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Review Article

Review on Macrophages: A Novel Approaches to Targeting Liver

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ABSTRACT

Targeted drug delivery through macrophages is an attractive and modified technique to improve therapeutic efficacy for various infection, viral and inflammatory disease and macrophages are the differentiating cell having precursor monocytes ,promocytes and monoblast.In liver 80-90% of total body macrophages are present RES and kupffer cells are the site of macrophages in liver where they present and RES having the sugar receptor highly phagocytosed and important for determination of foreign particles ,macrophages having self defense mechanism. Other techniques are receptor mediated targeting, negatively charged drug delivery Opsonization means the process by which a particular antigen are rendered more susceptible to phagocytosed. Opsonic material are used to enhance the extent of phagocytosis .Mannose binding lectins coat the microbes as opsonins and enhance neutrophil reactivity against them.RES ,phagocytosis membrane having negative charge in it and so as its target ,which make it difficult to come closer .so at the time of evaluation one must check the negative charged of target by zeta potential.

INTRODUCTION

Migraine is a recurrent incapacitating neurovascular disorder characterized by attacks of debilitating pain associated with photophobia, phonophobia, nausea and vomiting [1]. Almotriptan Malate (ALM), a triptan derivative is a novel selective 5-hydroxytryptamine$_{1B/1D}$ receptor agonist indicated for the acute treatment of migraine with or without aura in adults [2].During an attack, the blood vessels in the brain dilate and then draw together with stimulation of nerve endings near the affected blood vessels. These changes in the blood vasculature may be responsible for the pain. However, the exact cause of migraine, whether it is a vascular or a neurological dysfunction–still remains unclear.

Targeted drug delivery system is the goal oriented drug delivery in which the delivery is designed in such a way that it only signifies targeted compartment, either with the help of carrier, ligand, polymer, proteins (components through which the drug can be targeted) or by altering the molecular weight, size or shape of formulation.

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The science of targeted drug delivery is burgeoning with new information and explosive growth of technology and methodology in this area. .Targeting molecules can be antibody or non-antibody ligand .The delivery of drug can be done with the help of molecule that bind either with receptor or antigens targeting[1],[2] .Liver is the body's second largest organ; only the skin is larger and heavier, weighing about 1.4kg in an average adult. Liver having the capability of regeneration of damaged tissue .liver is responsible for various function as digestion, metabolism and immunity.[3]A complete failure of liver causes death of individual. Macrophages were widely distributed in all vertebrates and invertebrate's .The name macrophages first given by Metchnikoff in 1892 on the basis of phytogenetic studies Liver macrophages are locates in kupffer cells and RES. Macrophages play a key role in the immune response, protecting organisms against infection and regulating the development of inflammation in tissue. Macrophages differ depending on where they are located and which tasks they perform cond. The granulocyte macrophage colony stimulating factor gene is a potential candidate for the treatment of different pathological conditions [4]

Target drug delivery [5]

Target drug delivery as the name indicates is specific about an organ or cells implies for selective and effective localization of pharmacologically active moiety preselected target in therapeutic concentration. Thus minimizing toxic effects and maximizing the therapeutic effect. The concept of targeting was first specified by Paul enrlich,who proposed drug delivery as magic bullets .Gregoriadls,1981 described drug targeting using novel drug as old drug in new clothes.

Carriers used in drug targeting

- Colloidal carrier: microsphere, noisome and vesicular system
- Cellular system: lipoproteins, micelles
- Polymer based system: soluble synthetic, biodegradable
- Macromolecular carrier: proteins, glycoprotein

Methods of drug targeting

Passive targeting*:* Results in the formation of complex i.e. drug carrier complex, which avoid elimination due to body defense mechanism like metabolism, opsonization and excretion this complex will circulate in the blood and get attached to its targeted site due to property of drug. The properties are molecular weight, molecular size, nature of surface and surface charge. e.g. the sinus endothelium of liver where capillaries having open fenestration attachment of drug after escape from the blood site [6].It is possible to achieve polymeric drug concentration, 10 to 50 fold higher at tumor site than in normal tissue It demonstrated the principle of passive targeting of colloidal particles to tumors [7].

