Pathology of Granulomas

Editor

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PATHOLOGY OF GRANULOMAS

Preface

The term *granuloma* applies to an ill-defined group of lesions and diseases frequently observed in general medical practice. Their unifying feature is not their etiology, because a host of unrelated endogenous and exogenous factors can produce granulomas, but rather their morphologic appearance, which is similar in most cases regardless of the causative agents. In fact, the granulomatous lesion represents a particular tissue reaction triggered by particulate or insoluble agents and centered around the activity of monocytes. The numerous studies devoted in the past decade to these remarkable cells have resulted in the modern concepts of the mononuclear phagocyte system and have shed new light on the pathology of granulomas.

The opening chapter in this volume on the biology of granulomas, written by one of the major contributors to our present knowledge of this field, describes the mechanisms of the granulomatous reaction and reveals the common features in this broad spectrum of lesions. The following 16 chapters review granulomatous lesions and diseases occurring in various tissue and organ systems. Granulomas of the skin, heart, vessels, bone marrow, lymph nodes, spleen, upper and lower respiratory tracts, gastrointestinal tract, liver, kidneys, endocrine glands, female and male genital systems, bones, and central nervous system are described separately and richly illustrated. All chapters include comprehensive, up-to-date lists of references to the medical literature. More important, the authors of all chapters are eminent specialists, highly regarded and well recognized for their many contributions to their areas of expertise.

In the daily practice of pathology, granulomas are commonly encountered and diagnosed with relative ease. The etiologic diagnosis of granulomas, however, that is essential for the application of correct treatments, is often a difficult task owing to the large number and great diversity of the causative agents. To determine the etiology of granulomas often requires the collaborative efforts of pathologists, microbiologists, radiologists, and clinicians of different specialties. In view of the practical importance of granulomas and the difficulties encountered in their diagnosis, it seems curious that appropriate books are not available. Although a large amount of information can be found, widely scattered throughout the medical literature, definitive textbooks, atlases, or manuals on granulomas are not available. The present volume is intended to remedy this deficiency. The approach has been to cover all major organ systems and to reveal the particular aspects of granulomas in each location. A certain degree of overlap between various chapters, unavoidable in a multiauthored book, is amply compensated by the opportunity to present in one volume the experiences and opinions of so many experts. *Pathology of Granulomas* can be used as an authoritative textbook, a comprehensive source of references, a well illustrated atlas, and a practical diagnostic manual. I hope that readers will find it useful.

Harry L. Ioachim, M.D.

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The Biology of the Granuloma

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The granuloma is the hallmark of numerous human diseases of considerable significance and frequently poses a diagnostic problem to the surgical pathologist (for reviews, see refs. 1–4). Over the past decade, understanding of the fundamental biology of mononuclear phagocytes, the principal cellular constituents of granulomas, has increased dramatically (for general reviews, see refs. 5,6,104–111). This chapter reviews these advances and considers their impact on our understanding of the biology of granulomatous inflammation. Much of our current understanding of mononuclear phagocytes has come from their study in small rodents, particularly from studies of mononuclear phagocytes obtained from the peritoneal cavity of mice. Most of the studies described herein refer to such experimental systems, unless specific reference to human mononuclear phagocytes is made.

The definition of a granuloma is protean (1). In this laboratory, we have found the following definition to be useful: A granuloma is a compact (organized) collection of mature mononuclear phagocytes (macrophages and/or epithelioid cells), which may or may not be accompanied by accessory features such as necrosis or the infiltration of other inflammatory leukocytes (1). This definition offers the advantage of distinguishing a granuloma on histologic grounds alone, without the necessity of knowing its history or kinetics or the immune state of the host.

THE MONONUCLEAR PHAGOCYTE SYSTEM

Concept, Elements, Kinetics, and Identification

The mononuclear phagocytes of the host share a common origin, morphology and function and have been grouped as a system of cells known as the mononuclear phagocyte system (7). Included are monocytes, tissue macrophages, inflammatory macrophages, and the specialized progeny of these cells such as epithelioid cells (Table 1).

Mononuclear phagocytes arise in the marrow from a pool of rapidly dividing precursors (8). Monoblasts, arising from a stem cell shared with granular leukocytes (8), develop into promonocytes; these in turn develop into monocytes which are released into the blood (8). Monocytes circulate within the blood briefly (estimated half-life of 22 hr in mice) and immigrate at random into the tissues (8). A large body of evidence, accumulated in a variety of ways, indicates that most resident tissue macrophages arise from monocytes (9). The view that certain resident tissue macrophages may also arise from local proliferation has been presented (10).

