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RESEARCH ARTICLE

PLASMA CELLS IN HEALTH AND DISEASE

***Karuna Kumari, Shwetha Nambiar, K., Vanishree C Haragannavar, Dominic Augustine, Sowmya, S. V. and Roopa S Rao**

Faculty of Dental Sciences, M.S. Ramaiah University of Applied Sciences, Bangalore, Karnataka

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ABSTRACT

Plasma cells are the only cells that sustain antibody production and hence are an essential part of immune system. In the bone marrow plasma cells produce immunoglobulins which assure long-term humoral immune protection and in the mucosa-associated lymphoid tissues (MALT) plasma cells secrete IgA which protect the individual from pathogens invasion. This review illustrates plasma cell development and their role in both health and disease.

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INTRODUCTION

Plasma Cells (PCs) are non-dividing, effectors cells that represent the final stage of B cell differentiation. PCs, are the sole producers of antibody and main component of antibody mediated immunity (Shapiro-Shelef and Calame, 2005). PCs represent < 1% of the cells in lymphoid organs, still they are accountable for all antibodies in circulation (Fairfax *et al*., 2008). PCs secrete large quantities of specific antibody continuously with estimated rates as high as 10,000 molecules/second (Slifka *et al*., 1998). They are vital for an effective immune response, however they may be responsible for several pathologies ranging from autoimmune diseases to PC neoplasms (Shapiro-Shelef and Calame, 2005). Originally PCs were considered to be short-lived cells, more recent studies says that PCs residing in bone marrow (BM) are often long lived (Cuiling *et al*., 2016). The specific microenvironments which support PC survival is provided by various lymphoid organs (Chu *et al*., 2011). PCs consist of 2 different pools characterized by main differences in physical location and half-life: short-lived cells are found in extrafollicular locations such as medullary chords of lymph nodes or the red pulp of the spleen, and long-lived cells are found mainly in the BM (Bortnick and Allman, 2013).

Morphology of the Plasma cell

The PC is typically ovoid in shape, but when the cells areclosely packed or crowded, they appear angulated. The cytoplasm of the PCs contains large amount of rough endoplasmic reticulum (rER) and Golgi apparatus. The cytoplasm of PC displays strong basophilia due to presence of rER; the Golgi is unstained or lightly tinged with eosin & appears as a clear area adjacent to the nucleus (paranuclear hof). The nucleus of the PC is spherical and typically offset or eccentrically placed. It is smaller than nucleus of lymphocyte. It contains large clumps of peripheral heterochromatin alternating with clear areas of euchromatin resembling a "cartwheel" in histological sections (Ross and Pawlina, 2006) (Figure 1).

Origin and distribution of plasma cells

All PCs develop from activated B cells, but their fate depends greatly on the mode of activation (Chu *et al*., 2011). The PCs development and function is firmly regulated (Cuiling Yu *et al*., 2016). There are many factors that allow normal development of B-cells into mature PCs (Kumar *et al*., 2010). The end stage differentiation of B-cells into PCs with a distinctive secretory ultrastructure is usually accompanied by pronounced changes in the transcriptome and proteome (Cuiling Yu *et al*., 2016).

Antigen-independent B-cell development

The haematopoietic stem cells in the BM give rise to B cells. This stage is antigen independent. Multiple transcription factors, such as early B-cell factor, paired box protein 5 (PAX5) and E2A are required for initial commitment and development to the B-cell lineage (Busslinger, 2004). Subsequent to initial development in the BM they achieve the

Corresponding author: Karuna Kumari, Faculty of Dental Sciences, M.S Ramaiah University of Applied Sciences, Bangalore, Karnataka

ability to produce an intact immunoglobulin M (IgM), following which they migrate to the spleen (Kumar *et al*., 2010). B cells continues their development in the spleen where they go through T1 and T2 transitional phases and are open to a negative selection round before they become fully mature (Chung *et al*., 2003). A minor proportion of transitional B cells move to the splenic marginal zone and persist as naive non-circulating cells. Still, maximum B cells in the T2 stage transform into long-lived follicular B cells, which continue to circulate in the splenic follicles, lymph nodes and in the BM until they either encounter cognate antigen and undergo further maturation or die (Pillai *et al*., 2005).