Inverse targeting*:* In this the RE System take colloidal carrier to achieve its targeting, where pre administration of blank colloidal carrier is done, for saturation of RES.

Active targeting*:* active targeting includes the delivery of drug through antibody, antigens, receptors and proteins. Which are either uniquely expressed or over expressed on target cell populationligand such as peptide for nevosculature targeting [1],[2].

Types:

First order targeting: Targeted drug to organ or system increased chances of *in-vivo* targeting. E.g. eye, lymphatic

Second order targeting: Delivers to specific type of cell or tissue tumor cell not to normal cell E.g. - selective hapatocytes or kupffer cells in liver

Third order targeting: drug delivery to intracellular site if target
E.g. –ligand mediated drug delivery

Liver

Anatomy and physiology of liver*:*

Most of the liver's mass is located on the right side of the body where it descends inferiorly toward the right kidney. The liver is made of very soft, pinkish-brown tissues encapsulated by a connective tissue capsule. Liver is triangular in shape and covered by peritoneum mainly divided into four lobes: right lobe, left lobe, quadrate lobe and caudate lobe, the right and left lobe separated by falciform ligament [3].

Liver cells*:*

Lobules:

The internal structure of the liver is made of around 100,000 small hexagonal functional units known as lobules. Lobules are the functional unit, which made many lobes of liver. Liver consisting of various cells i.e. Hepatocytes and kupffer cells, blood vessels connected by various capillary like tubes and have larger space lined by endothelium called sinusoids [3].

Hapatocytes: these are specialized epithelial cells (hepatikos –liver)arranged around central vein ,that line the sinusoids and make up the majority of cells in the liver,70-85% of the liver's cytoplasmic mass[8]. Hapatocytes perform most of the liver's functions – metabolism, storage, digestion, and bile production. Tiny bile collection vessels known as bile canaliculi run parallel to the sinusoids on the other side of the hapatocytes and drain into the bile ducts of the liver Hapatocytes make up [3].

Kupffer cell: Kupffer cells are first protective cellular line in liver sinusoid and localized in the vicinity of hepatocytes.it is a location in liver where macrophages resides, about 80-90% of macrophages are present in liver. Function of kupffer cells is ,essential in liver injury as macrophages engulf the foreign material (bacteria, virus or any infectious material),in inflammation , KCs are important source of various inflammatory-related mediators, such as poor anti-inflammatory cytokines (TNF-_, IL-6, IL-10), chemokines(MCP-2, IL-8, IP-10) and other inflammatory-related mediators

(prostanoids, nitric oxide, reactive oxygen species)[9].

Sinusoidal endothelial cells: sinusoidal cells having large pores which allow most of the protein to freely pass through it. These pores are bidirectional by which the proteins created by liverand other substance stored or processed by liver can also be passing to the blood [10].

Bile duct epithelial cells: these are responsible for secreting bile into small intestine to break down fat [10].

Ito cells: located in space of disse.Plays essential role at the time of liver injury, as these cells transform into the collagen and leads to liver fibrosis [10].

Function of liver [10]:

- Synthesizing most of plasma proteins, that circulate in the body
- It acts as a exocrine gland for Secretion of bile
- Plays prominent role in metabolism of various nutrients i.e. carbohydrates, proteins and fat
- Store house for various substance such as glucose, lipid, vitamins and iron
- Plays protective role by detoxifying sustance include drug and alcohol
- Helps in the removal of unwanted particulate from blood through the mediation of macrophages.

Macrophages:

In Greek macrophages means big eaters ,from makros large and phagein eat **[11]** .Macrophages produced from cells by differenciatiating mononuclear phagocyte system basically precursor of macrophages are monocytes promocytes and monoblast and these commonly together called granulocyte macrophages.**[12]**Macrophages can change their physiology and switch types in human and non obese people. Monocytes precursor of macrophages is not detected in vertebrates while vertebrates having both monocytes and macrophages. Origin of macrophages from hematopoietic stem cell during yolk sac hematopoeisis and then differentiate from macrophage precursor cell through various pathways or stages, these pathways are granulocyte .macrophage colony forming cell and some derived from B-lymphoid **[13].**

Macrophage widely distributed in various organs and tissue throughout the body and the name first given by Metchnikoff termed large phagocytic cell and also describes their presence who received his Nobel Prize a century earlier the father of natural immunity. The concept of RES was given by Aschoff; include Histocytes as major members **[14]** Resident macrophages in the brain are known as microglia cells. Macrophages are found in various organ and different tissue where they localized having special function.