Mononuclear phagocytes are typified by characteristic nuclei, a shared cytoplasmic morphology, a common histochemistry, certain surface markers, and characteristic functions (Table 2). Particularly distinguishable characteristics of this series of cells include the presence of a single nucleus and the ability to phagocytose foreign materials via the F_c receptor (11). Lym-

TABLE 1. *Elements of the mononuclear phagocyte system*[a]

Location	Cell
Marrow	Monoblast
	Promonocyte
Blood	Monocyte
Tissues	Resident macrophages including
	Tissue macrophages or histiocytes
	Kupffer cells
	Alveolar macrophages
	Nodal macrophages
	Splenic macrophages
	Microglia
	Osteoblasts
Inflammatory sites	Inflammatory macrophages
	Epithelioid cells
	Giant cells

[a]From van Furth et al., ref. 7.

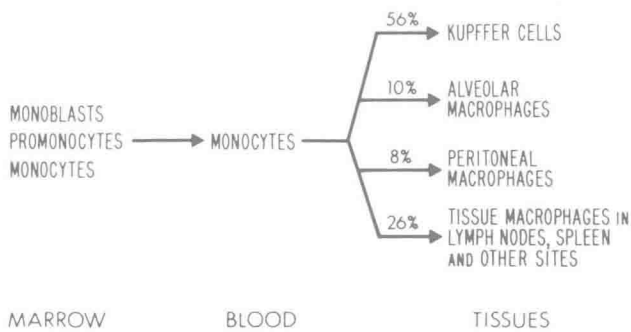

FIG. 1. The flow pattern of the mononuclear phagocyte system. (Adapted from ref. 8.)

TABLE 2. *Characteristics of mononuclear phagocytes*[a]

Morphology
Single, round to oval nucleus
Pinocytotic vesicles
Lysosomes
Ruffling of surface membrane
Variable cytoplasm
Histochemistry
Nonspecific esterase positive
Peroxidase present in immature elements
Lysozyme present
Surface properties
F_c receptors
C_3 receptors
Function
F_c-dependent phagocytosis

[a]From van Furth, ref. 8, and Morahan, ref. 11.

phocytes can be distinguished from mononuclear phagocytes by the use of surface markers and by histochemical staining for lysozyme and peroxidase (see the discussion of chronic inflammation, page 7). Distinction of various mononuclear cell types and, indeed, distinction of

various subpopulations of T lymphocytes, B lymphocytes, and mononuclear phagocytes has been made feasible by development of monoclonal antibodies (102,103).

Maturation

The development of monoblasts through promonocytes and monocytes into tissue macrophages is accompanied by striking morphologic changes including increases in size of the cells, decreases in nuclear : cytoplasmic ratio, increases in surface ruffling, and marked increases in the complexity of cytoplasm, typified by increased amounts of endoplasmic reticulum, mitochondria, and lysosomes (1,12,13). Observed in concert with these morphologic alterations are concomitant increases in the amount of esterase and lysozyme present and increases in pinocytosis, adherence to glass, F_c-mediated phagocytosis, and number of F_c receptors (8). Finally, there is a progressive loss of proliferative capacity (14,15). Further and particularly striking alterations in mononuclear phagocyte function are observed when macrophages from sites of sterile inflammation are compared to resident tissue macrophages (16,17) (Table 3). It is worth emphasizing that these changes are not strictly confined to inflammatory macrophages; resident tissue macrophages can be stimulated to develop such changes *in vitro* by exposing them to surface-active moieties such as lymphokines (soluble products of stimulated lymphocytes) or to digestible particles that are endocytosed (18–20).

Mononuclear phagocytes can be further stimulated so that they are capable of killing facultative or obligate intracellular microorganisms and parasites and of lysing neoplastic cells (21–23). This state, which is termed activation by some workers (17,24), can be elicited in a variety of ways but particularly by exposing young mononuclear phagocytes from inflammatory sites to lymphokines *in vitro* or by taking macrophages from sites of immunologically mediated inflammation *in vivo* (25). The metabolic attributes that distinguish the activated macrophage from the inflammatory macrophage, in addition to the ability to destroy parasites or tumor cells, are currently being studied (17,24). Activated macrophages possess many of the properties that distinguish inflammatory from resident macrophages (11,17). The metabolic changes characteristic of activated macrophages include increased secretion of H_2O_2, the secretion of a potent cytolytic protease that lyses tumor cells, the capacity to bind neoplastic targets to the surface of the macrophages, expression of I-region associated (IA) antigens, and changes in the receptors for F_c and for certain glycoproteins (103).

