

Origin, morphology, histochemistry and function of the mucosal mast cell and the globule leukocyte. A review.

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Summary: Parasites invading mucous membranes elicit an inflammatory response from the host. With appropriate fixation and staining methods, cells with intracytoplasmic granules may be observed. Closer examination may reveal several types of granular cells, the eosinophilic granulocytes being the most commonly identified in parasitic infections, but also observable are peculiar mast cells and globule leukocytes whose functions are not yet understood. This review describes the most important facts about the mucosal mast cell and the globule leukocyte relevant to their significance in parasitic infections.

Key words: inflammatory cells, histogenesis, parasitic infection, granular cells, anatomy.

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Introduction

Mast cells (= MC) belong to a heterogeneous group of granular cells (Michels, 1938). Their phenotypes may be regulated by factors in the microenvironment. Local growth factors may influence their differentiation, maturation, and development, and thus the function of the cells, (Selye, 1965, Dvorak & Galli, 1985, Befus & al., 1986, Enerbäck & Norrby, 1989). Accordingly, when the microenvironment changes, the phenotypic expression of MC also may change. For example, MC in the subserosal tissue of young rats became after 8–12 weeks positive for berberine sulfate and safranin, indicative of maturation of heparin (Arizono & Nakao, 1988). There are at least two specific MC-types; those in the connective tissue called connective tissue mast cells (= CTMC) and those at mucosal and serosal surfaces called mucosal mast cells (= MMC) (Enerbäck & al., 1986).

Globule leukocytes (= GL) are granular cells in the epithelium that resemble mast cells. Al-

though comparison of the properties of MMC and GL has led to the assumption that GL are derived from MMC (Miller & al., 1968), there are several indications that GL are an independent cell type (Ruitenbergh & Elgersma, 1976, 1979, Ruitenbergh & al., 1979, 1982). This question is reviewed in the light of facts on the morphology, histogenesis, histochemistry, and function of MMC and GL.

Occurrence of MMC and GL

MMC and GL are probably found in most vertebrates, but they are not equally distributed in different tissues. MMC are mainly located in lamina propria and also in the epithelium of the alimentary and respiratory tracts. GL occur only in the epithelium of those systems and also intraepithelially in the urinary and reproductive tracts. MMC are more frequent than GL in normal tissues. Parasitic infections influence the number of both cell types, but the

number of GL is especially increased during parasitic infections (Table I).

MC are particularly abundant beneath the epithelial surfaces, in the vicinity of peripheral nerves and blood and lymphatic vessels; in certain animal species, they are common within peritoneal and pleural cavities (Selye, 1965, Galli & al., 1984, 1987, Enerbäck & Norrby, 1989).

Maximow (1905) probably was the first to observe that lamina propria of the intestine of the rat contained MC which differed from the classical CTMC. An aberrant granular cell type first observed by Heidenhein (1888) was described by Weill as a «Schollenleukozyt» in 1919. The name «Schollenleukozyt» was translated into «globule leukocyte» by Keasbey (1923). Weill (1919) described GL in the epithelia of the alimentary tract of the dog, cat, pig, mouse, rabbit, guinea-pig, and man.

There are several reports on the presence of GL in the alimentary tract and bile ducts of ruminants (Keasbey, 1923, Duran-Jorda, 1945, Hill, 1951, Kent, 1952, Sommerville, 1956,

Dobson, 1966, Jarrett & al., 1967, 1968, Miller & al., 1968, Murray & al., 1968, Rahko, 1970, 1971, 1972, 1973, Blazek, 1971, Miller & Jarrett, 1971, Lawrence, 1977, Gregory, 1979, Akpavie, 1985, Akpavie & Pirie, 1985, Huntley & al., 1987b). GL has also been identified intraepithelially in the respiratory, urinary, and reproductive epithelium of ruminants, (Taliaferro & Sables, 1939, Kent, 1952, Kellas, 1961, Blazek, 1971, Breeze & al., 1975, Lawrence, 1977, Mahmoud & Pirie, 1982, Akpavie, 1985).

GL have been documented also in 11 species of birds (Clara 1926, Toner, 1965, Asdrubali & Mughetti, 1969, Holman, 1970, 1972, Kitagawa & al., 1979, 1988), in the gut mucosa of a fish, *Acipenser sp.* (Rogosina, 1928), and in several species of amphibians and reptiles (Törö, 1931).

Normally GL form a very small proportion of the cells of the epithelium: 0.001 % in the urinary tract of the rat. In rats fed a Mg-deficient diet, however, GL increased to 5 % of the epithelial cell population in the renal pelvis, uterus, and urinary bladder (Cantin & Veilleux, 1972).