Table1: Macrophages are even coined with different names depending on anatomical location are as following [11], [15]

S.No	Location of macrophage	Specific name
1	Lungs	Alveolar macrophage
2	Liver	Kupffer cells
3	Connective tissue	Histocytes
4	Spleen	Sinusoidal (free and fixed macrophage)
5	Bone marrow	Fixed macrophages
6	Brain (Neural tissue)	Microglia
7	Bone	Oestoclast
8	Skin	Langerhans cells

Concept of MPS that all macrophages are derived from monocytes was studied by Langevoort, Cohn, hirsh, van Furth and many other researchers. Committed cells within the mononuclear phagocyte lineage progress through a series of defined morphologically-distinct stages; a common progenitor called granulocytes macrophages giving rise to Monoblast, promonocytes and then monocytes which migrate into tissues [17].Although macrophages in tissues have many features in common, including extensive lysosomes, stellate morphology and location relative to epithelia, they are nevertheless extremely heterogeneous in terms of function and surface marker expression. Our knowledge of this plasticity is most extensive for the mouse. Two different transgenic lines have been used to delineate the MPS; the CX3CR1-EGFP and csf1r-transgenes Molecules expressed on the cell surface are of particular functional interest because they determine the ability of MPS cells to interact with pathogens, and with other cell types, to generate an appropriate innate and acquired immune response [18]

Function of macrophages:

Life of macrophages in kupffer cells are 3.8 days. Monocytes derived macrophages are short lived in peripheral tissue and die within 2 weeks.

