.
68. Zeidler, R. B., Yarbrow, J. W., Conley, N. S. (1987) Bleomycin increases superoxide production in the most active alveolar macrophage subpopulation. Int. J. Immunopharmacol. 9, 691–696.
69. Brannen, A. L., Chandler, D. B. (1988) Alveolar macrophage subpopulations' responsiveness to chemotactic stimuli. Am. J. Pathol. 132, 161–166.
70. O'Neill, S. J., Hoehn, S. K., Lesperance, E., Klass, D. J. (1984) Functional heterogeneity of isopycnic fractions of rat alveolar macrophages. Infect. Immun. 46, 282–284.
71. Zeidler, R. B., Flynn, J. A., Arnold, J. C., Conley, N. S. (1987) Subpopulation of alveolar macrophages inhibits superoxide anion generation by macrophages. Inflammation 11, 371–379.
72. Haugen, T. S., Nakstad, B., Lyberg, T. (1999) Heterogeneity of procoagulant activity and cytokine release in subpopulations of alveolar macrophages and monocytes. Inflammation 23, 15–23.
73. Oghiso, Y. (1987) Morphologic and functional heterogeneity among rat alveolar macrophage fractions isolated by centrifugation on density gradients. J. Leukoc. Biol. 42, 188–196.
74. Oghiso,Y. (1987) Heterogeneity in immunologic functions of rat alveolar macrophages—their accessory cell function and IL-1 production. Microbiol. Immunol. 31, 247–260.
75. Elias, J. A., Ferro, T. J., Rossman, M. D., Greenberg, J. A., Daniele, R. P., Schreiber, A. D., Freundlich, B. (1987) Differential prostaglandin production by unfractionated and density-fractionated human monocytes and alveolar macrophages. J. Leukoc. Biol. 42, 114–121.
76. Elias, J. A., Schreiber, A. D., Gustilo, K., Chien, P., Rossman, M. D., Lammie, P. J., Daniele, R. P. (1985) Differential interleukin 1 elaboration by unfractionated and density fractionated human alveolar macrophages and blood monocytes: relationship to cell maturity. J. Immunol. 135, 3198–3204.
77. Ferro, T. J., Kern, J. A., Elias, J. A., Kamoun, M., Daniele, R. P., Rossman, M. D. (1987) Alveolar macrophages, blood monocytes, and density-fractionated alveolar macrophages differ in their ability to promote lymphocyte proliferation to mitogen and antigen. Am. Rev. Respir. Dis. 135, 682–687.
78. Murphy, M. A., Herscowitz, H. B. (1984) Heterogeneity among alveolar macrophages in humoral and cell-mediated immune responses: separation of functional subpopulations by density gradient centrifugation on Percoll. J. Leukoc. Biol. 35, 39–54.
79. Rothberger, H., McGee, M. P., Lee, T. K. (1984) Tissue factor activity: a marker of alveolar macrophage maturation in rabbits. Effects of granulomatous pneumonitis. J. Clin. Invest. 73, 1524–1531.
80. Sitrin, R. G., Burbaker, P. G., Shellito, J. E., Kaltreider, H. B. (1986) The distribution of procoagulant and plasminogen activator activities among density fractions of normal rabbit alveolar macrophages. Am. Rev. Respir. Dis. 133, 468–472.
81. Nakstad, B., Boye, N. P., Lyberg, T. (1987) Procoagulant activities in human alveolar macrophages. Eur. J. Respir. Dis. 71, 459–471.
82. Sakai, K., Moriya, A., Ueyama, A., Kishino, Y. (1991) Morphological heterogeneity among fractionated alveolar macrophages in their release of lysosomal enzymes. Cell Mol. Biol. 37, 85–94.
83. Bursukee, I., Goldman, R. (1983) On the origin of macrophage heterogeneity: a hypothesis. J. Reticuloendoth. Soc. 33, 207–220.
84. Gant, V. A., Hamblin, A. S. (1985) Human bronchoalveolar macrophage heterogeneity demonstrated by histochemistry, surface markers and phagocytosis. Clin. Exp. Immunol. 60, 539–545.