Table I. Comparison of different characteristics of MMC and GL

	MMC	GL
Occurrence	lamina propria and epithelium of different mucous membranes	within mucosal epithelium
Number of cells	variable, no absolute counts made	normally 1-2 GL/1000 epithelial cells, experimentally max. 32/1000 epithelial cells
Function of cells	release biological active unknown mediators, take part in the expulsion of parasites and facilitate transport of antibodies into the lumen of intestine	associate with MC-proliferation in parasitic infections and take part in the «self cure» by local immediate hypersensitivity reaction
Nuclear form	spherical	ovoid, spherical, often indented
Structure of chromatin	lymphocytic-type distribution	cartwheel-type distribution
Cytomembrane	with pseudopodia, no desmosoms	with pseudopodia, no desmosoms
Size and ultra-structure of granules and globules	small, 1-2 μ , electron-dense, usually unevenly	large, usually 2-5 μ , electron-dense, usually diffusely

Structure of MMC and GL

The size and number of MMC-granules vary according to the size of the cell. The globules of GL are usually bigger and fewer in number than in MMC, causing indentations on the nucleus. Mitotic figures and cytoplasmic projections have been observed in both MMC and GL (Table I).

The fixation method is of extreme importance for the preservation of the structures of MMC and GL (Enerbäck, 1966, 1974, 1981, 1987, Enerbäck & Lundin, 1974, Ruitenbergh & al., 1982, Enerbäck & al., 1986). It influences the preservation and visualization of all types of MC. In tissue sections fixed in alcohol, no MC could be found by Maximow (1905). On the other hand, in biopsies of human duodenum fixed in both standard formalin and a formalin-acetic acid (FA) fixative, MC were equally well preserved, but an additional population of MC with MMC staining characteristics could be visualized when the FA-fixative was used (Guy-Grand & al., 1984, Enerbäck & Norrby, 1989).

MMC differ in size, the bigger being present in both mucosae and connective tissues, the smaller only subepithelially (Miller, 1980, Guy-Grand & al., 1984). The nucleus is of the lymphocytic type (Ruitenbergh & al., 1979, 1982). Cytoplasmic projections are often seen as an indication of motility (Enerbäck & Lundin, 1974). Numerous MMC without microvilli are seen between the epithelial cells during the «self cure» expulsion of intestinal nematodes (Enerbäck, 1974).

GL occur as solitary cells in the epithelium. Junctions between GL and epithelial cells have occasionally been observed. GL are able to migrate with the use of pseudopods through the epithelium (Toner, 1965). Accordingly, GL have been found freely in the tracheal lumen (Vandenberghe & Baert, 1981).

The nucleus of GL is usually eccentric, ovoid or spherical, and commonly indented by the cytoplasmic globules (Gregory, 1979). The nuclear membrane is distinct and the cartwheel distribution of the chromatin is common (Akpavie & Pirie, 1985). Binucleated cells have also been observed (Keasbey, 1923, Akpavie, 1985).

The cytoplasm of GL is filled with refractile, acidophilic and spherical globules (Keasbey, 1923, Kent, 1952). The number of globules in a cell section ranges from 5 to 40 (Keasbey, 1923,

Kent, 1952, Kellas, 1961, Akpavie, 1985). The largest globules are seen in cells with few globules. GL with only two large irregularly formed globules were observed in the main bile duct of a goat infected with liver flukes (Rahko, 1972).

The ultrastructure of individual globules varies (Toner, 1965, Kent, 1966, Whur & Johnston, 1967, Carr, 1967, Takeuchi & al., 1969, Holman, 1972, Baert, 1989). Occasionally bridge-like connections have been seen between the globules (Baert, 1989). Four types of globules have been distinguished; (1) globules with electron density only in the core; (2) usually larger globules with a homogeneous electron-dense matrix; (3) those containing paracrystalline structures; and (4) globules with an intermediate structure (Vandenberghe & Baert, 1981). The membrane surrounding the globules is always smooth. Rhomboid crystals have also been observed freely in the cytoplasm of GL (Cantin & Veilleux, 1972), with striation parallel to its long axis (Carr, 1967).

Histochemistry of MMC and GL

The electron-dense metachromatic granules of MMC and globules of GL are made up of proteoglycans which can be distinguished histochemically. Low sulphated mucins in MMC differentiate them from CTMC with highly sulphated compounds of heparin. In GL the sulphation degree is histochemically even lower than in MMC.

Ehrlich in 1878 pointed out that the specific feature of MC was the metachromatic granules in the cytoplasm (cited by Michels, 1938). A proteoglycan of MMC, a chondroitin sulphate, does not show fluorescent berberine binding. It stains preferentially with alcian blue in a staining sequence with safranin (Enerbäck & al., 1986). The cells possess IgE receptors (Ishizaka & Ishizaka, 1984) which respond very rapidly (Enerbäck, 1987). Conjugated avidin reacts with the granules of rodent and human MC (Tharp & al., 1985).