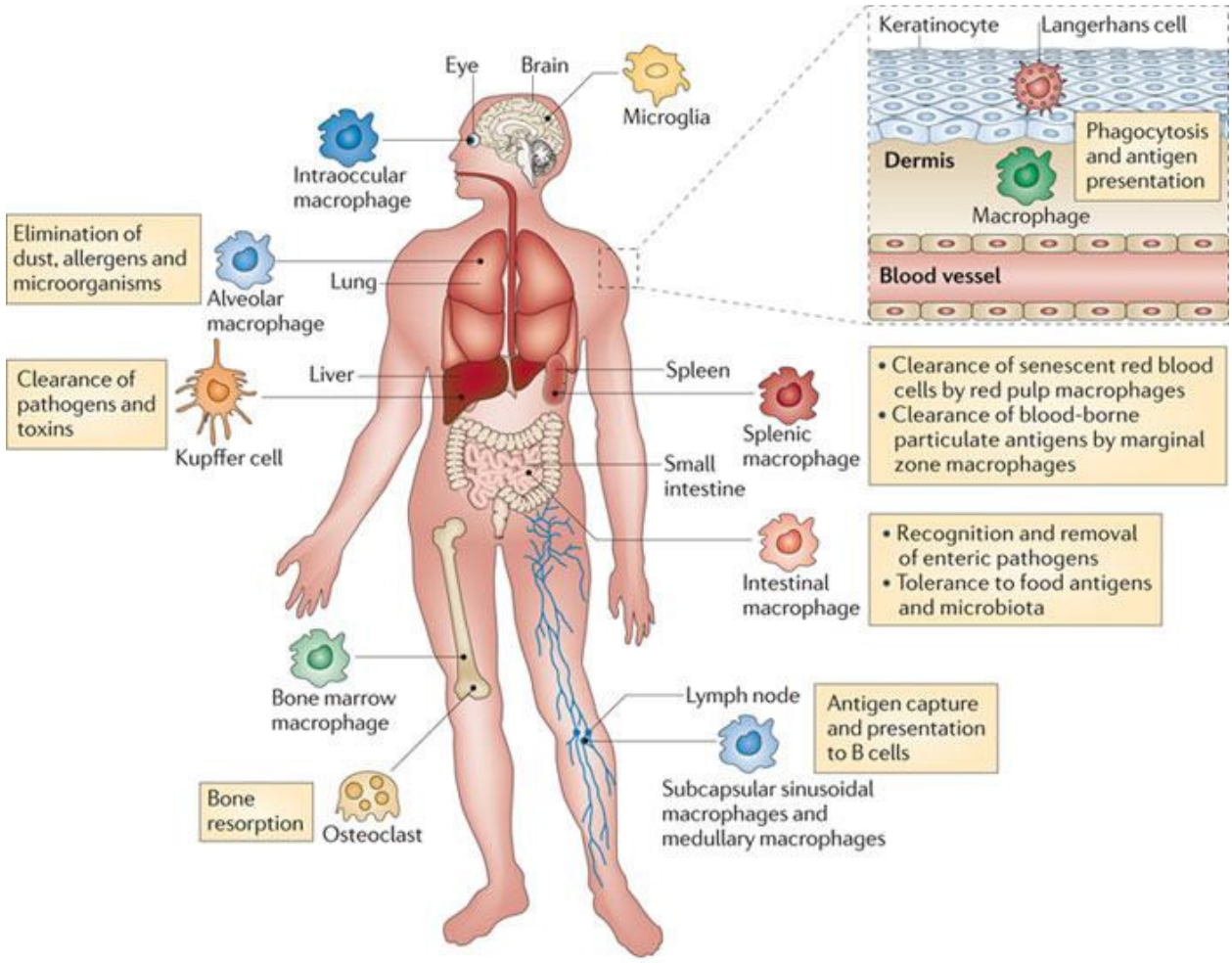


Figure 1: Macrophages location in various part of body and where they resides [16]

Hemopoeitic stem cells
↓
Committed stem cells BONE MARROW
↓
Monoblast
↓
Promocytes
↓
Monocytes PERIPHERAL BLOOD
↓
Monocytes TISSUE
↓
Macrophages
↓
Normal steady state (lung,liver,spleen etc)

Scheme 1: Mononuclear phagocytosis system (MPS) [14]

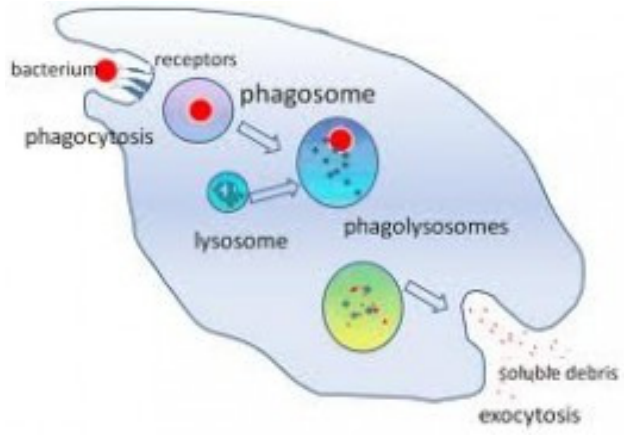
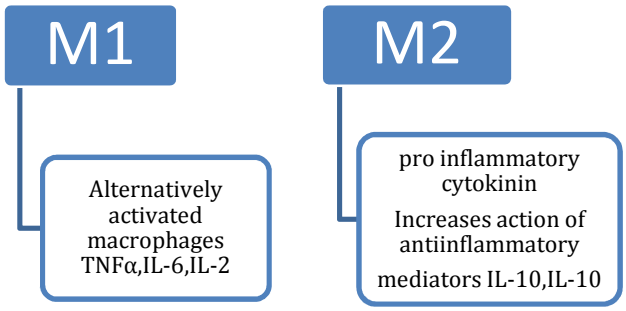


Figure 2: Working of macrophages [19]

Targeting to liver macrophages:

Importance of liver macrophages [13], [20], [18],[21]

