Indian Journal of Dental Sciences.
March 2013 Issue:1, Vol.:5

www.ijds.in

Review Article

Indian Journal
of Dental Sciences

E ISSN NO. 2231-2293 P ISSN NO. 0976-4003

The Mononuclear Phagocyte System In Health And Disease

[1] S.Leena Sankari
[2] N. ARAVINDHA BABU
[3] Mahaboob Kadar Masthan
[4] Tathagata Bhattacharjee

[1,2] Associate Professor
[3] Professor and Head
[4] Post Graduate Student
Department of Oral Pathology & Microbiology,
Sree Balaji Dental College & Hospital, Chennai.

Address For Correspondence:
Dr. S Leena Sankari, Associate Professor,
Department of Oral Pathology and Microbiology.
Sree Balaji Dental College & Hospital, Chennai-600100
Tamil Nadu, India
e-mail : drleena.sankari@gmail.com
Phone-09840591791

Submission : 11th September 2012
Accepted : 28th January 2013

Quick Response Code

Abstract
The mononuclear phagocyte system (MPS)) consist of cells which are derived from bone marrow hematopoietic stem cells, blood monocytes and cells which are associated with the connective tissue framework of the liver, spleen, and lymph nodes. Previously this system was known as reticuloendothelial system. Mononuclear phagocyte system is critical for immunity as well as homoeostasis. Any disturbance in this system leads to state of various diseases.

Key Words
Phagocyte, Macrophage, Monocyte, Immune.

Introduction:

The mononuclear phagocyte system (MPS) is a part of the immune system that consists of cell family derived from progenitor cells in the bone marrow. These cells differentiate to form blood monocytes and circulate in the blood and at last they enter tissues to become resident tissue macrophages[1]. In the last four decades there are several researches to detect the ontogeny of mononuclear phagocytes and it was found that there are several cellular similarities between the morphological, cytochemical and functional characteristics of monoblasts, pro-monocytes, monocytes and macrophages, so all these cells were recognized as members of a single cell family, collectively called mononuclear phagocytes and the concept of the mononuclear phagocyte system was developed.[2]

In the late 19th and early 20th centuries, eminent pathologist K.A.L. Aschoff along with several other pathologists, included macrophages (histiocytes) along with reticulum cells and phagocytic endothelia and proposed the concept of reticuloendothelial system, as all of these cells could internalize certain dyes. Later, however, it was found that endothelial cells are not phagocytes and the uptake of dyes is based on a completely different cellular mechanism. Hence they abandoned the term 'reticuloendothelial system'.[2],[3] In contrast van furth gave the concept of mononuclear phagocytic system and stated that all macrophages, either present in infection or residing in tissue at normal steady state derived from monocytes.[3]

Origin of mononuclear phagocyte system: Regarding formation of variety of blood cell from hematopoietic stem cell three models have been proposed. These are hierarchical model, stochastic model and sequential model.[2]

As per hierarchical model hematopoietic stem cell commits to a common myeloid precursor and a common lymphoid precursor. The common myeloid precursor generates precursors of megakaryocytes, erythrocytes, granulocytes and monocytes / macrophages, whereas precursor for T- and B-cells and NK cells derived from common lymphoid precursor.[2]

Stochastic model suggests that the commitment decision of haematopoietic precursors is stochastic which can occur at any time. [2]

Sequential model shows that precursors derived from hematopoietic stem cells express the potential for megakaryocyte, erythrocyte, granulocyte, monocyte, B-cell, T-cell and NK cell development progressively.[2]

In foetus Haematopoietic stem cells originate from the yolk sac which migrate to the foetal liver and develop immature mononuclear phagocytes.[2] On the other hand in adults bone marrow hematopoietic stem cells give rise to monoblast which differentiate into promonocyte, monocyte and macrophages which is short lived, nondividing terminating cells of mononuclear phagocyte system. Beside macrophages which are present during inflammation there are certain macrophages which are present under normal steady condition. These are microglia in brain, osteoclasts in bone and tissue macrophage such as kupffer cells in liver; histiocytes in connective tissue and skin; free macrophages in body cavities; free and fixed macrophages in spleen, lymph node, bone marrow and thymus; and macrophages in other various tissues.[3]