Differences in staining characteristics of the GL globules also have been attributed either to the fixatives or staining methods (Enerbäck, 1966, Rahko, 1971, 1972). Carnoy's fixative has been the best for the demonstration of mucopolysaccharides of MC (Enerbäck, 1966). In cattle the GL globules were more adequately fixed with corrosive formol (Miller & al., 1967) or Bouin's solution (Rahko, 1971, 1972).

After fixation in Zenkers-formol or 25% formaline, GL are positive for PAS and alcian blue (Cantin & Veilleux, 1972). The globules stain metachromatically with thionin, toluidine blue, and brilliant cresyl blue (Kirkman, 1950, Kent, 1952). The presence of a sulphated acid mucopolysaccharide is documented also by the positive reaction with astra blue stain (Jarrett & al., 1968, Miller & al., 1968, Murray & al., 1968). The metachromatic reaction of the globules seems to vary; in the respiratory tract of old cows, GL do not show metachromatic staining with toluidine blue (Akpavie, 1985). It has been supposed that the globules contain iron because of the resemblance to erythrocytes (Keasbey, 1923). Earlier investigations found no evidence for either iron (Dawson, 1943) but subsequently Kirkman (1947, 1950) found indications of hemoglobin and Kent (1952) found evidence for iron. Glycosaminoglycans, as well as serine esterase, are present in the granules of MMC and GL. GL does not contain 5-hydroxy-tryptamine (Whur & Gracie, 1967, Jarrett & al., 1968) although the globules contain strongly basic proteins (Rahko, 1971, 1972). The negative reaction with toluidine blue at pH 4.2 also confirms that heparin is absent from the globules of GL (Whur & Gracie, 1967).

Function of MMC and GL

MC play an important role in many biological processes. They probably interact with the cells of many tissues, organs, and body cavities. The cells can elaborate and release a variety of biologically active compounds. Obviously, this hold true specifically for CTMC. MMC and GL are, on the other hand, involved in the ex-

pulsion of parasites, the «self-cure» phenomenon. GL is thus possibly associated with the immune response to parasitic infections (Table I).

Numerous stimuli cause MC to release biologically active mediators (Selye, 1965). Morphological studies have documented structural changes in MC during different inflammatory, immunological, reparative, metabolic, and neoplastic responses but the role of MMC has remained unclarified.

Hyperplasia of instestinal MMC occurs in the rat after an infection with *Nippostrongylus brasiliensis*. The reaction in *N. brasiliensis* «self cure» expulsion is considered to be of an anaphylactic type. (Miller, 1971). However, there was no documentable change in the permeability during the expulsion of *N. brasiliensis* in the mast-cell-deficient mice (Crowle & Reed, 1981). Nevertheless it is suggested that biogenic substances released from MMC are responsible for mucosa lysis and that this causes the increase in mucosal permeability which is known to occur during worm expulsion (Miller & al., 1968).

The function of GL was originally connected with the assimilation of food substances (Weill, 1919). The observation that GL contained hemoglobin led to the theory that they had the same function as the erythrocytes (Keasbey, 1923). Later it was supposed that GL had a nutritive function for the surrounding tissue (Heine & Schaege, 1977).

The first to suggest that GL could be involved in parasitic infections was Hole in 1937. In 1939 Taliaferro & Sarles showed that GL were associated with parasitic infections and mast cell proliferation. Others also have observed a correlation between parasites and GL (Kirkman, 1947, Sommerville, 1956, Ahlqvist & Kohonen,

Table II. Theories and arguments on the origin and histogenesis of MMC

Supposed precursors for MMC	Evidences of relationship
1. Hemopoietic tissue	MMC are thymus-independent cells of bone marrow?
2. Lymphocytes	Lymphocytes are known to be migrating cells with capability to transform.
3. Basophilic granulocytes	Analogous composition of the granules in both basophilis and MMC.

Table III. Theories and arguments on the origin and histogenesis of GL

Supposed precursors for GL	Evidences for relationship
1. Hemopoietic tissue	Thymus-dependent cell of bone marrow with intracytoplasmic granules and short life span (2-3 months)?
2. Lymphocytes	A complete morphological series from lymphocyte to GL is demonstrable.
3. Mast cell	Analogous ultrastructure and composition of granules of MMC and globules of GL.
4. Large granular lymphocyte	Intraepithelial granular cell with similar nuclear structure to GL.
5. Russel body cell	Globules of GL resemble the Russel body-inclusions with the same fluorescence, being surrounded by pyroninophilic cytoplasm like in plasma cells.
6. Eosinophilic granulocyte	Analogous acidophilic granules in GL and eosinophils, both associated with parasitic infections.
7. Mesenchymal cell	GL is an independent mesenchymal cell which undergoes mitosis and forms local tumors.