As liver has a simple structure composed of hepatic parenchymal cell and sinusoidal cell: kupffer cells (macrophages) are present in hepatic sinusoidal lumen and monocytes circulate in peripheral blood. Called blood monocytes which are around 20% of the peripheral blood mononuclear cell (PBMC) fraction. The macrophages are professional phagocytes as having the self defense mechanism. People in developing countries having higher risk of acute liver failure due to viral infection and about 50% is due to drug induced liver injury.Identification of macrophages and CD8+ T cells, which are actively recruited to the injured liver, the contribution of macrophages to the liver progenitor cells response in rats that were treated with gadolinium chloride and subjected to bile duct ligation was deemed to be crucial as it was almost completely suppressed. That conclude of finding that macrophages are the principal initiators of the liver progenitor cells response liver macrophages are a very heterogeneous population it is possible that invading macrophages adapt to the liver environment and adopt features of KCs. This could explain the increased numbers and intermediate phenotype of CRIg+CD11b+ cells .Activation of immune responses in drug induced liver infection involves activation of cell ,adaptive and innate immune system including resident macrophages i.e. kupffer cells in liver, which are serve as a first line defense against particulates and immunoreactive material which passes from GI tract via portal vein circulation. Kupffer cells are highly poised for phagocytosis .Major cellular component of phagocytosis is reticular endothelial system also termed as mononuclear phagocytic system. peripheral blood monocytes when enter into liver get maturation and have phenotype characteristic of tissue macrophages which are very plastic in nature and having functional activity of metabolism and immune environment macrophages are subcategorized into two types which are M1 and M2. Multiple studies have shown that alternative activated M2macrophages produce TGFβ.



Approaches to target liver macrophages, using carriers:

Targeting to liver macrophages is a promising drug delivery system as liver is a vital organ and plays important role in metabolism digestion, enzymes secretion and various other body function [3],[8].Macrophages play a important role in treatment of the of upcoming several microbial diseases affecting visceral organs such as liver and spleen [22]so via using different technique one can deliver drug to macrophages either by binding to specific receptor present in liver or by targeting to liver cells kupffer cells where macrophages resides by ,using opsonins material or polymers [9].

Liposome: Liposome used from ago for the delivery of macrophages .liposome having lipid bilayer structure ranging 20nm in size and microscopic in nature, they attaches to cellular membranes such as endothelia where on adhesion they release their drug content [23].liposome adsorption to the cell surface is rate limiting step ,detailed study on liposome as carrier for macrophages were given by Kelly [24].liposome deliver biologically to mononuclear phagocytes, and studied widely to target macrophages and inclusion of negatively charged phospholipids enhances the phagocytic activity of liposome [12].

Micro particles:

Micro particles are particulate dispersion comes under the range of1-1000µm.by using different method microspheres, microcapsule and micro

particle are prepared[25] these can be made by using biodegradable ,non biodegradable polymers ,used widely for delivering of macrophages by phagocytosing the particle by coating of opsonins material [26],[12].

Nanoparticles: nanoparticles varies in the range of 10-1000nm.due to their small size they easily recognized by RES and phagocytosised by macrophages in liver and spleen. [27]Hydrophobic surface of nanoparticles helps it to easily bind with opsonins, for prolong action hydrophilic surface is used[28].targeted drug delivery by using nanocarriers at diseased site by passive or active targeting is admirable as it reduces dose and increases therapeutic efficacy [29].

Enhanced phagocytosis using Opsonization technique: coating with opsonins

Phagocytosis means to engulf occur in macrophages, monocytes , dendrite cells and in fibroblast endothelial ,non endothelial cells called professional and non professional phagocytosis respectively [30][31]Opsonization is a process by which particular antigens are rendered more susceptible to phagocytosis, foreign particle attaches to protein and prone to increase phagocytosis called opsonins ,which are easily recognized by macrophages.eg of opsonins are immunoglobin ,bovine serum albumin [32]gelatin, human fibrinocetin,bovine tuftsin, enhance phagocytosis [12]

Hepatic receptor mediated targeting [8] [12],[33]: After several research researchers come into conclusion that macrophages having different types of receptor which helps the carrier to interact with macrophages specifically for better phagocytosis in liver macrophages posses various receptors such as

- Fc receptor
- Mannose receptor or N acetyl galactosyl mannose- terminated- (neo)ligand
- Fibronectein lipoprotein receptor
- Hyaluran receptor
- Scavenger receptor

As hepatic macrophages having various receptors and each receptor have specific properties as Fc receptor, present on the surface of macrophages and neutrophil and promotes ligand incorporation on surface of macrophage. Fc receptor via their Fc region or to target the antigen on the cell surface.

