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Review

The discovery of plasma cells: An historical note

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ABTSRACT

The name plasma cell was introduced by the anatomist Heinrich H. von Hartz-Waldeyer in 1875. Plasma cells derive from small B lymphocytes after their activation. A fully mature plasma cell lacks surface immunoglobulin expression. Its form is round or oval, with characteristic basophilic cytoplasm and an eccentric nucleus that contains coarse heterochromatin. Antigen activation of mature B cells leads initially to germinal center development, the transient generation of plasmablasts that secrete antibody while still dividing, and short-lived extrafollicular plasma cells that secrete antigen-specific germ line-encoded antibodies. Plasma cells are characterized by the co-expression of CD138 and CD38, which allows their identification in flow cytometry in bone marrow, peripheral blood, or cell suspensions from tissues. The identification of plasma cells as antibody producers was a key discovery that paved the way for the development of monoclonal antibodies.

1. The first description of plasma cells

The name plasma cell was introduced by the anatomist Heinrich H. von Hartz-Waldeyer in 1875 [1] (Fig. 1). From his work it is not clear that he described a specific type of cell that later other authors denote with the same word. A definite cell strain was first recognized in 1890 by Santiago Ramon y Cajal, Nobel Prize in Physiology or Medicine in 1906, [2] in the condylomata of syphilis, and he named these cyanophil cells. In 1891 Paul Gerson Unna [3] found in lupus vulgaris dermal lesions caused by *Mycobacterium tubercolosis* cells which he called plasma cells. He described them as having a basophilic, spongy, or granular cytoplasm, the granuloplasm. Their nuclei were either centrally or eccentrically placed, and the chromatin content and arrangement were variable. His only constant specializing criterion was basophilic granuloplasm, and as a result of this he included under the category of plasma cells many cells with basophilic cytoplasm, which were probably derivatives of other strains.

Unna definition of the plasma cell was somewhat wider than that formulated in 1895 by Marshalko. His description more closely parallels our modern conception what is currently implied in the term plasma cell, that is, a round or, more commonly, oval cell with a strong basophilic cytoplasm, often containing a juxtanuclear light zone, and possessing an eccentrically situated nucleus with chromatin material somewhat grouped together. This form of the plasma cell is referred in the literature as the Marshalko cell type.

In 1902, Maximow's experiments with tissue culture seemed to establish the lymphocytic origin of the plasma cells [4]. In tissue cultures he had observed transitions between lymphocytes and plasma cells. However, his opinion of the lymphocytic genesis of the plasma cell was shared by Michels in 1931 [5]. In the same year, in a study of the histogenesis of plasma cells [6], Miller reported finding plasma cells normally present in the subserosal connective tissue of the rabbit omentum and the connective tissue cords of lymph node. with an increase in number of these cells when the rabbits are injected with toxic irritants. He concluded that plasma cells arose near blood vessels from a primitive connective tissue cell.

In 1943, Bjørneboe and Gormsen were the first to experimentally show that repeated immunization of rabbits with polyvalent vaccines leads to massive proliferation of plasma cells in most organs and that this proliferation correlates with antibody concentration [7]. This finding was confirmed by in 1947 by Fagraeus, who reported that plasma cells produce antibodies in vitro [8]. Tissue cultures of spleens from rabbits immunized with live bacteria showed abundant formation of plasma cells. Fagraeus concluded that plasma cells appear in connection with strong antigen stimulation.

2. Which is the role of plasma cells in the immune response?

In 1898, Pfeiffer and Marx proved that the spleen was a major site of production of antibodies protecting against cholera and that lymph nodes, bone marrow also significantly contributed [9]. They immunized rabbits and guinea pigs with a single dose of heat-killed cholera bacilli

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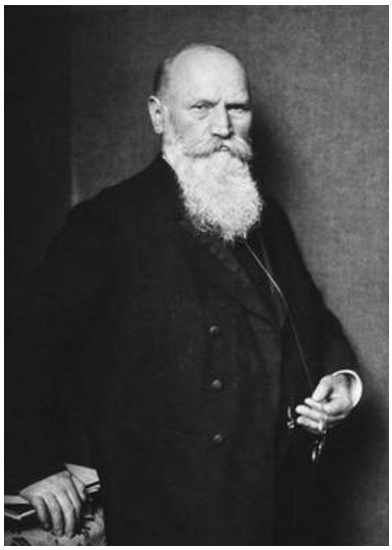

Fig. 1. A port trait of Heinrich H. von Hartz-Waldeyer.

