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Review

Heterogeneity of Peritoneal Macrophages

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INTRODUCTION

Macrophages are morphologically and functionally diverse. It is clear that macrophages display a great variety of functions which are either constitutive or inducible by activation (van Furth, 1980). An important function is endocytosis, not only as scavengers of microorganisms, effete cells and cell debris, but also as accessory cells in immune responses. Macrophages are also active as secretory cells. They produce a number of biological active substances such as enzymes, interferon, prostaglandins, complement components and lymphocyte-stimulating factors (Nelson, 1976). Macrophages can be powerful effectors of immunity to experimental tumors. It is the purpose here to survey briefly the nature and origin of heterogeneity among the peritoneal macrophages and to consider the role of macrophage subpopulations as effector cells in antimicrobial immunity.

MACROPHAGES AT DIFFERENT SITES

Macrophages display numerous regional differences in morphology, physiology and function. the differences between alveolar and peritoneal macrophages have been recognized and extensively studied (Walker, 1976, Lee, 1980). These two most commonly studied populations of macrophages are known to differ functionally in many ways (Hopper, 1979, Walker, 1983). Alveolar macrophages rely almost entirely on oxidative metabolism, whereas peritoneal macrophages utilize mainly anaerobic metabolism. This difference in energy metabolism appears to be due to local adaptation since the levels of enzymes involved in 0_2 metabolism can be modulated, depending upon whether the macrophages are maintained in an aerobic or anaerobic environment (Simmon *et al.*, 1977, Bar-Eli *et al.*, 1980). Thus the differences between the alveolar and peritoneal macrophages may represent adaptions to the local environment.

HETEROGENEITY IN PERITONEAL MACROPHAGES

Peritoneal exudates are commonly used for the study of various properties of macrophages. To elicit these exudates, a variety of inflammatory agents, polysaccharides and glucan have been used. Intraperitoneal injection of these substances leads to the migration and intraperitoneal accumulation of blood monocytes which differentiate into mature macrophages. The nature and behavior of the macrophages in peritoneal exudates appears to be dependent on the stimulus used (Daems, 1980). Macrophages from the unstimulated peritoneal cavity show heterogeneity according to their size and density (Morahan *et al.* 1982). However, with respect to morphology and cytochemical localization of peroxidatic activity, they form a relatively homogenous population (Daems, 1980). Macrophages from the stimulated peritoneal cavity display an enhancement of the above-mentioned heterogeneity, resulting in the

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expression of a number of characteristics which are obviously distinct from those observed in macrophages from the unstimulated peritoneal cavity (Daems, 1980, Morahan *et al.*, 1982).

Macrophage heterogeneity has been investigated on the basis of the ultrastructural localization of peroxidatic (PO) activity. The unstimulated peritoneal cavity showed predominantly resident macrophages with PO activity in the nuclear envelope (NE) and rough endoplasmic reticulum (RER). A small percentage of exudate macrophages (with PO activity in granules only) could be seen in the unstimulated peritoneal cavity.

After stimulation of the cavity, four subpopulations of macrophages were distinguished. Resident macrophages (with PO activity in NE and RER), exudate macrophages (with PO activity in granules only), PO-negative macrophages, and under specific circumstances, exudate resident macrophages (with PO activity in NE, RER and granules) were observed (Ginsel *et al.*, 1983, de Water, 1983). The latter two subpopulations of macrophages have been postulated to be transitional forms between bone marrow-derived monocytes and resident macrophages (Beelen *et al.* 1978, van der Meer *et al.* , 1979, Daems and de Bakker, 1982). PO-negative macrophages, however, give rise to problems in classification. The absence of reaction products could be due to the absence of enzyme activity or to enzyme activity that is not demonstrable under the cytochemical conditions used, but it is difficult to decide which is the case. It is known that monocytes can lose their peroxidase positive granules and ultimately become PO-negative macrophages (Daems, 1980). A second problem in the classification of cells by PO cytochemistry is caused by the occurrence of cells with PO-positive RER and NE as well as PO positive granules (Beelen *et al.*, 1978, Bodel *et al.*, 1977, Daems and van der Rhee, 1980), called exudate-resident macrophages. According to Beelen, these cells represent transitional forms between monocytes or monocyte-derived macrophages and resident macrophages. The nature of this cell type remains uncertain.