Current models states that blood monocytes, majority of macrophages and most dendritic cells originate in vivo from hematopoietic stem cell-derived progenitors which is having myeloid restricted differentiation potentiality.[4]

Genetic control of generation of the MPS:

Exact interaction between specific gene and transcription factors is very essential for specification of blood cell lineage. Colony stimulating factors (CSFs) are secreted glycoprotein. They bind to receptors which are located on surface of hematopoietic stem cells and activate intracellular signalling pathway to proliferate and differentiate blood cells, especially white blood cells. There are main three natural colony stimulating

factors. These are colony stimulating factor- 1 (CSF-1) , colony stimulating factor-2(CSF-2) and colony stimulating factor-3(CSF-3).CSF-1 is also called macrophage colony stimulating factor(MCSF). They secret cytokine, which take major role in differentiation of macrophages from hematopoietic stem cells. In mononuclear phagocyte system colony stimulating factor-1(CSF-1) play the key role in proliferation and differentiation of all mononuclear phagocytic cells.CSF-1 binds to it receptor protein colony stimulating factor -1R (CSF-1R) on the cell surface and is encoded by c-fms proto oncogene for activation of cells.[2] The expression of CSF-1R gene is dependent on the expression of transcription factor PU-1.Hence expression of PU-1 as well as CSF-1R is very critical for myelopoiesis, macrophage differentiation as well as generation of mononuclear phagocyte system.[2]

PU.1 is called master transcription factor. It is not only essential for development of myeloid lineages but it also prevents the activation of genes which plays major role to differentiate other pathways.[2]

Cells of mononuclear phagocyte system :

Monocytes - Monocytes are produced from its hematopoietic precursors stem cell monoblasts. They are the largest corpuscles in the blood. About one to three days monocytes circulate in the bloodstream and then move into tissues throughout the body. In the tissues they mature into different types of macrophages at different anatomical locations. Monocytes in tissues differentiate into tissue resident macrophages or dendritic cells. Monocytes, their macrophage and dendritic-cells serve mainly three functions in the immune system. These are phagocytosis, antigen presentation, and cytokine production. Monocytes migrate from blood to tissue during infection are equipped with pathogen recognition receptors and chemokines receptors.

Monoblasts & promonocytes - Monoblast develop from pluripotent hematopoietic stem cells which in turn mature into pro monocytes, monocytes and at last into macrophages.

Macrophages: Monocytes differentiate into macrophages in tissue and helps in innate as well as adaptive immunity. They are resident phagocytes in lymphoid and non-lymphoid tissues and help in clearing of apoptotic cells and production of growth factor. A broad range of pathogen recognition receptors are attached with macrophages which make them efficient for phagocytosis and production of inflammatory cytokines.[5]

Dendritic cell: Dendritic cells are antigen presenting cells. They capture antigen, process them and present them on the cell surface. Along with regulation of adaptive immune response dendritic cells maintain B cell function and recall response. In human the dendritic cell originates from myeloid precursor consider as classical dendritic cell whereas plasmacytoid dendritic cells have lymphoid lineage.

Classical Dendritic cells (cDCs): The main functions of these cells are antigen processing and its presentation. They show high phagocytic activity when they are immature whereas mature cells shows high cytokine producing capacity. [6],[7] Classic dendritic cells are present in human circulation and move from tissues to the T-cell and B-cell zones of lymphoid organs via afferent lymphatics and high endothelial venules. They are generally short-lived, replaced by blood-borne precursors and T cell responses both in the steady-state and during infection. [8],[9]

Plasmacytoid Dendritic Cells (PDCs): These cells have lymphoid lineage and are relatively long lived compared to classical dendritic cells. These cells are present in bone marrow as well as all peripheral organs and produce massive type I interferons (IFN), as a result they respond well against viral infections. Plasmacytoid dendritic cells carry immunoglobulin as well as they act as antigen presenting cells and control T cell responses[10].