Antigen-dependent phases of B-cell development

Early PC response

PCs develop from naive marginal-zone B cells, activated germinal-centre (GC) B cells, follicular B cells, and from memory B cells after they come across an antigen. The site of the encounter and the nature of the antigen, dose, and form of the antigen decides B-cell subset(s) differentiation. The former 'natural' Igs that are secreted by B1 cells (BOX 1) provide the earliest antibody response to some pathogens (Shapiro-Shelef and Calame, 2005). Marginal-zone B cells are the first to react with the foreign antigen by differentiating into PCs (Pillai *et al*., 2005; Lopes-Carvalho and Kearney, 2004). Initial encounter with blood-borne antigens, is facilitated by non-circulating naive marginal-zone B cells.Within a few hours of immunization with a T-cell-independent type 2 (TI-2) antigen, marginal-zone B cells travel from the marginal zone to thes plenic red pulp and the bridging channels, where they go through a proliferative burst. This happens concurrently along with the differentiation to produce plasmablasts foci which secrete Ig but still continues its proliferation (Lopes-Carvalho and Kearney, 2004). The threshold for antigen activation is lower for marginal-zone B cells than follicular B cells. The marginal B cells have inherent ability to respond quickly and proliferate to a greater extent as they encounter an antigen and they get stimulated with lipopolysaccharide (Oliver *et al*., 1997).

Post-germinal-centre response

GC is formed when folllicular B cells, receive help of T-cell and come across anantigen. GCs are specialized areas in the follicle where proliferation of B cells occur, that is convoyed by class-switch recombination (CSR) of Ig and affinity maturation. Follicular dendritic cells (FDCs) and antigen-specific T helper cells are important for the GC response (Shapiro-Shelef and Calame, 2005).

Memory-cell response

Due to the intrinsic ability Memory B cells respond more quickly than naive B cells, and on secondary encounter with antigenthey show a proliferative burst (Shapiro-Shelef and Calame, 2005).

Immunoglobulin synthesis

PCs produce an intact Ig which is made up of 2 similar lights chains and 2 heavy chains. The heavy chains have 5 major classes, represented as alpha, mu, gamma, delta, and epsilon each corresponding to the major classes of Igs; IgA, IgM, IgG, IgD and IgE respectively. The heavy chains are bound to 1 of the 2 light chains (either Lambda or Kappa) in each of the Ig molecules (Kumar *et al*., 2010). Igs are synthesized within the ribosomes of PCs. They are then transported to the Golgi apparatus, where they are processed and packaged into secretory granules that then fuse with the outer cell membrane. In certain monoclonal gammopathies and in occasional instances of reactive PC hyperplasia associated with intense Ig production, Igs may precipitate within the PC, forming inclusion bodies (Krishnan and Thiagarajan, 2005).

Bizzare plasma cell

Mott cells

PCs that have spherical inclusions packed in their cytoplasm are called as Mott cells (or morula cells). The Russell bodies are inclusions of Mott cells which are dilated ER cisternae containing condensed Igs (Bavle, 2103) (Figure 2). Genetic locus-microsatellite marker (D4 Mit 48 & D4Mit70) has been linked to formation of Mott cells. There are many pathological conditions in which Mott cells can be sighted eg. reactive plasmacytosis, various hematolymphoid malignancies like, Burkitt's lymphoma, lymphoplasmablastic lymphoma, large B-cell lymphoma, multiple myeloma (MM), and syndromic conditions like von Recklinghausen's neurofibromatosis and Wiskott–Aldrich syndrome.

