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TARGETED DRUG DELIVERY SYSTEM TO MACROPHAGES

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Abstract

In appealing idea to increase the therapeutic efficacy of the encapsulated medicine is targeted drug delivery to macrophages. Thus, macrophages can be used to deliver drugs to specific areas of the body. Nanocarriers are able to go between various membrane barriers and deliver their drug cargo at infection sites. Since macrophages may prolong the circulation and release of pharmaceuticals, boost their stability and targeting capacity, lengthen their half-life, and decrease immunogenicity, they have been widely exploited in the development of drug delivery systems. Additionally, they are biocompatible anddegradability and offer a large number of surface receptors for tailored drug administration. Drugs or drug-laden nanoparticles can be injected into macrophages, macrophage membranes, or macrophage-derived vesicles to create macrophage-mediated drug delivery systems.Although these systems can be used to treat diseases like HIV infection, cancer, and inflammation, they still need to be improved upon because they were put together from many sources.It can consequently have a wide range of physical and chemical characteristics.

Keyword

Dendrimers, drug delivery, macrophages targeting, nanocarriers,nanoparticle.

Introduction:-

What are macrophages

Macrophages are a type of white blood cell that play an important role in the human immune system and carry out various functions including engulfing and digesting microorganism;clearing out debris and dead cells ;and stimulating other cells involved in immune function.

The majority of medications used in clinics have short half-lives, erratic blood concentrations, difficult removal from the body, poor targeting, and negative side effects. Numerous chemical and biological carriers that act as medication delivery systems have been created to address these drawbacks. Nano-drug delivery technologies have gotten a lot of attention among them as drug, gene, order to their high biocompatibility, minimal toxicity, and controlled release in vivo, vaccination carriers.[1]However, due to the fact that nanoformulations, like other exogenous biomaterials, are perceived as intruders by the immune system and are promptly removed from the circulation by the mononuclear phagocyte system, their applications have been restricted thus far (MPS).[2,3]Currently, the most popular way to decrease MPS clearance is to Add polyethylene glycol to nanoparticles (NPs) to change their surface (PEG).[4-6]In mammalian biology, macrophages have a number of functions, including innate immunity, cellular repair, and cellular homeostasis[7]

Numerous obstacles must be overcome in order to create effective drug delivery systems, including those related to drug solubility, effective targeting, in vivo stability, and hemolytic and cytotoxic effects. With several benefits, including increased solubility and bioavailability of hydrophobic drugs, high drug payload, prolonged half-life, improved therapeutic index, controlled release of bioactives, along with reduced immunogenicity, and toxicity, nanotechnology-based drug delivery systems are emerging as promising candidates to meet the need for new delivery.[8,9]

By increasing drug delivery to the target tissue and the target-to-non-target tissue ratio, targeted drug delivery systems promise to increase the therapeutic windows of medications. This reduces the lowest effective dose of the drug and the associated drug toxicity. Targeted administration is a particularly appealing strategy for bioactives with narrow therapeutic windows and/or active at very low concentrations due to the small number of receptor sites on any given tissue. Active and passive tactics are the two basic methods for delivering targeted drugs. The extravasation of the nanocarriers at the sick region, where the microvasculature is leaky, results in passive targeting. When stimulated, macrophages become activated, resulting in unique patterns of gene and protein expression.[10,11]

Sometimes when describing activated macrophages, an apparent M1/M2 dichotomy is used, which implies that macrophages are "polarised" to have either pro-inflammatory or anti-inflammatory phenotypes.[12]Populations of both M1 and M2 are present in some illnesses. There are macrophages[13-15]