Function of mononuclear phagocyte system:

The main function of mononuclear phagocyte system is phagocytosis. It is mainly done by Macrophages.The antigens liberated by macrophages activate the B lymphocytes & helper T lymphocytes. Cells of this system Secrete IL-1, IL-6, and IL-12 in which IL-1 accelerates the maturation & proliferation of specific B lymphocytes & T lymphocytes, IL-6 causes growth of B lymphocytes & production of antibodies whereas IL-12 influences the T helper cells. These cells also Secret TNF -alpha and TNF -beta. TNF-alpha causes necrosis of tumor & activates immune system on the other hand TNF-beta stimulates immune system & causes vascular response in addition. The cells secrets platelet derived growth factor (PDGF) which accelerates repair of damaged blood vessel & wound healing. Macrophages remove carbon particle & silicone; destroy senile red cells and hemoglobin. Macrophage also acts as an antigen presenting cell to sensitized T cell.

Disease associated with monocyte macrophage cell line-

Numerous human disorders are associated with abnormalities of cells which are having macrophage like origin.[11]

These are

- Mild blood monocytosis which may be associated with infectious, inflammatory or collagen vascular diseases.
- Neoplastic proliferation of histiocytes which are seen in monocytic leukemia,malignant histiocytosis.
- Histiocytic proliferation of unknown origin such as sarcoidosis,granulomatous vasculitides and Wegener granulomatosis.
- reactive proliferation secondary to infection as an example Tuberculosis.
- chemical exposure such as beryllium and zirconium salts. [11]

In monocyte - macrophage dysfunction syndrome there are subtle defect in macrophage function which impair host defence. These defects and its consequent situations are

- Chemotaxis - present in Neoplasia
- Abnormal degranulation - Chediak Higashi syndrome
- Abnormal oxygen metabolism - Chronic granulomatous disease
- Suppressor monocytes - Miliary tuberculosis
- Suppressor monocytes - Lepromatous leprosy
- Chemotaxis,Suppressor monocytes - Disseminated fungal infection
- Chemotaxis,Microbial killing - Glucocorticoid treatment
- Neoplastic proliferation of macrophages - Hodgkin disease [11]

A number of recent studies showed that there are macrophage dysfunctions in

neoplastic diseases.These dysfunctions can be considered in relation to cell maturation, migration and chemotaxis, phagocytosis, cytotoxicity and related phenomenon, lysozyme secretion and macrophages in malignant tumors.[12]

Scanning electron microscopic studies showed that the surface appearance of macrophages were more varied in lymphoma.[12]

It has also been demonstrated that patient with disseminated carcinoma had fewer macrophages whereas in localised carcinoma there were increased monocytic mobilisation.

Increased phagocytic activity in monocyte/macrophages is related to untreated hodgkin's disease.On the other hand decreased phagocytic activity is related to stage III and IV hodgkin's disease.[12]

There are also lysozyme secretion disorder in malignancy. Favourable clinical condition showed enhanced lysozyme secretion whereas depressed lysozyme secretion is related to poorer prognosis.

It has also been proved that presence of macrophages are more in non metastasizing tumour and less in metastasizing tumour.[12]

Alzheimer disease is also related to MPS disorder. Neurotoxicity in Alzheimer is related to higher brain A beta levels. Monocytes accumulate at sites of A-beta deposition is an initial attempt to clear these deposits and stop or delay their neurotoxic effects. Interaction of CCL2(A major monocyte chemokine), with its receptor CCR2 regulates mononuclear phagocyte accumulation and its clearance. CCR2 deficiency leads to lower mononuclear phagocyte accumulation as a result, higher brain A-beta levels and neurotoxicity.[13]

Conclusion:

This article has first, briefly gives a review and current concept on reticuloendothelial system and mononuclear phagocyte system.

In particular, the review pointed out the cells of mononuclear phagocyte system, how these are developed and its genetic control. It has also described the essential role of macrophages between health and disease.

Better understanding of mononuclear phagocyte system will provide us various scope of further investigation in the field of its clinical and basic research.