Mannose receptor: Expressed excessively on hepatic endothelial cells and limited on sinusoidal and kupffer cell of liver. Directly bind with the prokaryotic cells having mannen and orosomucoid content on its cell wall and being exploited by neoglycoproteins.present in mature macrophages.

Fibronectein lipoprotein receptor: being endogenous in nature, lipoproteins and their Apo-lipoproteins are non-immunogenic ligand and escape recognition by RES system.Acylated LDL as a ligand could be exploited to target endothelial liver cells exploring scavenger receptor.

Scavenger receptor: scavenger receptor are discovered 1979 during attempts to learn how cholesterol from low density lipoprotein accumulates in macrophages expressed exclusively on endothelial liver cells and macrophages ,mediate uptake of variety of proteins or macromolecules complexes. High binding sites conserved on macrophages negatively charged vehicles are used so the negatively charged molecule bind via scavenger receptor due to chemical modification by coupling of two molecule net negative charge will form and act as a ligand for scavenger receptor.

Proteins coating [8]: As receptor having specific properties that's why specific carrier are used according to receptor specificity. as modified proteins are used such as albumins which are directly phagocytosised by macrophages.

Targeting to kupffer cells and RES [8], [9] [20]: As discussed above those liver macrophages resides in kupffer cells and an extent to RES, so by targeting to these cells macrophages targeted automatically. Mainly targeted anti inflammatory and immunosuppressive drugs.

Therapeutic importance of targeting macrophages: macrophages having self defense mechanism phagocytosised the foreign particle either bacteria or viruses. Macrophage targeting using antiviral drug for HIV treatment ,is important as macrophages are known to be as reservoir of viruses.[34] Targeting to macrophages is an promising method for infectious disease, rheumatoid arthritis ,parasitic disease .macrophage targeting can occur for liver disease due to alcoholism ,acute liver failure ,fibrosis ,cirrhosis, hepatitis, inflammatory disease, protozoal such as leishminiasis, geriadisis, amoebisis by using modified carrier as nanoparticles ,liposomes, microspheres. In inflammation, macrophages have three major function; antigen presentation, phagocytosis, and immunomodulation through production of various cytokines and growth factors [35].

CONCLUSION

From entire review it is concluded that targeted drug delivery has crossed the infancy period and now touching the height of success and growth from pharmacy point and targeting to macrophages is a newer and advanced method for better results in various infectious disease. as macrophages are the most functionally diverse cells of the Hemopoeitic system found in all tissues having versatile cells that play central role against foreign particles and various other biological proccesses.targeting to liver macrophages is a promising approach for future aspect as liver is the most vital organ responsible for various body function. So targeting to macrophages is specific and more restricted due to its phagocytic receptor like mannose receptor, Fc receptor after specific Opsonization with antibody and the various carriers used for drug delivery such as liposome, nanocarriers and microspheres.

REFERENCES:

[1] Plank C, Oberhauser B, Mechtler K, Koch C and Wagner E. The influence of endosome-disruptive peptides on gene transfer using synthetic virus-like gene transfer system. J Biol chem1994; 269: 12918-24.

[2] Plank C, Zauner W and Wagner E: Application of membrane-active peptides for drug and gene delivery across cellular membranes. Adv Drug Deliv Rev Rev. 1998; 34(1): 21-35.

[3] Tortora. Principles of anatomy and physiology. 8th edition: 777-781.

[4] Salva E, Turan SO and Akbuğa J. Increased *in vitro* Cell Proliferation by Chitosan/pGM-CSF Complexes. Indian J Pharm Sci. 2011; 73(2):131-8.

[5] Vyas SP. Targeted and controlled drug delivery; novel carrier system.rev 1st edition.p.p38-79.

[6] Frankel Alan D. Cellular uptake of tat protein from human immunodeficiency virus. Cell.1988; 55: 1189-93.

[7] Maeda H. Tumor-selective delivery of macromolecular drugs via the EPR effect: background and future prospects, Bioconjugate Chem. 2010; 21(5):797-802.

[8] Klaas poelstra, Jai Prakash and Leonie Beljaars:Drug targeting to diseased liver, J Control Rel. 2012;161:188-97.

