Megakaryocytes: Morphogenesis, Biochemistry and Physiology, A Review

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**Morphology**

Ackerman (1955) described the megakaryocyte morphologically as a giant cell which may reach over 80 microns in diameter, that possesses an irregular cytoplasm contour, a large lobulated nucleus with coarse chromatin and a thin nuclear membrane. The cytoplasm is packed with small granules and mitochondria, giving a "ground-glass" appearance. (See Figures 1 - 3)

Miale (1972) stated that occasionally in pathologic conditions, the nucleus may be segmented or polynuclear. There may be zero to many nucleoli present but these are usually not visible due to superimposed nuclei.

Diggs, et. al., (1970) described the morphology of the maturation sequence of the megakaryocyte as follows:

**Megakaryoblast** - the cytoplasm is smooth and light blue. There may be blunt pseudopods and foamy marginal cytoplasm structures. The chromatin strands are less linear and have a more granular appearance than in other early cells.

**Promegakaryocyte** - large, fine, bluish granules have appeared in the cytoplasm. The nucleus may or may not have divided. This cell is larger than the blast cell.

**Megakaryocyte** - this cell is larger than the promegakaryocyte. The nucleus is indented and lobulated. The chromatin pattern is linear and coarse with spaces between the strands.

**Metamegakaryocyte** - this cell is differentiated from the above cell by the fact that particles of granules have aggregated and granular platelets have begun to form at the periphery of the cytoplasm.

Currently, the trend in modern hematology considers the metamegakaryocyte as an originally diploid cell in which the chromatin material has undergone successive duplications without concomitant cytoplasm changes (Garcia, 1964).

**Fine structure**

The fine structure of the megakaryocyte was first described by Yamada (1957) and since that time several accounts have been published.

At low magnification, it is possible to recognize three zones in the cytoplasm of the mature megakaryocytic. The per nuclear zone contains a Golgi complex, mitochondria, endoplasmic reticulum and free ribosomes. However, electron micrographs by Weiss (1967) have demonstrated that the peripheral cytoplasm is partitioned into platelet zones by smooth-surfaced endoplasmic reticulum. Each of these platelet zones contains lysosomes, ribosomes and glycogen. The greater part of the cytoplasm is occupied by an intermediate zone which is rich in granules, mitochondria and strands of reticulum.

**Pathological Morphology**

In his studies on giant cells, Rebuck (1947) has described several morphology changes in megakaryocytic which he believes to be due to various pathological conditions. In idiopathic thrombocytopenic purpura, he described the adult megakaryocyte as presenting an absence of azurophilic granules. There is a normal or increased number of cells but a decrease in platelet production. On the other hand, in hemorrhagic or hemolytic anemias, the megakaryocytes are increased and platelet formation is abundant. In diseases such as hemophilia, polycythemia vera, Gaucher’s disease and aplastic anemia, there are quantitative but not qualitative changes.

Cells in all stages of development have been noted in the peripheral blood in myeloid megakaryocytic hepatosplenomegaly. These conditions may also exist in chronic myelogenous leukemia. Rohr (1940) has described marked hyper segmentation of the megakaryocytic nucleus in pernicious anemia, much the same as the hyper segmentation of neutrophils in this disease. Further studies have shown abnormal and incomplete platelet formation in certain areas of cytoplasm in secondary toxic thrombocytopenia.
Morphogenesis

In the fetus, giant cells resembling megakaryocytes have been observed in the blood islands of the yolk sac. Megakaryocytes appear concomitantly with active hematopoiesis in the liver, bone marrow and spleen. In adults, megakaryocytes are formed primarily in the red bone marrow in close approximation to the sinusoids. Occasional megakaryocytes are found in the lungs, presumably transported there by venous blood (Bierman, 1961).

The maturation time for the megakaryoblast to mature megakaryocyte in the rabbit is estimated at 6.5 days. The megakaryoblast in the rabbit has an indefinite resting period which is also measured in days (1-3 days). It is assumed that the resting and maturation times for megakaryopoiesis in man are at least equal to, if not longer than, that of the rabbit (Kinoshita and Bierman, 1957).

In the past, the origin of the megakaryocyte has been investigated by many researchers and almost as many theories have evolved. Megakaryocytes were described as giant multinuclear cells and were considered to be osteoclasts. In 1905, Bizzozero described a second type of giant cell as multilobular and these cells were similar to those called megakaryocytes by Howell (1890).

Jolly (1923) said that megakaryocytes arise from indifferent lymphoid cells by hypertrophy of the cytoplasm and nucleus, and that they are also derived from myelocytes with homogeneous protoplasm in which the nucleus and the cell body hypertrophy.