MACROPHAGE SUBPOPULATIONS IN THE PERITONEAL CAVITY AND THEIR ANTIBACTERIAL PROPERTIES

It is not clear, however, whether these macrophage subpopulations reflect functional heterogeneity. To explore this problem, in our laboratory the macrophage subpopulations in the peritoneal cavity of Listeria monocytogenes infected mice and the listericidal activity of these macrophage subpopulations have been examined (Ogawa, 1978, 1983). L. monocytogenes is a facultative intracellular bacterial parasite which replicates within the macrophages of infected hosts. Acquired cellular resistance of L. monocytogenes requires sensitization of specific T-lymphocytes and subsequent macrophage activation (Mackaness, 1969, Sperling *et al.*, 1984).

There was a strong increase in the number of PO-positive macrophages (=exudate macrophages) in the early phase of infection. The number of PO-negative macrophages gradually increased. PO-positive macrophages consistently exhibited a significantly greater and more rapid bactericidal capacity than those of PO-negative macrophages and resident macrophages. They had a greater bactericidal capacity than PO-negative macrophages and resident macrophages. The greater bactericidal activity was apparent in PO-positive macrophages which could offer more scope for such a role, following possible fusion between lysosomal peroxidase and bacteria containing phagosomes (unpublished observation).

CONCLUSIONS

When an inflammation is induced in the peritoneal cavity, there is an influx of bone marrow derived monocytes from blood into the peritoneal cavity, these monocytes differentiate into mature macrophages (PO-positive macrophages and PO-negative macrophages).

Killing activity of L. monocytogenes was displayed by PO-positive macrophages, i.e. newly appearing macrophages. In resident macrophages and PO-negative macrophages, i.e. old macrophages, most bacteria were intact. These observations indicated that the host's defence was induced by prompt influx and purposeful development of monocytes in the center of the infection.

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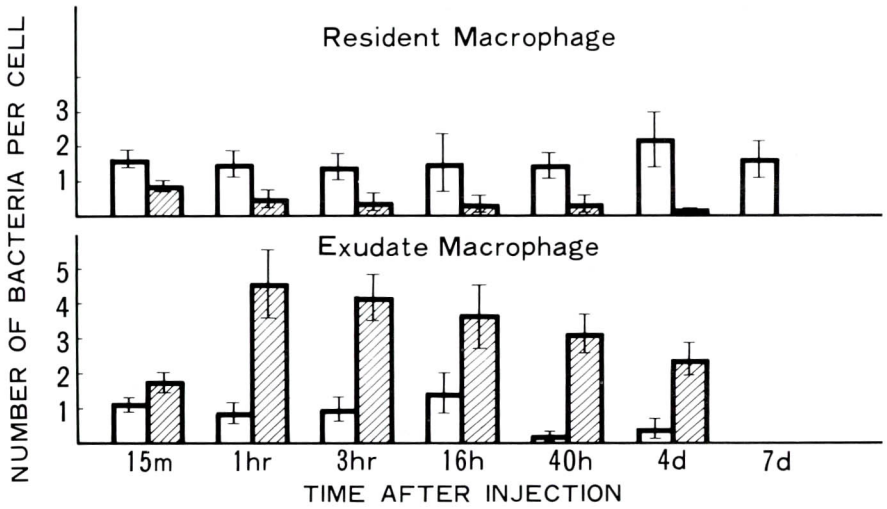

Fig. 1 Number of intact (□) and damaged (▨) bacteria ingested by macrophages (assessed by electron microscopy). Vertical bars give s.e.

