Plasma Cells Containing Iron
An Electron Micrographic Study

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There have been a limited number of reports of iron inclusions in plasma cells. This finding has essentially been limited to a few cases of anemia. The presence of iron in plasma cells was mentioned by Jaffe in 1938. Kosewski studied iron in plasma cells in nine cases of hemochromatosis with megaloblastic anemia. This iron was considered to be phagocytized by plasma cells as an emergency response to an overload of body hemosiderin. He thought plasma cells containing iron were pathognomonic for megaloblastic anemia with hemochromatosis. Sundberg supported Kosewski's finding of iron in plasma cells with six additional cases of hemachromatosis; however, she did not observe this in megaloblastic anemia. Iron inclusions in plasma cells were described recently by Parsons in cultures of plasma cell tumors in mice. He suggested that these might be breakdown products of red blood cell contamination at the time of culture. These reports were all based on light microscopic stains. Using the electron microscope, we have observed iron in plasma cells of four patients representing a variety of hematologic disorders. These four cases include hemochromatosis, megaloblastic anemia in relapse with no known hemachromatosis, refractory normoblastic anemia, and porphyria cutanea tarda. The mode of entry of the iron, its role in the cell, and its release are discussed.

Method

Marrow was aspirated from the iliac crest in a versenate-wet syringe. The particles were transferred directly into cold 1 per cent buffered osmium tetroxide, pH 7.3, fixed for one hour, and dehydrated through changes of alcohol, infiltrated with propylene oxide, and embedded in Epon or Maraglas. After polymerization sections were cut on a Porter-Blum MT-2 microtome with glass knives, the sections were mounted on carbon grids, stained with uranyl acetate and lead citrate, and examined in an RCA-EMU-3F electron microscope. Light microscope slides were prepared and stained for iron with the Prussian blue method.

Clinical Material

Case 1: Q. J., a 62-year-old Chinese man, was diagnosed as having idiopathic hemochromatosis with cirrhosis, pancreatic insufficiency, and diabetes mellitus. Evidence of iron overload was based on an iron excess in liver and bone marrow by light microscopy. Subsequent iron kinetic studies showed a high rate of iron turnover in the liver but no

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Fig. 1.—A portion of a plasma cell (Case III) showing four single membrane vesicles (V) containing dense granules. These are located between the endoplasmic reticulum (ER) and the golgi (G). Several mitochondria are also present. Mag. × 36,500. The mark at the bottom of each print represents one micron, unless otherwise indicated.

abnormal rate of plasma iron marrow exchange. He was maintained on insulin, pancreatin, and periodic phlebotomies as tolerated.

Case II: V. S., a 70-year-old white woman, had a diagnosis of megaloblastic anemia. She demonstrated a good reticulocyte response to oral folic acid. The bone marrow specimen was taken prior to the folic acid therapy.

Case III: N. F., a 65-year-old white woman, had a diagnosis of sclerodermoid type of porphyria cutania tarda with diabetes mellitus. She excreted 8 grams uroporphyrin per 24 hours; the packed red cell volume ranged from 44 to 47. In the three months prior to the bone marrow sample, she had had six phlebotomies removing a total volume of 2750 cc.

Case IV: W. S., a 60-year-old white man, had a diagnosis of refractory normoblastic
Fig. 2.—A Prussian blue stain of bone marrow from Case IV, showing a typical plasma cell in the middle. The dense blue-green granules are located between the golgi and endoplasmic reticulum. The nucleus is eccentrically situated. Mag. × 1200.

anemia. The clinical details have been previously documented.\textsuperscript{2} Several bone marrow samples have been studied over a 2-year period. During this time the anemia failed to respond to folic acid, pyridoxine, phenylalanine and to the use of desferrioxamine. The patient has been maintained on whole blood transfusions (77 units in the past 3 years). The iron in the plasma cells of the bone marrow was observed in all the bone marrow examinations and did not seem to increase with additional transfusions.

**RESULTS**

Plasma cells containing iron were infrequent in the cases of hemochromatosis, megaloblastic anemia, and porphyria. The iron particles were contained in single-walled vesicles, which were often located between the endoplasmic reticulum and the Golgi apparatus (Fig. 1). When present, there were usually one or two of these inclusions per cell section, and the particles were quite dense and closely packed.

In contrast, many plasma cells containing iron were seen in the case of refractory normoblastic anemia with both the light and electron microscopes. With the light microscope (Fig. 2) there was some difficulty in distinguishing
between the iron-containing plasma cells and ringed sideroblasts also present in this patient. However, the plasma cells had Prussian blue staining granules that corresponded both in size and orientation in the cell to the vesicles with dense particles seen in the electron microscope. The electron micrographs clearly demonstrated numerous plasma cells with iron. The iron particles were contained in unit membrane vesicles (V) in an amorphous matrix (Fig. 3). These vesicles varied in size from 0.5 μ up to 4–5 μ in length and were generally located near the junction of endoplasmic reticulum and golgi. Large, well-developed mitochondria often were nearby.
Fig. 4.—A plasma cell (Case IV) with several vesicles (V) that have various amounts of iron. A large well-developed golgi (G) is present as well as an extensive area of endoplasmic reticulum (ER). N is a portion of the nucleus. Mag. × 34,500.

Generally, the dense iron particles were uniformly scattered throughout the amorphous material in the vesicle; however, occasionally there were vesicles or areas that contained a very dense accumulation of particles within a matrix (Fig. 4). Less frequently the particles were oriented in rows with a periodicity of 110 Å. These rows occurred within a structured lattice apparent in the otherwise amorphous material (Fig. 5). The particles were fairly uniform in size (about 55 Å) and had the structure of ferritin (Fig. 6).