85. Ahmad, N., Laskin, D. L. (1999) Coordinate regulation of inducible nitric oxide synthase and cyclooxygenase-2 expression in hepatic macrophages during endotoxemia. Toxicol. Sci., 48:256.
86. Hoffman, I. M., Lopez, D., Husmann, L., Meyer, P. R., Taylor, C. R. (1984) Heterogeneity of macrophage subpopulations in human lymphoid tissue and peripheral blood. Cell Immunol. 88, 61–74.
87. Laskin, D. L., Pendino, K. J. (1995) Macrophages and inflammatory mediators in tissue injury. Annu. Rev. Pharmacol. Toxicol. 35, 655–677.
88. Laskin, D. L., Laskin, J. D. (1996) Macrophages, inflammatory mediators, and lung injury. Methods 10, 61–70.
89. Eischen, A., Duclos, B., Schmitt-Goguel, M., Rouyer, N., Bergerat, J. P., Hummel, M., Oskam, R., Oberling, F. (1994) Human resident peritoneal macrophages: phenotype and biology. Br. J. Haematol. 88, 712–722.
90. Miles, E. A., Wallace, F. A., Calder, P. C. (2000) Dietary fish oil reduces intercellular adhesion molecule 1 and scavenger receptor expression on murine macrophages. Atherosclerosis 152, 43–50.
91. Morio, L. A., Chiu, H., Sprowles, K. A., Laskin, D. L. (2000) Functional heterogeneity of rat hepatic and alveolar macrophages; effects of chronic ethanol administration. J. Leukoc. Biol., 68, 614–620.
92. Gjomarkaj, M., Pace, E., Melis, M., Spatafora, M., Profita, M., Vignola, A. M., Bonsignore, G., Toews, G. B. (1999) Phenotypic and functional characterization of normal rat pleural macrophages in comparison with

autologous peritoneal and alveolar macrophages. Am. J. Respir. Cell Mol. Biol. 20, 135–142.
93. Tamatani, T., Kotani, M., Miyasaka, M. (1991) Characterization of the rat leukocyte integrin, CD11/CD18, by the use of LFA-1 subunit-specific monoclonal antibodies. Eur. J. Immunol. 21, 627–633.
94. Geertsma, M. F., Van Furth, R., Nibbering, P. H. (1997) Monocytes incubated with surfactant: a model for human alveolar macrophages? J. Leukoc. Biol. 62, 485–492.
95. Hinglais, N., Kazatchkine, M. D., Mandet, C., Appay, M. D., Bariety, J. (1989) Human liver Kupffer cells express CR1, CR3, and CR4 complement receptor antigens: an immunohistochemical study. Lab. Invest. 61, 509–514.
96. Hazenbos, W. L. W., Heijnen, I. A. F. M., Meyer, D., Hofhuis, F. M. A., de Lavalette, C. R., Schmidt, R. E., Capel, P. J. A., van de Winkel, J. G. J., Gessner, J. E., van den Berg, T. K., Verbeek, J. S. (1998) Murine IgG1 complexes trigger immune effector functions predominantly via FcγRIII (CD16). J. Immunol. 161, 3026–3032.
97. Walker, W. S. (1976) Functional heterogeneity of macrophages. In *Immunobiology of the macrophage* (D. S. Nelson, ed.), New York, Academic Press, 91–110.
98. Armbrust, T., Ramadori, G. (1996) Functional characterization of two different Kupffer cell populations of normal rat liver. J. Hepatol. 25, 518–528.
99. Farver, C. F., Kobzik, L. (1999) Lung macrophage differentiation antigens in developing fetal and newborn rat lungs: a quantitative flow cytometric analysis with immunohistochemistry. Lung 177, 205–217.
100. Dijkstra, C. D., Dopp, E. A., Joling, P., Kraal, G. (1985) The heterogeneity of mononuclear phagocytes in lymphoid organs: distinct macrophage subpopulations in the rat recognized by monoclonal antibodies ED1, ED2 and ED3. Immunology 54, 589–599.
101. McCloskey, T. W., Todaro, J. A., Laskin, D. L. (1992) Lipopolysaccharide treatment of rats alters antigen expression and oxidative metabolism in hepatic macrophages and endothelial cells. Hepatology 16, 191–203.