Ferrata and Negreiros-Rinaldi (1915), in studying the histogenesis by smears, found evidence that the megakaryocyte is derived from hemocytoblasts which become hypertrophied. Some authors postulated the origin of the megakaryocyte to be a fusion of many cells which develop into a polycaryocyte derived from histoid elements. Bianchi (1921), studying cases of myeloid leukemia, also concluded the formation of the megakaryocyte was due to fusion of cells.

Downey, Palmer and Powell (1930) published a case in which they concluded the origin of the megakaryocytes to be a result of hypertrophy of myeloblasts or of reticular cells. Other investigators agree since they have accounted for a number of megakaryocytes arising from reticulo-endothelium in a case of aleukemia myelosis. Agreement with Downey, et. al., that megakaryocytes usually develop from hemocytoblasts but may also come from the reticulum came from Jones in 1938 (1961), Rohr in 1949 and Bessis in 1956.

In 1963, Becker, et. al., in studies using irradiated mice, demonstrated that certain hematopoietic cells in the spleen differentiated along three lines into cells of the erythrocytic, granulocytic and megakaryocytic series respectively. Work by Wolf and Trentin (1968) appears to substantiate this conclusion.

Physiology

The primary function or physiology of the megakaryocyte appears to be the formation of platelets (Wright, 1910). Some prefer to call this platelet-forming cell a metamegakaryocyte. They differentiate this from a megakaryocyte by the fact that it has granular platelets at the periphery of the cytoplasm (Diggs, 1970). To adhere to this nomenclature, one must think of the mature megakaryocyte as a mature cell at rest.

Some authors have demonstrated motility of the megakaryocyte (Hiraki, 1956; Albrecht, 1956). In one of these studies, the average of the migration was 3.3 microns per minute. Immature megakaryocytes

Figure 1

Figure 2

Figure 3
(promegakaryocytes) showed only rotary motion, no forward migration.

Phagocytosis of carbon particles was absent in the mature and the immature megakaryocytes (Hiraki, 1956).

Maximow and Bloom (1947) believe the cells of the megakaryocytic series reached their maturity by means of multipolar mitosis, in which the cytoplasm undergoes no contraction and daughter nuclei fuse into a pachychromatic polymorphous nucleus.

Bessis (1959) described the formation of platelets as development of cytoplasm pseudopods in the mature megakaryocytes. These pseudopods comprise most of the cell cytoplasm and, as they become more and more elongated, small enlargements which are platelets tend to break off and escape into the blood as free structures. Estimates are that a single megakaryocyte is able to give "birth" to anywhere from 2,000 to 11,000 platelets in this manner (Kaufman et al., 1965).

Kaufman, et al., (1965) felt that the "platelet production" which is noted in stained smears is an artifact produced by the shearing off of bits of cytoplasm from mature megakaryocytes in the preparation of the smear. According to them, it is unlikely that platelets are released in the extra vascular marrow, since they are incapable of amoeboid movement. Thus it is believed that the megakaryocyte must first enter vascular channels before platelets are released.

Weiss (1967), using electron micrographs, concluded that megakaryocytes active in platelet production have endoplasmic reticulum organized circumferentially and radially in their peripheral cytoplasm with the result that platelet zones are delineated much like a perforated sheet. The segments of endoplasmic reticulum elongate and fuse with the result that a platelet is detached. In the bone marrow, the megakaryocytes lie just outside the sinus, pressing against the outer surface. Platelets are discharged directly into the sinus lumen through gaps in the sinus wall.

**Biochemistry**

Weiss (1967) has shown that the cytoplasm of the megakaryocyte contains lysosomes, ribosomes and glycogen.

Chatterjea, et al., (1956) attempted to correlate activity of megakaryocytes with cytochemical characteristics. Special reference was made to the alkaline phosphates activity and periodic acid-Schiff (PAS) reaction. Results demonstrated that cytoplasm of most of the megakaryocytes could be correlated with morphological activity. Therefore, they postulate that the alkaline phosphates content of the megakaryocytes may thus be an index of their physiological activity.

Overall knowledge regarding the cytochemical pattern of the megakaryocyte is fragmentary and incomplete, but this same biochemical information in regard to the individual platelet is very extensive. It is logical to assume that qualitatively, those biochemical constituents present in the platelet are also present in the megakaryocyte, and it is under this assumption that the following information is presented.

**Inorganic Constituents**

Studies by Marcus and Zucker (1965) indicate that platelets contain sodium and potassium, magnesium and calcium, with about 80% of the calcium bound to lipid. RNA phosphorous, protein-bound phosphorous and lipid phosphorous have all been noted in the platelet. The lipid has been demonstrated both as phospholipid and cholesterol.