TABLE 3. *Selected properties of murine peritoneal macrophages*[a]

Property	Resident	Inflammatory
Protein content (μg/10^6 mϕ)[b]	80	130
Spreading (% cells/hr)	4	90–95
Ectoenzyme (content 5′ nucleotidase in U/mg protein)	58.6	6
Pinocytosis (nl/10^6 mϕ/hr)	46	247
Lysosomal hydrolases		
Acid phosphatase (μg P/mg N/hr)	98	670
Phagocytosis (SRBC/100 mϕ)		
E-IgG	600	1,600
E-IgM-C	40	1,000
Secretory products		
Lysozyme (U/mg protein)	56	47
Plasminogen activator (U/mg protein)	1	800
Elastase (U/10^7 cells)	1–8	68
O_2^- (nM/mg protein after stimulation *in vitro*)	49	493

[a]Adapted from reference 99 with additional data from references 16,17,100, and 101.
[b]mϕ = macrophage.

Activation, viewed in several ways, is a complex set of alterations. Macrophages activated for tumoricidal function may not be activated for microbicidal function and vice versa (32). Studies on activated macrophages generally refer to populations of macrophages, which may be heterogeneous with respect to the individual mononuclear phagocytes in the population (33). Finally, the development of young mononuclear phagocytes into activated macrophages, which pass through the stage of the inflammatory macrophage, could represent either the modulation or differentiation of the macrophages (104). At present, these problems are not resolved, but current studies with monoclonal antibodies directed against specific populations of mononuclear phagocytes may help to clarify them (34).

Taken together, the above observations point out that mononuclear phagocytes mature considerably after leaving the marrow and are capable of even further maturation when exposed to inflammatory stimuli, particularly lymphokines.

Physiologic Properties of Mononuclear Phagocytes

The function characteristically associated with mononuclear phagocytes is endocytosis or uptake of material in their environment by both pinocytosis and phagocytosis. Pinocytosis, the uptake of solutes and of particles less than 100 Å in diameter, can also serve to clear the surface of the macrophage of receptor-bound ligands (16,35). Pinocytosis, apparently requiring protein synthesis and oxidative phosphorylation, is a steady ongoing process, the basal level of which depends on the extent of maturation of the mononuclear phagocytes (35). The basal level can be raised by interaction of the surface of the macrophage with certain surface-active molecules (16). Phagocytosis, the ingestion of particles larger than 100 Å in diameter, is particularly dependent on glycolysis (16,35). Mononuclear phagocytes are well equipped for phagocytosis, as they have a high inherent capacity for particulate uptake and specific binding sites for certain ligands on opsinized particles (35). At present, mononuclear phagocytes have been shown to have several binding sites for the F_c portion of immunoglobulins, binding sites for fragments of C_3, receptors for glycoproteins, binding sites for tumor cells and parasites (103,110,111), and an ill-defined binding capacity for denatured particles or molecules (35). Attachment of particles to mononuclear phagocytes via one of the binding sites facilitates the rate of uptake (35). Once a particle is interiorized within a portion of the plasma membrane, primary lysosomes can fuse with the endocytosed vesicle and hydrolase-mediated attack on the particle can begin (35). This attack can lead to degradation of the ingested material, which in the case of proteins can be reduced to peptides (6). It is of interest that this degradative process can be modified, so that antibody-coating of certain viruses permits lysosomal fusion for viral digestion, whereas certain intracellular pathogens (including *Mycobacterium tuberculosis*) can inhibit fusion of lysosomes with the phagosome (6,16).