102. Kurushima, H., Ramprasad, M., Kondratenko, N., Foster, D. M., Quehenberger, O., Steinberg, D. (2000) Surface expression and rapid internalization of macrosialin (mouse CD68) on elicited mouse peritoneal macrophages. J. Leukoc. Biol. 67, 104–108.
103. Zeibecoglou, K., Ying, S., Meng, Q., Poulter, L. W., Robinson, D. S., Kay, A. B. (2000) Macrophage subpopulations and macrophage-derived cytokines in sputum of atopic and nonatopic asthmatic subjects and atopic and normal control subjects. J. Allergy Clin. Immunol. 106, 697–704.
104. Kubicka, U., Olszewski, W. L., Tarnowski, W., Bielecki, K., Ziolkowska, A., Woerzbicki, Z. (1996) Normal human immune peritoneal cells: subpopulations and functional characteristics. Scand. J. Immunol. 44, 157–163.
105. Pulford, K. A., Rigney, E. M., Micklem, K. J., Jones, M., Stross, W. P., Gatter, K. C., Mason, D. Y. (1989) KP1: a new monoclonal antibody that detects a monocyte/macrophage associated antigen in routinely processed tissue sections. J. Clin. Pathol. 42, 414–421.
106. Rosseau, S., Hammerl, P., Maus, U., Walmrath, H. D., Schutte, H., Grimminger, F., Seeger, W., Lohmeyer, J. (2000) Phenotypic characterization of alveolar monocyte recruitment in acute respiratory distress syndrome. Am. J. Physiol. Lung Cell Mol. Physiol. 279, L25–L35.
107. Wrenger, E., Baumann, C., Behrend, M., Zamore, E., Schindler, R., Brunkhorst, R. (1998) Peritoneal mononuclear cell differentiation and cytokine production in intermittent and continuous automated peritoneal dialysis. Am. J. Kidney Dis. 31, 234–241.
108. Klimp, A. H., Regts, J., Scherphof, G. L., de Vries, E. G. E., Daemen, T. (1999) Effect of peritoneally administered recombinant murine granulocyte-macrophage colony-stimulating factor (rmGM-CSF) on the cytotoxic potential of murine peritoneal cells. Br. J. Cancer 79, 89–94.
109. Yamamoto, K., Ohmoto, M., Matsumoto, S., Nagano, T., Kobashi, H., Okamoto, R., Tsuji, T. (1995) Activated liver macrophages in human liver diseases. J. Gastroenterol. Hepatol. 10, S72–S76.
110. Striz, I., Wang, Y. M., Teschler, H., Sorg, C., Costabel, U. (1993) Phenotypic markers of alveolar macrophage maturation in pulmonary sarcoidosis. Lung 171, 293–303.
111. Striz, I., Wang, Y. M., Svarcova, I., Trnka, L., Sorg, C., Costabel, U. (1993) The phenotype of alveolar macrophages and its correlation with immune cells in bronchoalveolar lavage. Eur. Respir. J. 6, 1287–1294.
112. Lichtman, S. N., Wang, J., Lemasters, J. J. (1998) LPS receptor CD14 participates in release of TNF-α in RAW 264.7 and peritoneal cells but not in Kupffer cells. Am. J. Physiol. 275:G39–G46.
113. Andreesen, R., Brugger, W., Scheibenbogen, C., Kreutz, M., Leser, H. G., Rehm, A., Lohr, G. W. (1990) Surface phenotype analysis of human monocyte to macrophage maturation. J. Leukoc. Biol. 47, 490–497.
114. Friedlander, M. A., Hilbert, C. M., Wu, Y. C., Finegan, C. K., Rich, E. A. (1994) Disparate cytochemical characteristics and production of cytokines and prostaglandin E2 by human mononuclear phagocytes from the blood, lung, and peritoneal cavity. J. Lab. Clin. Med. 123, 574–584.
115. Laskin, D. L., Sirak, A. A., Pilaro, A. M., Laskin, J. D. (1988) Functional and biochemical properties of rat Kupffer cells and peritoneal macrophages. J. Leukoc. Biol. 44, 71–78.