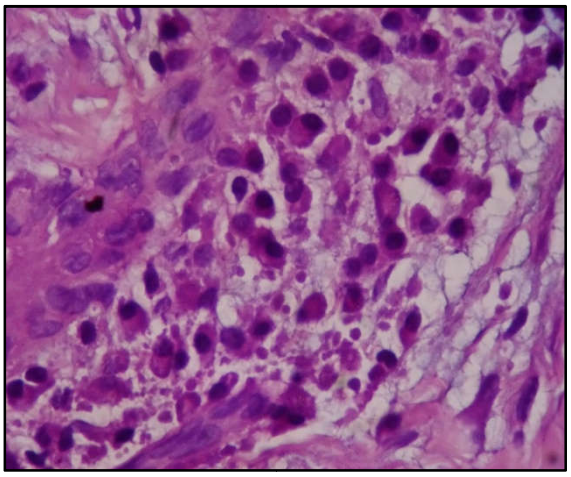

Figure 1: Plasma cells

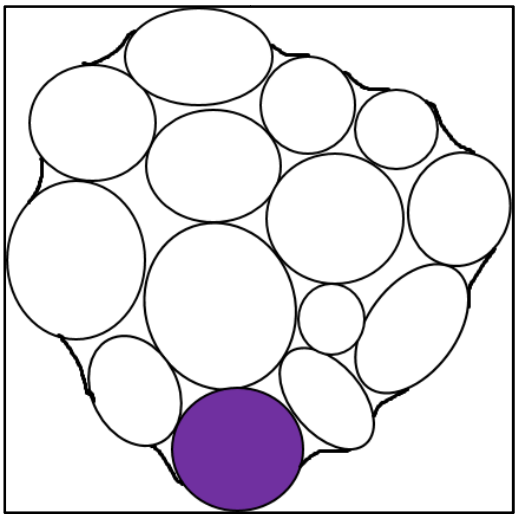

Figure 2. Mott cell

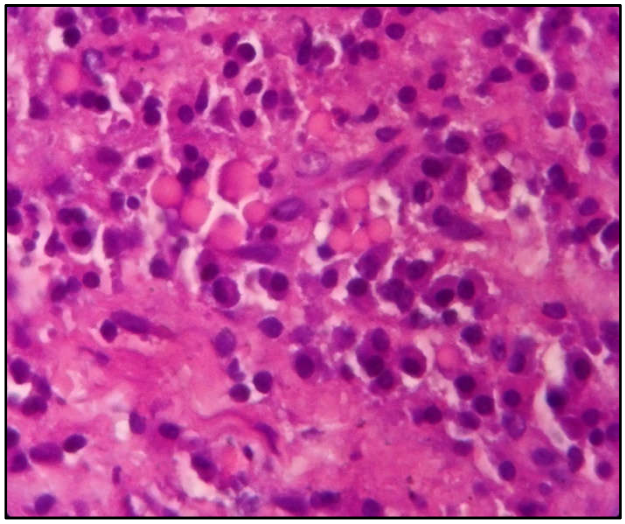

Figure 3. Russell bodies

The special stains used to demonstrate Mott cells are May-Grünwald-Giemsa (MGG) and Periodic Acid-Schiff (PAS) stain. Mott cells are characterised by the expression of following immunohistochemical markers: B220, CD5, CD43, CD11b (Bavle, 2013).

Inclusion Bodies

A variety of inclusions may be present, including Russell bodies and Dutcher bodies.

Russell Bodies are elliptical, homogenous, eosiniphilic, intracytoplasmic inclusions within PCs. They are 20-40µm in size and two or three in number. Sometimes they enlarge so much that the cell size is increased and the nucleus is virtually invisible, giving the appearance of an extracellular body (Figure 3).

Pathogenesis: Reactive plasmacytosis and plasma cell neoplasms are associated with intense Ig production. Igs may precipitate within the PC, forming inclusion bodies.

Stain: H&E, Gram, PAS, Millon reaction, and Phloxine-tartrazine (Patil *et al*., 2013).

Dutcher bodies: Dutcher and Fahey described Dutcher bodies as intranuclear inclusions in patients of Waldenstrom's macroglobulinemia in 1959 (Dutcher and Fahey, 1959). Dutcher bodies which resemble nuclear inclusions are actually cytoplasmic inclusions that are either invaginated into or are overlying the nucleus. There are no vital differences between the inclusions of Mott cells, single or multiple Russell bodies and Dutcher bodies. They are all spectrum of the similar phenomenon, representative of spherical cytoplasmic inclusions that are either overlying the nucleus or invaginated into it or are clearly within the cytoplasm (Bain, 2009).

Plasma cell identification / antibodies useful for plasma cell immunohistology

Initially identified by their characteristic morphology and abundant intracellular Ig, cell-surface markers such as the CD38 and CD138 (Syndecan-1) antigens are often used to identify PCs (Cuiling Yu *et al*., 2016). CD38 marker is also expressed by other cells like activated T lymphocytes cells, but expression in PCs is intense and make it reasonably specific for PCs. It is used routinely for identification of PCs (Kumar *et al*., 2010; Harada *et al*., 1993). CD138 or syndecan-1, which is also typically expressed by PCs, increases the sensitivity to demonstrate PCs (Kumar *et al*., 2010). CD 19 and CD45 can also be used for further refinement of the PC identification. Normal PCs are generally positive for CD38, CD138, CD19 and CD45 whereas abnormal PCs characteristically lack CD19 and variably express CD45 (Kumar *et al*., 2010).

Classification of Plasma cell disorders

Plasma cell disorders (PCD) comprises of wide range of diseases which are characterized by presence of an abnormal clone of PCs. Manifestations of PCD is seen as production of monoclonal Ig protein (monoclonal gammopathy). These monoclonal Ig proteins can be either a complete molecule (paraprotein) or light chains (Bence Jones protein), or both and generally accumulates in serum or urine. The overproduction of PCs and consequent monoclonal gammopathy can be a premalignant or malignant process (Sobol and Stiff, 2013). An example of a benign process with a malignant potential is monoclonal gammopathy of undetermined significance (MGUS). Waldenström macroglobulinemia, MM, AL amyloidosis (immunoglobulin light chain amyloidosis) and POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome are examples of malignant PCD. While each disorder has a distinct diagnostic and clinical phenotype, there is a large degree of overlap between them and hence they are often investigated and clinically managed together (Sobol and Stiff, 2013).