1959, Dobson, 1966, Jarrett & al., 1967, 1968, Whur, 1967, Fernex, 1968, Miller & al, 1968).

A *Trichinella*-induced proliferation of MMC occurred in the intestine of thymus-bearing and not in athymic mice. The enhanced behaviour was both antigen- and thymus dependent but only observed for the stromal intestinal MMC and not for the intraepithelially located GL. In congenitally mast cell-deficient mice infected with *Trichinella*, no proliferation of GL was observed. In contrast, an increasing number of GL was observed intraepithelially in the intestine of normal mice. A positive correlation between the infiltration of GL and the rapidity of *T. spiralis* expulsion from the intestine was suggested, (Kamiya & al., 1985).

Differential counts indicated that an increasing proportion of the MC population migrated intraepithelially, possibly to be transformed to GL (Miller & Jarrett, 1971). Also Dobson (1966), Carr (1967), Whur (1967), Miller & al. (1968), Murray & al. (1968), Lawrence (1977)

and Huntley & al. (1984b) have associated the presence of GL with the immune response to parasitic infections.

Origin of MMC and GL

There is evidences that MMC are derived from the hemopoietic tissue, possibly having the same precursors as other types of MC. The differentiation of MC precursors may be locally regulated. The histogenesis of GL, on the contrary, is doubtful. Erythrocytes, plasma cells, Russel body cells, and other types of leukocytes and mast cells have been proposed as precursors for GL. However, GL seem to be an independent migrating cell type of nonepithelial origin and the histogenesis of GL-like cells may be different in different vertebrate classes. Furthermore, cytochemical dissimilarities between tracheal and intestinal GL might indicate that they represent different phenotypes or even different types of GL (Tables II and III).

Practically pure populations of one specific MC phenotype exist in the mucosa and of another phenotype in connective tissue (Enerbäck, 1981, 1987, Kitamura & al., 1983). Peritoneal MC themselves might give rise to MC phenotypically similar to either CTMC or MMC (Nakano & al., 1985).

There is evidence that MC derived from cultured hemopoietic tissues are MMC (Jarrett & Haigh, 1984). The cells are regarded as an independent cell population. Their histogenesis is thymus-independent, but the response to *Trichinella* infections is mainly thymus-dependent (Ruitenbergh & al., 1979, Galli & al., 1984).

Similarities between GL-globules and erythrocytes led to the opinion that the globules are derived from phagocytosed erythrocytes (Gregory, 1979). Duran-Jorda (1945) considered that GL secreted erythrocytes, then becoming epithelial lymphocytes. The morphology and staining properties also contributed to the hypothesis that GL belong to the erythrocytic series. Dawson (1943) proposed that GL occupy an intermediate position between erythrocytes and leukocytes. Kent in 1952 and Toner in 1965 suggested a lymphocyte origin on the basis of finding a complete series, with transitional forms, from the small lymphocytes to the GL. Kitagawa & al. (1979) reported that GL in chicken originated from the thymus lymphocytes, being stainable with anti T-lymphocyte serum. Baert & Frederix (1985) considered large granular lymphocytes as a possible precursors for GL. Other origins have also been suggested, including eosinophils, plasma cells, and mast cells (Kent, 1952). The inclusions of Russell body cells and the globules fluoresced similarly, and the cytoplasm in both cells was pyroninophilic (Dobson, 1966, Carr, 1967, Whur & Johnston, 1967). But GL differ from plasma and Russell body cells because they lack immunoglobulins (Whur & White, 1970).

In 1977 Heine and Schaege stated that their results indicate that the GL may originate both from MC and from eosinophilic granulocytes. GL were considered to be MMC which have migrated to the epithelium and partly discharged their granules; the conclusion was based on their similarities both ultrastructurally and histochemically with MMC (Jarrett & al., 1967, 1968, Miller & al., 1968, Murray, al., 1968, Miller & Jarrett, 1971).

Huntley & al. (1984) showed transitional cells

between MC and GL in the intestine of sheep infected with nematodes. The size of the globules changed from small to large and proteoglycans, serine esterase, dopamine, and immunoglobulins were demonstrated in all cell types. When the globules increased in size, their amine content decreased. Histochemical analyses thus supported the view that MMC and GL have a common lineage (Huntley & al., 1984).

GL has been proposed to be a specific cell type of mesenchymal origin (Kirkman, 1950). There are several indications that GL probably are an independent cell type. This fact is supported by the findings of a neoplastic behaviour of GL in the intestine of the cat (Finn & Schwartz, 1972). Furthermore, GL undergo mitosis during *Trichinella* infection. Ruitenbergh & Elgersma (1979) did not totally discard the MMC origin of GL. Some other data suggest a common source for MMC in intestinal mucosae and support the idea that MMC and GL are two independent cell populations (Parmentier & al., 1982).

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