116. Friedman, R. L., Moon, R. J. (1980) Role of Kupffer cells, complement, and specific antibody in the bactericidal activities of perfused livers. Infect. Immun. 29, 152–157.
117. Collins, F. M., Niederbuhl, C. J., Campbell, S. G. (1983) Bactericidal activity of alveolar and peritoneal macrophages exposed in vitro to three strains of *Pasteurella multocida*. Infect. Immun. 39, 779–784.
118. van Dissel, J. T., Stikkelbroeck, J. J. M., van den Barselaar, M. T., Sluiter, W., Leijh, P. C. J., van Furth, R. (1987) Divergent changes in antimicrobial activity after immunologic activation of mouse peritoneal macrophages. J. Immunol. 1439, 1665–1672.
119. Decker, T., Lohmann-Matthes, M. L., Baccarini, M. (1986) Heterogeneous activity of immature and mature cells of the murine monocyte-macrophage lineage derived from different anatomical districts against yeast-phase *Candida albicans*. Infect. Immun. 54, 477–486.
120. Wang, M. J., Jeng, K. C. G., Shih, P. C. (1999) Differential expression of inducible nitric oxide synthase gene by alveolar and peritoneal macrophages in lipopolysaccharide-hyporesponsive C3H/HeJ mice. Immunology 98, 497–503.
121. DiGregorio, K. A., Cilento, E. V., Lantz, R. C. (1991) Heterogeneity in superoxide production as measured by nitro blue tetrazolium from individual PAM. Am. J. Physiol. 260, L464–L470.
122. Wu, J. Z., Ogle, C. K., Ogle, J. D., Alexander, J. W. (1993) A comparison of hepatic, splenic, peritoneal and alveolar macrophages with respect to PGE2, TXB2 production and ADCC function. Prostaglandin Leukot. Essent. Fatty Acids 48, 149–153.
123. Seki, S., Osada, S. I., Ono, S., Aosasa, S., Habu, Y., Nishikage, T., Mochizuki, H., Hiraide, H. (1998) Role of liver NK cells and peritoneal macrophages in γ-interferon and interleukin-10 production in experimental bacterial peritonitis in mice. Infect. Immun. 66, 5286–5294.
124. Condos, R., Rom, W. N., Liu, Y. M., Schluger, N. W. (1998) Local immune responses correlate with presentation and outcome in tuberculosis. Am. J. Resp. Crit. Care Med. 157, 729–735.
125. Wang, J., Wakeham, J., Harkness, R., Xing, Z. (1999) Macrophages are a significant source of type 1 cytokines during mycobacterial infection. J. Clin. Invest. 103, 1023–1029.
126. Schindler, H., Lutz, M. B., Rollinghoff, M., Bogdan, C. (2001) The production of IFN-γ by IL-12/IL-18-activated macrophages requires STAT4 signaling and is inhibited by IL-4. J. Immunol. 166, 3075–3082.
127. Fultz, M. J., Barber, S. A., Dieffenbach, C. W., Vogel, S. N. (1993) Induction of IFN-γ in macrophages by lipopolysaccharide. Int. Immunol. 5, 1383–1392.
128. Fenton, M. J., Vermeulen, M. W., Kim, S., Burdick, M., Strieter, R. M., Kornfeld, H. (1997) Induction of gamma interferon production in human alveolar macrophages by *Mycobacterium tuberculosis*. Infect. Immun. 65, 5149–5156.
129. Di Marzio, P., Puddu, P., Conti, L., Belardelli, F., Gessani, S. (1994) Interferon γ upregulates its own gene expression in mouse peritoneal macrophages. J. Exp. Med. 179, 1731–1736.
130. Le Moine, O., Marchant, A., Durand, F., Ickx, B., Pradier, O., Belghiti, J., Abramowicz, D., Gelin, M., Goldman, M., Deviere, J. (1994) Systemic release of interleukin-10 during orthotopic liver transplantation. Hepatology 20, 889–892.