Working classification of plasma cell disorders of oral cavity

Reactive Lesions

1. Plasma cell gingivitis
2. Plasma cell granuloma

Neoplastic lesions

1. Multiple Myeloma
2. Plasmacytoma (Solitary and Extramedullary)
3. Lymphoplasmacytic Lymphoma/Leukemia

Unclassified

1. Monoclonal Gammopathy of Undetermined Significance (MGUS)
2. Primary Amyloidosis

Plasma cell gingivitis

Plasma cell gingivitis (PCG) is a rare benign condition appearing as generalised edema and erythema of the attached gingiva. It can cause severe gingival discomfort, inflammation, and bleeding. It is basically a hypersensitivity reaction to some antigen, often flavoring agents or spices found in chewing gums, lozenges and toothpastes (Serio *et al*., 1991). It is marked by a dense infiltration of normal PCs separated into aggregates by strands of collagen (Serio *et al*., 1991). PCG is known by other names such as plasmacytosis, atypical gingivostomatitis, allergic gingivostomatitis and idiopathic gingivostomatitis (Bhaskar *et al*., 1968).

Plasma cell granuloma

Plasma Cell Granuloma (PCG) is a non-neoplastic lesion which results from an inflammatory condition, mainly occurring in the lungs. It is also occur in the kidney, brain, stomach and heart. In the oral cavity in involves tongue, oral mucosa and gingiva. PCG is very rare in the oral cavity. These lesions may occur at any age and have no sex predilection. PCG has been reffered by various terms, namely; inflammatory pseudotumor, inflammatory myofibroblastic tumor, inflammatory myofibrohistiocytic proliferation, and xanthomatous pseudotumor (Manohar and Bhuvaneshwari, 2011).

Solitary plasmacytoma

Solitary plasmacytoma (plasma cell tumor) is the only known potentially curable PCD. It can arise in bone or soft tissue. When it is confined to bone it is called as solitary bone plasmacytoma (SBP) (also known as intramedullary plasmacytoma or osteosclerotic myeloma); when it occurs in soft tissue sites (most commonly the upper respiratory tract but also gastrointestinal tract, CNS, bladder, thyroid, breast, testes, parotid gland, and lymph nodes) it is called extramedullary plasmacytoma (Sobol and Stiff, 2013). SBP is a single, often destructive, collection of clonal PCs without other evidence of myeloma and is confined to bones only. It is rare and the median age at diagnosis is 60 years. The commonest site is the axial skeleton (Plasma Cell Disorders, 2015).

Monoclonal gammopathy of undetermined significance (MGUS)

MGUS is a common pre-malignant disorders and mainly affects people older than 50 years. The diagnostic criteria for MGUS :Serum paraprotein <30g/L, BM PC percentage <10%, no related organ damage or tissue impairment and no evidence of other B – lineage lymphoproliferative disorder such as chronic lymphocytic leukaemia (CLL) or B-cell lymphoma, immunoglobulin light chain (AL) amyloidosis and Waldenström's macroglobulinemia (WM) (Plasma Cell Disorders, 2015). While most patients with MGUS will have no clinical symptoms, a small number can be associated with peripheral neuropathy (MGAN), bleeding abnormalities or skin lesions. Patients with renal impairment caused by paraprotein-related renal lesions is being recognised and labelled as monoclonal gammopathy of renal significance (MGRS). MGUS does not require treatment but does require indefinite monitoring at periodic intervals for evidence of progression to a malignant condition (Plasma Cell Disorders, 2015). 0.5–1% cases of MGUS progresses to MM per year (Rajkumar *et al*., 2014).