References

1. Van Furth. R. Production and migration of monocytes and kinetics of macrophages. In: Van Furth R. editor. Mononuclear Phagocytes Biology of Monocytes and Macrophages. Dordrecht: Kluwer Academic Publishers;1992. p. 3-12.
2. Zong-Liang Chang. Recent development of the mononuclear phagocyte system: in memory of Metchnikoff and Ehrlich on the 100th Anniversary of the 1908 Nobel Prize in Physiology or Medicine. Biology of the Cell. 2009; 101: 709-721.
3. Kiyoshi Takahashi. Development and differentiation of macrophages and related cells historical review and current concept. Journal of clinical and experimental hematopathology.2001 May; Vol 41 no 1.
4. Frederic Geissmann, Markus G. Manz, Steffen Jung, Michael H. Sieweke, MiriamMerad, and Klaus Ley. Development of monocytes, macrophages and dendritic cells. Science. 2010 February 5; 327(5966): 656-661.
5. Gordon S. Pattern recognition receptors: doubling up for the innate immune response. Cell. 2002 Dec 27;111(7):927-30.
6. Banchereau J, Steinman RM. Dendritic cells and the control of immunity. Nature 1998 Mar 19; 392:245-52.
7. Mellman I, Steinman RM. Dendritic cells: specialized and regulated antigen processing machines. Cell.2001 Aug 10; 106:255-8.
8. Liu K, Victora GD, Schwickert TA, Guermonprez P, Meredith MM, Yao K, Chu FF et al. In vivo analysis of dendritic cell development and homeostasis Science. 2009 Apr 17;324(5925):392-7. Epub 2009 Mar 12.
9. Claudia Waskow, Kang Liu, Guillaume Darrasse-Jèze, Pierre Guermonprez, Florent Ginhoux, Miriam Merad et al. The receptor tyrosine kinase Flt3 is required for dendritic cell development in peripheral lymphoid tissues. Nature Immunology.2008; 9: 676 - 683. Published online: 11 May 2008.
10. Colonna M, Trinchieri G, Liu YJ. Plasmacytoid dendritic cells in immunity.Nat Immunol.2004Dec; 5:1219-26.
11. Mononuclear phagocytes: Immunological functions and disease implications-Medical Staff Conference, University of California, San Francisco. West J Med.1979Feb; 130:153-157.
12. Rj sokol, G hudson. Disordered function of mononuclear phagocytes in malignant disease. J Clin Pathol. 1983;36:316-323.
13. Hickman SE, El Khoury J.Mechanisms of mononuclear phagocyte recruitment in Alzheimer's disease. CNS Neurol Disord Drug Targets. 2010 Apr;9(2):168-73.
14. Auffray C, Sieweke MH, Geissmann F. Blood Monocytes: Development, Heterogeneity, and Relationship with Dendritic Cells. Annu Rev Immunol. 2009;27:669.
15. Swirski FK, Matthias Nahrendorf1,Martin Etzrodt, Moritz Wildgruber,Virna Cortez-Retamozo, Peter Panizzi, et al. Identification of Splenic Reservoir Monocytes and Their Deployment to Inflammatory Sites Science. 2009 31 July: 612-616.
16. Corcoran L, Ferrero I, Vremec D, Lucas K, Waithman J, O'Keeffe M et al. The lymphoid past of mouse plasmacytoid cells and thymic dendritic cells J Immunol.2003 May 15;170:4926-32.
17. Bonifer, C. and Hume, D.A. The transcriptional regulation of the colony-stimulating factor 1 receptor (csf1r) gene during hematopoiesis. Front. Biosci. 2008.13: 549-560.
18. Sasmono R.T., Oceandy D., Pollard J.W., Tong W., Pavli, P.Wainwright et al .A macrophage colony-stimulating factor receptor-green fluorescent protein transgene is expressed throughout the mononuclear phagocyte system of the mouse. Blood. 2003 Feb 1;101(3):1155-63. Epub 2002 Sep 12
19. DeKoter, R.P., Walsh, J.C. and Singh, H. PU.1 regulates both cytokine-dependent proliferation and differentiation of granulocyte/macrophage progenitors.EMBO J 1998; 17:4456-4468.
20. David A. Hume, Ian L. Ross, S. Roy Himes, R. Tedjo Sasmono, Christine A. Wells et al. The mononuclear phagocyte system revisited. J. Leukoc. Biol. 2002;72:621-627.

Source of Support : Nill, Conflict of Interest : None declared