[9] Qiao Yang, Yu Shi, Jiliang He and Zhi Chen. The evolving story of macrophages in acute liver failure. Immunology Letters. 2012; 147:1-9.

[10] Marieb EN. Human anatomy and Physiology.5th edition. 2001.

[11] Vega MA, Corbí AL. Human macrophage activation: Too many functions and phenotypes for a single cell type, Inmunologia. 2006; 25:248-72.

[12] Fakhrul ahasan, Isabel P. Rivas, Mansoor A. Khan,Ana I, Torres Suarez. Targeting to Macrophages: role of physicochemical properties of particulate carriers–liposome and microspheres–on the phagocytosis by macrophages. J Control Rel. 2002;79:30-39.

[13] Kiyoshi Takahashi. Development and differentiation of macrophages and related cells: Historical view and current concepts, J Clin Exp Hematopathol. 2000; 41:1-22.

[14] Aschoff L. Das. Reticulo endothelial system ergels inn med kinder herlked.1924; 26: 1-118.

[15] Sridhar Rao, P.N.:Cells and organs of immune system.dept of microbiology JJMMC. Devangere.www.microrao.com

[16] www.macrophages.com.

[17] Owais M Gupta and C.M: Targeted drug delivery to macrophages in parasitic infection. Current drug delivery.2005; 2: 311-318.

[18] QURESHI M. A: Role of Macrophages in Avian Health and Disease, Poultry Science. 1998; 77: 978–982 .

[19] https://www.google images.co.in

[20] Mark Barnes ,Laura J. Dixon, Zhang-Xu Liu, Hui Tang, Laura and E. Nagy: Macrophages and Kupffer Cells in Drug-Induced Liver Injury ,Elsevier Inc.2013,147-153

[21] Cornelia S. Viebahn: Invading macrophages play a major role in the liver progenitor cell response to chronic liver injury, Journal of Hepatology. 2010 ,53,500–507

[22] Sijumon Kunjachan: Chitosan based macrophage mediated drug targeting for the treatment of experimental visceral leishmaniasis, Journal of microencapsulation. 2011; 28 (4): 301-310.

[23] Sunil Kamboj: Vesicular drug delivery systems: A novel approach for drug targeting, International Journal of Drug Delivery. 2013; 5:121-130.

[24] Ciara Kelly, Caroline Jefferies and Sally-Ann Cryan. Targeted liposome drug delivery to monocytes and macrophages. J Drug Delivery 2011; 2011: 1-11.

[25] Padalkar abhay N. Microparticles an approach for betterment of drug delivery system, International Journal of Pharma Research and Development 2011;3:99-115.

[26] Tabata Y: .Phagocytosis of polymer microspheres by macrophages,Adv. polymeric.science.1990; 94: 107-141.
[27] Fabienne Danhier, Eduardo Ansorena, Joana M.Silva, Regis Coco et al. PLGA based nanoparticles: an overview of biomedical application, Journal of controlled release. 2012; 161: 505-522.
[28] Ganesh kumar, dhyani Archana and kothiyal Preeti. Nanoparticles: An Overview, Indian Journal of Novel Drug Delivery. 2013; 5(3):115-129.
[29] Jain Narendra K., Mishra Vijay and Mehra Neelesh Kumar. Targeted drug delivery to macrophages. Academia.edu. 2013: 726.
[30] Aderem. Mechanism of phaggocytosis in macrophages. Annual Rev Imunol.1999; 17: 593-623.
[31] Rabinovitch M.:Professional and non professional phagocytesan introduction. Trends Cells Boil.1995; 5: 85-87.
[32] Groves E. Molecular mechanism of phagocytic uptake in mammalian cell. Cell Molecular Life Science 2008; 65: 1957-76.
[33] Kaneda Y. Virosomes: evolution of liposome as targeted drug delivery system. Adv Drug Deliv Rev 2000; 43:197-205.
[34] Hillaireau Herve. Nanocarriers entry into the cell: relevance to drug delivery. Cellular and Molecular Life Science 2009; 66: 2873-2896.
[35] Fujiwara N. Macrophages in inflammation, Curr.Drug Targets Inflamm Allergy 2005; 4(3): 281-6.