Mononuclear phagocytes, so-called resting wandering cells, accumulate at sites of inflammation *in vivo*. Although evidence relating chemotaxis of mononuclear phagocytes to their accumulation *in vivo* is not complete, considerable evidence indicates a relationship between the two (36–38). Chemotaxis, the unidirectional migration of cells along a concentration gradient of a chemoattractant, is observed as the phagocytes extend lamellipodia or cytoplasmic veils toward the chemoattractant. The gradual flow of cytoplasmic contents into these lamellipodia ultimately results in motion of the mononuclear phagocyte toward the chemoattractant. The regulation of chemotaxis is currently under intensive investigation and appears to include sequentially the binding of chemoattractant to surface receptors, membrane depolarization at that site, localized influx of Ca^{2+}, and localized activation of microfilaments and probably of microtubules (37,38). Regulatory roles in these events have been attributed to surface proteases,

cyclic nucleotides, and methylation reactions (36,37). Mononuclear phagocytes are chemotactically attracted by a wide variety of substances, some of which apparently attract the mononuclear phagocytes specifically (Table 4) (36,37). It is of note that the mature mononuclear phagocytes are more chemotactically responsive than immature ones (36,37).

In the past decade, another property of mononuclear phagocytes, that of secretion, has been recognized (Table 5) (39,40). Mononuclear phagocytes are currently known to secrete over 60 different moieties into the extracellular compartment (40,107). Secretion is usually enhanced after the mononuclear phagocytes have been stimulated. The precise conditions of stimulation leading to the enhanced secretion of each product differ, not only from basic group to group of secretory products but from product to product within a given group. Within this general context, several broad generalizations may be useful. First, inflammatory macrophages tend to have a greater propensity for secretion than do resident tissue macrophages (17), although resident macrophages secrete certain products more than do inflammatory macrophages (40). Second, a population of mononuclear phagocytes is often primed for enhanced secretion by one signal, so that a second and different signal (trigger) must be applied to obtain release of the product in question (41,42). Finally, certain stimuli in sufficient doses can lead directly to enhanced secretion (41); lymphokines applied to resident tissue macrophages, for example, can lead to enhanced secretion of plasminogen activator (20).

TABLE 4. *Substances chemotactic for mononuclear phagocytes*[a]

C5a
Lymphocyte-derived chemotactic factor[b]
Supernatants of bacterial cultures
N-formylated methionyl peptides
Kallikrein
Basic peptides from neutrophils[b]

[a]From refs. 36–38.
[b]Reported to attract mononuclear phagocytes but not neutrophils.

TABLE 5. *Selected secretory products of mononuclear phagocytes*[a]

Reactive oxygen intermediates
Lysozyme
Neutral proteinases
Plasminogen activator
Elastase
Collagenase
Lysosomal enzymes including acid hydrolases
Complement components
Pyrogen
Prostaglandins
Interferon
Factors modulating other cells
Factors stimulating fibroblasts
Factors stimulating angiogenesis
Cytolytic factors
Factors affecting T cells
Factors affecting B cells
Factors stimulating colony formation
Procoagulant factors

[a]From Davies and Bonney, ref. 40.

Functions of Mononuclear Phagocytes

One of the most important functions of mononuclear phagocytes involves the regulation of the induction and expression of the immune response (43,44,109). Macrophages are currently viewed as having three roles in the immune response: a) removal and catabolism of exogenous antigen, b) appropriate presentation of antigen to lymphocytes, and c) secretion of soluble factors regulating lymphocytes. Certain polymeric antigens with replicating and identical subunits can stimulate B and T lymphocytes directly and apparently do not require the intervention of either macrophages or T lymphocytes. Most antigens, particularly cellular antigens such as those on bacteria like *L. Monocytogenes*, require collaboration between T lymphocytes and accessory cells such as macrophages to induce a response in either T or B lymphocytes. Macrophages are required in this collaboration to present the antigen to the lymphocytes and to produce soluble regulatory factors which act on T lymphocytes, such as T-helper cells or certain T-effector cells; T cells of the subset T-effector$_{DH}$ are the lymphocytes principally responsible for mediating delayed hypersensitivity reactions. Thus, the ingestion and presentation of an antigen by macrophages favors the development of T-helper and T-effector lymphocytes responsive to that antigen.