Fig. 2. A port trait of Max D. Cooper.

Fig. 3. A port trait of Robert A. Good.

and showed that the organs contained antibody as early as two days after immunization and that in the first 5 days the antibody concentration in them exceeded the concentration in the serum.

In 1939, Sabin postulated that the monocyte produced normal globulin, and that when it took up antigen the synthetic process was so modified as to lead to the appearance of specific antibody [10]. In 1944–45, Dougherty et al. and Ehrlich and Harris, suggested that lymphocytes are a source of antibodies. In the late 1940, the cellular source of antibodies was identified: it was shown that plasma cell development correlated with antibody responses after immunization [11,12].

In 1965, Cooper and Good (Figs. 2 and 3) using chicken as an experimental model, showed that B cells that develop in the bursa of Fabricius (equivalent to the bone marrow in mouse and human) are responsible for antibody production, whereas T cells that develop in the thymus are responsible for delayed-type hypersensitivity responses [13]. In 1965–67, Moore and Owen proposed that the lymphocyte precursors were blood-borne of extrinsic origin which colonized the thymic and bursal rudiments at a precise stage of their ontogeny [14–16]. Under the influence of thymus and bursa or bursa equivalent, stem cells arising from the yolk sac in the embryo and from the bone marrow in the adult, undergo antigen-independent proliferation and differentiate into immunocompetent T and B lymphocytes, respectively. These reenter the bloodstream and populate the lymph nodes, the spleen, and the connective tissues of the body. Upon meeting their appropriate antigen, T and B lymphocytes are stimulated to transform, proliferate, and differentiate, giving rise to cytotoxic T lymphocytes and antibody secreting B lymphocytes and plasma cells.

3. The modern view

Plasma cells are found in the medullary cords of resting lymph nodes, the marginal zone and cords of resting spleen, and scattered throughout the connective tissue of the bodies. They are numerous in the lamina propria of intestinal mucosa.

Plasma cells derive from small B lymphocytes after their activation. A fully mature plasma cell lacks surface immunoglobulin expression. Its form is round or oval, with a diameter of 9–20 μm, has characteristic basophilic cytoplasm and an eccentric nucleus that contains coarse heterochromatin distributed much like the spokes of a wheel (Fig. 4A). The plasma cell is packed a rough-surfaced endoplasmic reticulum having numerous attached ribosomes as seen by electron microscopy (Fig. 4B). In a small percentage of plasma cells, one or more cisternae of the granular reticulum are greatly distended with a mass of dense material (Russel bodies) consisting of incomplete immunoglobulin molecules. A large Golgi zone forms a paranuclear halo and mithocondria are located between the strands of endoplasmic reticulum.

When the immunoglobulins fill and expand the cisternae of the endoplasmic reticulum prior to release, the cytoplasm is acidophilic due to the staining properties of immunoglobulins. Experiments involving immunolabeling with ferritin or horseradish peroxidase have demonstrated that the content of cisternae of the granular reticulum consists largely of antibodies [17].

Antigen activation of mature B cells leads initially to germinal center development, the transient generation of plasmablasts that secrete antibody while still dividing, and short-lived extrafollicular plasma cells that secrete antigen-specific germ line-encoded antibodies. Plasmablasts are induced to circulate for a short period until they will reach a niche in bone marrow, spleen, mucosa associated lymphoid tissues (MALT) or lymph nodes [18]. The major constituents of the gut-associated lymphoid tissues (GALT) are the Peyer's patches and the isolated lymphoid follicles. Other GALT components include the appendix, mesenteric lymph nodes, intraepithelial lymphocytes and diffusely distributed cells located in the lamina propria, which is the layer of intestine between the epithelial cells and the superficial smooth-muscle layer. The importance of the GALT in mice and human is emphasized by the fact that more than 80% of all plasma cells are located in the gut.

These niches will provide circulating early plasma cells with those