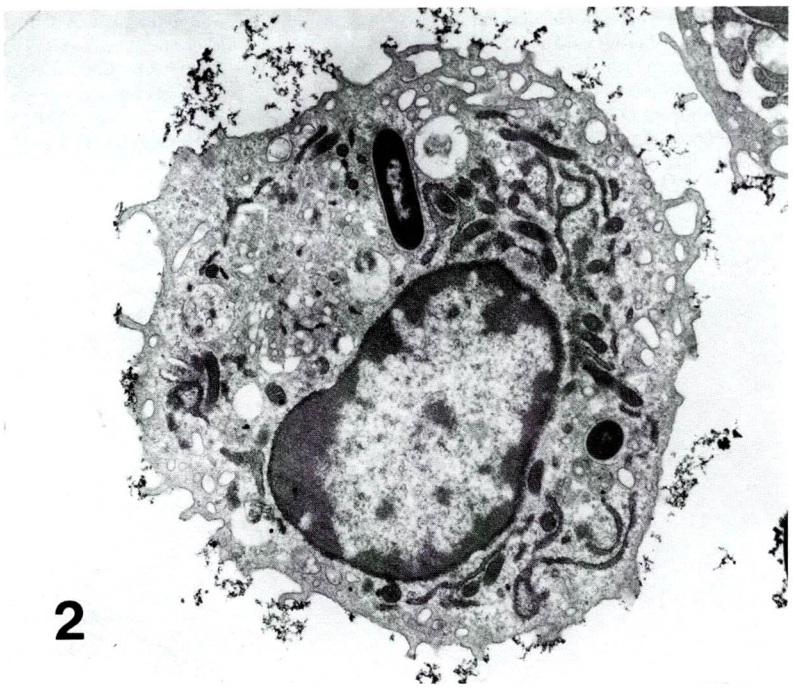

Fig. 2 Resident macrophage. Note peroxidatic activity in rough endoplasmic reticulum and nuclear envelope. Two intact bacteria are present. × 12,000

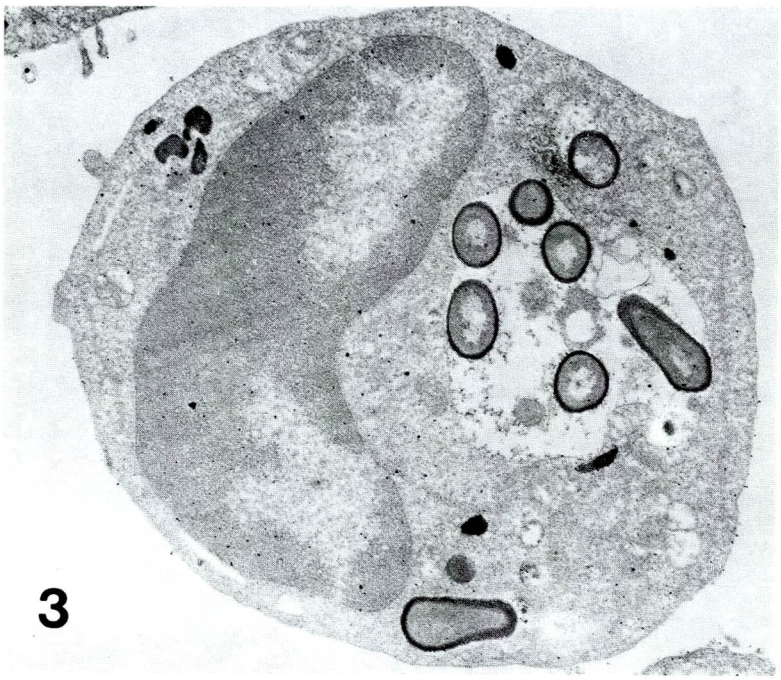

Fig. 3 Exudate macrophage (Po-positive acrophage). Bacteria are completly surrounded by peroxidase and are damaged. ×20,000.

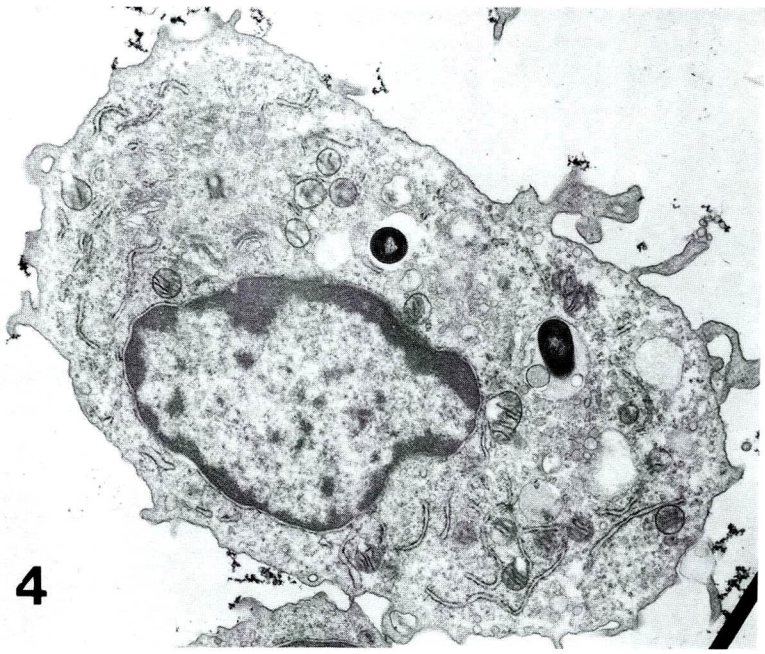

Fig. 4 PO-negative macrophage. Bacteria are morphologically intact. × 14,000.