Another significant function of macrophages is host protection against microbial invasion (22). Although their relative contribution vis-à-vis that of the neutrophil to natural and acquired resistance to many pathogens (i.e., obligate extracellular parasites) may be less, macrophages participate in host resistance against common pathogens (45). Macrophages are certainly capable of destroying a wide variety of gram-positive and gram-negative bacteria, the killing of which can be effected by tissue or inflammatory macrophages in the presence of specific opsonins against the micro-organisms (6,45). By contrast, macrophages are principal cellular elements in the destruction of facultative or obligate intracellular parasites such as *M. tuberculosis*, *Toxoplasma gondii*, or *Histoplasma capsulatum* (22,46). This complex host defense system, which has been termed cellular immunity or cellular resistance, depends on a) sensitization of T-effector lymphocytes, b) interaction of the invasive organism with macrophages and T cells to stimulate secretion of lymphokines by the T cells, c) recruitment of mononuclear phagocytes to the area by lymphokines, and d) microbicidal activation of the macrophages to effect heightened endocytosis and destruction of the offending organism by the lymphokines (47). Thus, cellular resistance consists of a) a specific component mediated by T lymphocytes and directed only against the particular infecting agent and b) a nonspecific component mediated by activated macrophages and directed against most pathogens once the macrophages have been activated. The significance of acquired cellular resistance *in vivo* has been well established (21,22). The microbicidal mechanism or mechanisms of activated macrophages are not yet fully established, but considerable emphasis is placed on the role of activated oxygen intermediates such as H_2O_2 (42,104,107,108).

The role of macrophages in host protection against the development and spread of neoplasia is an area of emerging interest (23,48). Although it is not yet established that mononuclear phagocytes participate in all types of immune-mediated attacks on tumors, clear examples of an obligate role for macrophages in such destruction are known (48). For example, the tumor rejection produced by injection of *Mycobacterium bovis*, strain bacillus Calmette Guérin (BCG), has been identified as requiring the presence of activated macrophages at the site of tumoral destruction (49). Also, macrophages from sites of chronic, lymphokine-mediated inflammation are activated for cytolysis (24). Activated macrophages can selectively destroy a wide variety of malignant-but-not-nonmalignant cells *in vitro*, even though their donors have not been

immunized against the tumor targets (23). The mechanisms by which activated macrophages selectively recognize and destroy neoplastic targets are incompletely defined but may involve selective binding of the tumor cells to the macrophages and subsequent release of cytolytic materials such as H_2O_2 and neutral proteases from the macrophages (25–31).

CHRONIC INFLAMMATION

Chronic inflammation, which may be defined as a loose or nonapposed infiltrate of leukocytes bearing single nuclei (mononuclear cells), can be defined in histologic terms (50). This basic definition, which admittedly does not recognize variations in the temporal history of the lesion, does provide a readily applicable classification by histologic examination alone and avoids the infrequent but real paradox of mononuclear cells constituting a lesion which is only hours old (50).

This definition is clearly quite broad, and chronic inflammation, viewed in any of several ways, encompasses a multiplicity of inflammatory responses (50). However, most of these varied responses can now be better defined, since histologically similar mononuclear cells can be specifically distinguished from one another by use of appropriate markers (Table 6). Monoclonal antibodies against various mononuclears and against subsets of the various mononuclears are proving particularly useful in distinguishing these cells (102,104,106). Mononuclear phagocytes, T lymphocytes, B lymphocytes, and mast cells, have all been identified in chronic inflammatory sites (50,51); various proportions of these leukocytes have been recovered from such lesions, depending on the cause of the inflammatory response and the state of the host (50,51). Mononuclear phagocytes are the predominant element of many sites of chronic inflammation (e.g., delayed hypersensitivity skin test sites) (1). Such lesions, however, do not constitute granulomas, because the mononuclear phagocytes are not mature macrophages, do not form clusters, and are not apposite (1).

TABLE 6. *Histological and histochemical markers for identification of inflammatory mononuclear cells*[a,b]

Cell type	Morphology	Histochemical	Surface	Functional
T lymphocytes	Small mononuclear	None	Receptor for sheep erythrocytes (E)	Not used
B lymphocytes	Small mononuclear	None	Receptors for F_c, C_{3b}, and C_{3d} (EA and EAC)	Surface immunoglobulin
Plasma cell	Mononuclear with characteristic cytoplasm and nucleus	Methyl green pyronin	As for B cells	Surface immunoglobulin
Mononuclear phagocytes	Mononuclear with variable cytoplasm	Peroxidase in immature elements Nonspecific esterase Lysozyme	Receptors for F_c and C_{3b}	Phagocytic via F_c
Mast cells	Mononuclear with basophilic granules	Metachromatic Chloracetate esterase	Not yet established	Not used

[a]Adapted from Adams and Turner (50).

[b]It is worth noting that T and B lymphocytes may contain nonspecific esterase, usually in small amounts (8). Neutrophillic leukocytes contain lysozyme but have a characteristic nucleus (50).