131. Williams, J. A., Pontzer, C. H., Shacter, E. (2000) Regulation of macrophage interleukin-6 (IL-6) and IL-10 expression by prostaglandin E_2: the role of p38 mitogen-activated protein kinase. J. Int. Cytokine Res. 20, 291–298.
132. Berkman, N., John, M., Roesems, G., Jose, P. J., Barnes, P. J., Chung, K. F. (1995) Inhibition of macrophage inflammatory protein-1α expression by IL-10. J. Immunol. 155, 4412–4418.
133. Thomassen, M. J., Divis, L. T., Fisher, C. J. (1996) Regulation of human alveolar macrophage inflammatory cytokine production by interleukin-10. Clin. Immunol. Immunopathol. 80, 321–324.
134. Salez, L., Singer, M., Balloy, V., Creminon, C., Chignard, M. (2000) Lack of IL-10 synthesis by murine alveolar macrophages upon lipopolysaccharide exposure: comparison with peritoneal macrophages. J. Leukoc. Biol. 67, 545–552.
135. Ogle, C. K., Wu, J. Z., Mao, X., Szczur, K., Alexander, J. W., Ogle, J. D. (1994) Heterogeneity of Kupffer cells and splenic, alveolar, and peritoneal macrophages for the production of TNF, IL-1, and IL-6. Inflammation 18, 511–523.

136. Ge, Y., Ezzell, R. M., Clark, B. D., Loiselle, P. M., Amato, S. F., Warren, H. S. (1997) Relationship of tissue and cellular interleukin-1 and lipopolysaccharide after endotoxemia and bacteremia. J. Infect. Dis. 176, 1313–1321.
137. Yassad, A., Husson, A., Bion, A., Lavoinne, A. (2000) Synthesis of interleukin-1β and interleukin-6 by stimulated rat peritoneal macrophages: modulation by glutamine. Cytokine 12, 1288–1291.
138. Pellon, M. I., Fernandez-Gallardo, S., Gijon, M. A., Garcia, M. C., Liu, F. T., Sanchez Crespo, M. (1993) Effect of immunological stimulation on the production of platelet-activating factor by rat peritoneal cells: its relevance to anaphylactic reactions. Immunopharmacology 26, 73–82.
139. Hursh, D. M., Hsueh, W., Kartha, R. K. (1990) PAF metabolism in resident and activated alveolar macrophages: role of protein kinase C. Cell Immunol. 130, 429–436.
140. Mustafa, S. B., Gandhi, C. R., Harvey, S. A. K., Olson, M. S. (1995) Endothelin stimulates platelet-activating factor synthesis by cultured rat Kupffer cells. Hepatology 21, 545–553.
141. Kopydlowski, K. M., Salkowski, C. A., Cody, M. J., van Rooijen, N., Major, J., Hamilton, T. A., Vogel, S. N. (1999) Regulation of macrophage chemokine expression by lipopolysaccharide in vitro and in vivo. J. Immunol. 163, 1537–1544.
142. Katoh, S., Matsumoto, N., Fukushima, K., Mukae, H., Kadota, J., Kohno, S., Matsukura, S. (2000) Elevated chemokine levels in bronchoalveolar lavage fluid of patients with eosinophilic pneumonia. J. Allergy Clin. Immunol. 106, 730–736.
143. Barsig, J., Flesch, I. E., Kaufmann, S. H. (1998) Macrophages and hepatocytic cells as chemokine producers in murine listeriosis. Immunobiology 199, 87–104.
144. VanOtteren, G. M., Standiford, T. J., Kunkel, S. L., Danforth, J. M., Burdick, M. D., Abruzzo, L. V., Strieter, R. M. (1994) Expression and regulation of macrophage inflammatory protein-1α by murine alveolar and peritoneal macrophages. Am. J. Respir. Cell Mol. Biol. 10, 8–14.
145. Marra, F., DeFranco, R., Grappone, C., Milani, S., Pastacaldi, S., Pinzani, M., Romanelli, R. G., Laffi, G., Gentilini, P. (1998) Increased expression of monocyte chemotactic protein-1 during active hepatic fibrinogenesis: correlation with monocyte infiltration. Am. J. Pathol. 152, 423–430.