In all four cases plasma cells were at times observed to form peripheral cytoplasmic blebs (clasmatois). A portion of cytoplasm containing both protein in cisterni and some endoplasmic reticulum separated in two ways. The
Fig. 5.—Two small vesicles (Case IV) with laminated structure showing a periodicity of 110 Å. Endoplasmic reticulum (ER) is also present. Mag. × 72,500.

Separation was initiated in some cases by the appearance of small vesicles along the base of a cytoplasmic protrusion (Fig. 7). These vesicles then coalesced to form a membrane which became the dividing surface that separated the bleb from the rest of the cell (Fig. 8). Other blebs appeared to pinch off without the development of small vesicles (Fig. 9). Final lysis of these fragments was not observed.

Discussion

Light microscopists have reported 1–3,8 iron in plasma cells in some anemic patients and in one case of β plasmacytoma.6 Bessis10 has published electron micrographs of iron containing vesicles in reticular cells in a case of hemochromatosis. Our electron micrographs demonstrated iron in plasma cells in hemochromatosis, porphyria cutanea tarda, megaloblastic anemia, and refractory normoblastic anemia. The presence of iron in these cells raises questions concerning its entry, role, and release from the cell.

There are at least three mechanisms for admission of material into a cell: phagocytosis, pinocytosis, and direct transport through the cell membrane.

Kosewski1 suggested phagocytosis of iron by plasma cells as an emergency storage function in hemochromatosis. Izarn8 compared plasma cells to histiocytes, suggesting that iron may phagocytize as hemosiderin or erythrocytic material which may then degrade. The appearance of intracellular iron in the two cells is not the same if one studies electron micrographs of iron contained in plasma cells and histiocytes. In the latter, material identical in appearance to erythrocytic cell fragments can be followed through various stages of disintegration to either vesicles containing iron or iron-protein particles free in the
Fig. 6.—A portion of a vesicle (Case IV) with many small ferritin particles. The typical tetrad structure is seen in the circles. Mag. × 230,000.

cytoplasm. There is no evidence in our pictures to support the concept that plasma cells have phagocytized erythroid material to produce iron residues in the manner comparable to histiocytes. Bessis' simply states that “plasma cells are not capable of phagocytosis.”

If one considers some of the suggested multiple origins of plasma cells from lymph cells, reticuloendothelial cells, or macrophages, phagocytosis in the latter two may have been the primary process of entry before the maturation (transformation) into plasma cells.

Other known processes of material entry into the cell include pinocytosis and direct absorption of soluble material. In the specific instance of iron
Fig. 7.—A portion of a plasma cell (Case IV). A cytoplasmic bleb (b) has formed with a row of small vesicles at its base. Mag. × 33,000.

transport, this is exemplified by the erythroblast's accumulation of iron by pinocytosis of hemosiderin and ferritin, and by the surface absorption of iron from transferrin (Pollycove). We have seen some finger-like extensions of plasma cell cytoplasm reminiscent of Thiery's micropinocytosis, but again, no actual iron particles could be demonstrated apparently entering the plasma cell either by this process or in the manner observed on erythroblast surfaces. This does not exclude pinocytosis as a possible mode of ingestion, but infers surface absorption of iron from transferrin, or the phagocytosis of iron-containing material before cell maturation (transformation), as the more probable mechanism of iron entry into plasma cell.
PLASMA CELLS CONTAINING IRON

The reason for iron accumulation in plasma cells is speculative at this time. Kosewski suggested that it was a response to an overload of iron, assuming plasma cells were capable of phagocytosis, and that they functioned in the storage of the excess iron. Many studies (Movat and Fernando, Bernhard and Grandboulan, Pearse, White) indicate that plasma cells are primarily concerned with protein (gamma globulin)—that is, antibody synthesis. The work of Schooley on the rate of protein synthesis in plasma cells following an antigenic stimulus demonstrated a short lifespan and minimal labeling of protein in the more mature plasma cells. Apparently most of the protein synthesis takes place in the immature cell. It is impossible to connect directly the presence of iron to antibody synthesis at this time. The concept of the plasma cell storing iron in these vesicles is inconsistent with the recent data showing a short lifespan for these cells. However, the presence of iron in cells that have an endoplasmic reticulum, large Golgi bodies, and numerous mitochondria suggests a possible relationship to synthesis of protein (amorphous matrix) and its transmission into the vesicles via the Golgi body similar to the zymogen containing vesicles of pancreatic cells (Palay). The crystalline or laminated structure of protein material found in some vesicles bears close resemblance to formations reported by Thiery and Wellensiek. That iron particles identifiable as ferritin should appear periodically along the lattice structure suggests some correlation between the concentrated protein and ferritin.

The process of blebbing (clasmatosis) demonstrates one mode of excretion of protein. However, we have not seen iron apparently being excreted from the plasma cell, or eventual lysis of plasma cell or blebs as described by Thiery.
Fig. 9.—A cytoplasmic bleb (b) apparently about to separate by constricting at its base. Vesicles (V) containing iron are present near the golgi (G), mitochondria (M), and the base of the endoplasmic reticulum (ER). Mag. × 33,500.

SUMMARY

The presence of iron in plasma cells was demonstrated by light and electron microscopy. The iron compound was identifiable as ferritin in at least one patient. Possible modes of origin, function, and fate of iron in these cells was discussed.

SUMMARY IN INTERLINGUA

Le presentia de ferro in plasmoeytos esseva demonstrate per microscopia optic e electronic. Le composito de ferro esseva identificabile como ferritina in al minus un del patientes. Es commentate le possibile modo de origine, le function, e le destino de ferro in iste cellulas.
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REFERENCES


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