Multiple myeloma

MM, plasma cell myeloma, or myelomatosis is a malignancy that results from clonal neoplastic cells proliferation in the BM. The neoplastic cells are closely related, both functionally and morphologically, to PCs. MM is the 2nd most common haematological malignancy and predominantly seen in middle-aged and elderly people. In majority of cases the protein which is secreted by the neoplastic cells is either a whole Ig or an Ig light chain. Clinical features are consequences of neoplastic proliferation or from effects of the protein, often labelled a paraprotein, which are produced by myeloma cells (Bain *et al*., 2010). MM is divided into different clinical phases. The first stage is MGUS which is a pre-malignant phase in which population of clonal PCs produce monoclonal protein; however, patients are generally asymptomatic but there is a risk of progressing from MGUS to myeloma (Plasma Cell Disorders, 2015). MGUS can be diagnosed if there is absence of hypercalcaemia, renal failure, anaemia, and bone lesions (CRAB features) that can be recognised as underlying PCD (absence of all features) (Rajkumar *et al*., 2014). The next stage is termed as smouldering myeloma/ asymptomatic myeloma. The percentage of PCs in the BM is high but still does not cause end organ damage and mostly does not require treatment apart from in high risk patients. Myeloma requiring treatment, in contrast, causes suppression of normal BM function and detectable damage to the kidneys or bones (Plasma Cell Disorders, 2015).

The following are clinical variants of myeloma

1. Smouldering/asymptomatic myeloma

Smouldering MM is an intermediate clinical stage between MGUS and MM. The risk of malignant transformation is about 10% per year in the initial 5 years post diagnosis (Rajkumar *et al*., 2014).

Following two criteria's must be met to diagnose smouldering MM:

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg/24 h and/or clonal BM PCs 10–60%.
- Absence of myeloma defining events or amyloidosis (Rajkumar *et al*., 2014). This disorder has diagnostic features consistent with myeloma by virtue of monoclonal protein level or BM PC infiltration but without myeloma-related organ or tissue injury, thus usually not requiring myeloma-directed therapy (Plasma Cell Disorders, 2015).

2. Symptomatic MM

The term MM refers to MM requiring therapy. Recentlya revised diagnostic criteria has been introduced for MM by International Myeloma Working Group (IMWG) (Rajkumar *et al*., 2014).

Plasma cell leukaemia: Plasma Cell Leukemia (PCL) is an aggressive subgroup of myeloma characterised by the presence of neoplastic PCs in the peripheral blood. It can either arise de novo (primary PCL) or from an existing case of MM (secondary PCL). Primary PCL has a distinct phenotype, aggressive clinical course and occurrs in 2–4% of new myeloma patients (Plasma Cell Disorders, 2015). The commonly used antigens for PC identification are CD38 and CD138, are also expressed similarly in PCL and MM. Nevertheless, CD20 is more likely to be expressed in PCL and CD56, CD117 and HLA-DR expression is usually negative. Primary PCL can be differentiated from secondary PCL by expression of CD27 and CD28 (Kumar *et al*., 2010).

POEMS syndrome: This is a rare plasma cell proliferative syndrome which combines polyneuropathy, a monoclonal protein with a wide range of other organ or tissue abnormalities. It can be associated with MGUS, MM and with other PCPD such as Castleman's disease (Plasma Cell Disorders, 2015).

AL amyloidosis

It is a rare condition caused by tissue deposition of protein fibrils derived from circulating monoclonal light chains and may lead to end organ damage. Deposition can occur throughout the body but renal, liver and cardiac involvement is more common. It also arises de novo as primary AL amyloidosis with an average age of 63 years at the diagnosis and an incidence of 8–10 per million persons (Plasma Cell Disorders, 2015). In 80–90% of patients with primary amyloidosis monoclonal protein are found in the serum or urine. Lambda (λ) light chains outweigh in a 3:1 ratio over kappa (k) light chains, in contrast to a 2:1 k to λ ratio in patients with MGUS and plasma cell myeloma. In approximately 50% of patients with amyloidosis Congo red staining in vascular structures is positive (Wei and Juneja, 2003).

Waldenström's macroglobulinemia

Waldenström's macroglobulinemia (WM) is classified as a lymphoplasmacytic lymphoma (LPL) by the World Health Organization (WHO) and REAL classifications. It is an indolent B-cell lymphoproliferative disorder. It show male predominance. Signs & symptoms are characteristically related to BM infiltration of lymphoplasmacytoid cells (normocytic anaemia, cytopenias) and IgM paraproteinemia (hyperviscosity, neuropathy, cryoglobulinemia, cold agglutinin disease, rarely amyloidosis). Lymphadenopathy, organomegaly and extranodal masses can also be a presenting feature (Plasma Cell Disorders, 2015). The lymphoplasmacytic cells are positive for CD19 & CD38 and variably express CD138 (Kumar *et al*., 2010).

Conclusion

PCs were attributed in the pathogenesis of various conditions ranging from autoimmune to neoplastic conditions. The role of PCs in progression of various diseases make it prudent to perform thorough investigation to diagnose and rule out any underlying systemic disease. Understanding the unique properties of PCs and its interactions with other immune cells provide a basis for novel therapies.

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