**Proteins and Amino Acids** By use of ion exchange chromatography, 20 free amino acids plus taurine, phosphoethanolamine and phospho serine have been isolated from platelets. A very important protein was extracted in the form of thrombasthenin. This represents approximately 15% of the platelet protein (Marcus and Zucker, 1965).

**Enzymes and energy metabolism**

Studies concerned with the energy metabolism of platelets, especially glycolytic intermediates, have provided some very useful information (Marcus and Zucker, 1965): (1) Fifty per cent of the metabolized glucose was recovered as pyruvic and lactic acid; (2) 20% of the metabolized glucose was recovered as C02 and H2O; and (3) 25% of the glucose was presumed metabolized to glycogen, amino acids and lipids.

These findings as well as those from other investigators indicate that the principal source of ATP in the platelet is a glycolytic pathway.

This is in agreement with Morita (1965) who estimated glycolytic activity and postulated a tricarboxylic acid cycle and an Embden-Meyerhof system.

**Lysosomal enzymes**

Morita has also indicated several hydrolytic enzymes, such as monophosphatase, ATPase, adenosine pyrophosphates, esterase and acetyl cholinesterase.

Analysis of isolated granules has demonstrated acid phosphatase, beta glucuronidase and cathepsin.

**Carbohydrates**

According to Woodside and Khocolaty (1960), over 8% of the dry weight of the platelet is carbohydrate. The following were detected: glucose, galactose, mannose, fucose, ribose, glucosamine, galactosamine, glucuronic acid and sialic acid.

From the standpoint of the megakaryocyte per se, the important biochemical constituents are alkaline phosphates activity and periodic-acid-Schiff (PAS) reaction. The presence of lysosomal enzymes in the
megakaryocyte is of importance only when discussing the phenomenon of phagocytes by platelets but not necessarily an important consideration in the megakaryocyte itself. The glycogen is of course necessary for the metabolic systems of the cell.

Summary
The giant megakaryocyte develops from the blast cell. The mature megakaryocyte may reach a size of 40 -100 microns. The contour of the cell is irregular. The cytoplasm is moderately basophilic and filled with granules presenting a "ground-glass" appearance. Fragmentation of the peripheral cytoplasm may be seen as platelets and platelet clusters form. The large nucleus is generally lobulated and possesses a dense chromatin pattern.

It appears that while motility of the megakaryocyte has been demonstrated, the primary function is the "shedding" of platelets. Estimates of up to 11,000 platelets have been given as the resultant products of a single megakaryocyte.

There has been some disagreement as to the release mechanism of the platelets, Kaufman, et al. (1965) feeling that the megakaryocyte must first enter vascular channels before platelets are released. They claimed that megakaryocytes are normal constituents of the blood and estimate 7 -17 % of the body’s platelets are released in pulmonary capillaries. Weiss (1967), on the other hand, maintained that platelets are in fact released in the bone marrow. He stated that the megakaryocyte is pressed against the sinusoid and platelets are shed directly into the lumen of the sinus.

Biochemically, the importance of the PAS positive material in confirming a glycolytic pathway for energy and the correlation of the alkaline phosphates activity with morphological and physiological characteristics of the cell are of prime interest in the megakaryocyte.

Also mentioned is the presence of lysosomes and lysosomal enzymes. This may be of interest in discussing the possibility of phagocytosis by platelets.

References


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In the following, choose the one best answer for each question.

1. The primary physiology of megakaryocyte is the formation of platelets.
   A. True
   B. False

2. According to some authors, the cells in the megakaryocytic series reach maturity by multipolar mitosis.
   A. True
   B. False

3. One author believes that platelet production is an artifact produced in preparation of the blood smear.
   A. True
   B. False

4. Described first in 1957, one author notes the greater part of the cellular cytoplasm contains a zone of granules, mitochondria, and reticulum.
   A. True
   B. False

5. This giant cell may grow as large as 1,000 microns.
   A. True
   B. False

6. Use of electron microscopy by Weiss lead him to conclude that platelets are released in the blood.
   A. True
   B. False

7. Regarding the origin of the megakaryocyte, several authors noted the formation of the cell was due to a fusion of many cells.
   A. True
   B. False

8. Studies have indicated that megakaryocytes are not capable of motion.
   A. True
   B. False

9. The megakaryocyte and the neutrophil both may demonstrate a hyper segmentation of the nucleus during pernicious anemia, according to some authors.
   A. True
   B. False

10. Researchers believed that one index of the physiological activity of the megakaryocyte may be demonstrated by the content of the alkaline phosphate present in the cell.
    A. True
    B. False