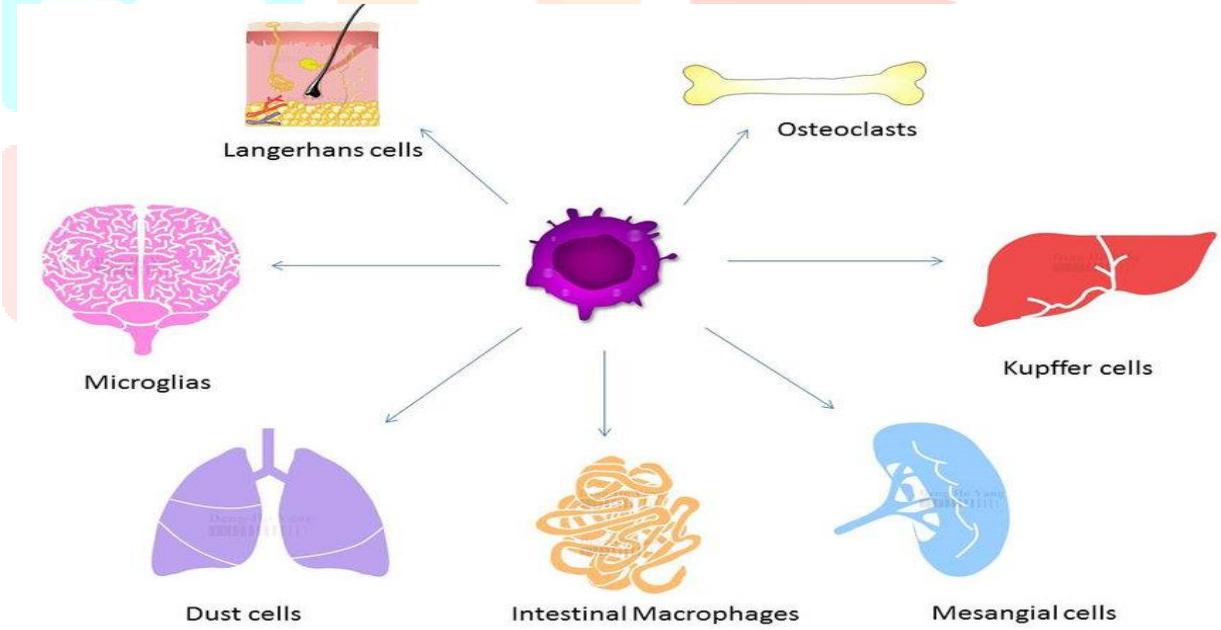

Fig.1 Macrophages exist in different tissues including lung, liver, and brain and have different functions. Different forms of macrophages include Kupffer cells in the liver, alveolar macrophages in the lung, osteoclasts in the bone, and microglia in the brain.

Similarly, macrophages may simultaneously and to varying degrees exhibit M1 and M2 markers, indicating intermediate activation levels. Due to the preservation of the cited literature, we should mention that the M1/M2 language is occasionally employed in this review as a shorthand explanation of macrophage activation.However, it has been demonstrated that macrophages with prolonged M1 phenotypes encourage autoimmune disorders because they secrete Th1 response elements, iNOS-dependent RNIs, chemokines, and cytokines such IFN-1, IL-12, IL-23, and TNF-Moreover, M1 macrophages exhibit poorIL-10 phrases. The strong expression of scavenging molecules, mannose and galactose receptors, ornithine, and polyamines, on the other hand, makes M2 macrophages typically anti-inflammatory.However, M2 phenotyped macrophages have been found in malignant tissues.connected to tumour metastasis and growthPro-inflammatory and anti-inflammatory therapies should be balanced.is frequently essential to how inflammatory disorders turn out (IDs).

Additionally, because macrophages play a role in innate immunity across the body, immunological reactions to drug action in IDs, particularly in cancer and autoimmune illnesses, are also covered.The tumour microenvironment is heavily populated with macrophages, which has a profound impact on tumour development, metastasis, and therapeutic treatment.

These characteristics make macrophages effective transporters of macromolecules like proteins and nucleic acids as well as tiny molecules like medicines. Utilizing macrophages, macrophage membranes, or macrophage-derived vesicles, biomimetic drug delivery methods take use of the extended circulation duration, plethora of surface receptors, and active targeting capacity of macrophages. They have a significant deal of promise to overcome the typical carrier materials' unfavourable immunogenicity, short cycle time, and poor biocompatibility. In this study, we provide an overview of macrophage-mediated drug delivery systems' development, sources, benefits, drug-loading techniques, and possible therapeutic uses. This can serve as a resource for more investigation.

1.1 Sources of macrophages:-

The blood contains monocytes, which can pass the endothelium barrier to become tissue macrophages, also referred to as mononuclear macrophages.[16 17]Alveolar macrophages and primary macrophages taken from animals, primarily those produced from bone marrow, are the two main groups of macrophages that have been examined.[18,19]Biological roles:-Blood is the most well-known source of tissue-resident macrophages.Since hematopoietic stem cells in the bone marrow are the source of monocytes,which commit to becoming a monocyte after a number of differentiation processesLineage.[20] Depending on their anatomical placements, tissue-resident macrophages perform a variety of tasks. The liver's kupffer cells play a major role in the elimination of waste, including the removal of germs and cell debris from the circulation.[21]According to a linear scale, macrophages can be divided intoM1 macrophages, which are typically activated macrophages, are at one extreme, while M2 macrophages, which are alternatively (activated macrophages) on the other.[20]Cellular or external triggers like interferon-γ (IFN-γ), tumour necrosis factor (TNF), and lipopolysaccharide (LPS) trigger to the M1 phenotype . To aid in the destruction of alien organisms and tumour cells, M1 macrophages secrete pro-inflammatory cytokines, oxygen and nitrogen radicals, and other chemicals.[20,22].As opposed to this, polarisation into the M2 phenotype entails interleukin-4 (IL-4), and IL-13, and Transforming growth factor (TGF-β), produce the immunosuppressive cytokine IL-10.[23].By taking part in tissue remodelling, scavenging for debris, and angiogenesis, M2 macrophages help to resolve inflammatory responses.[20,22,23].

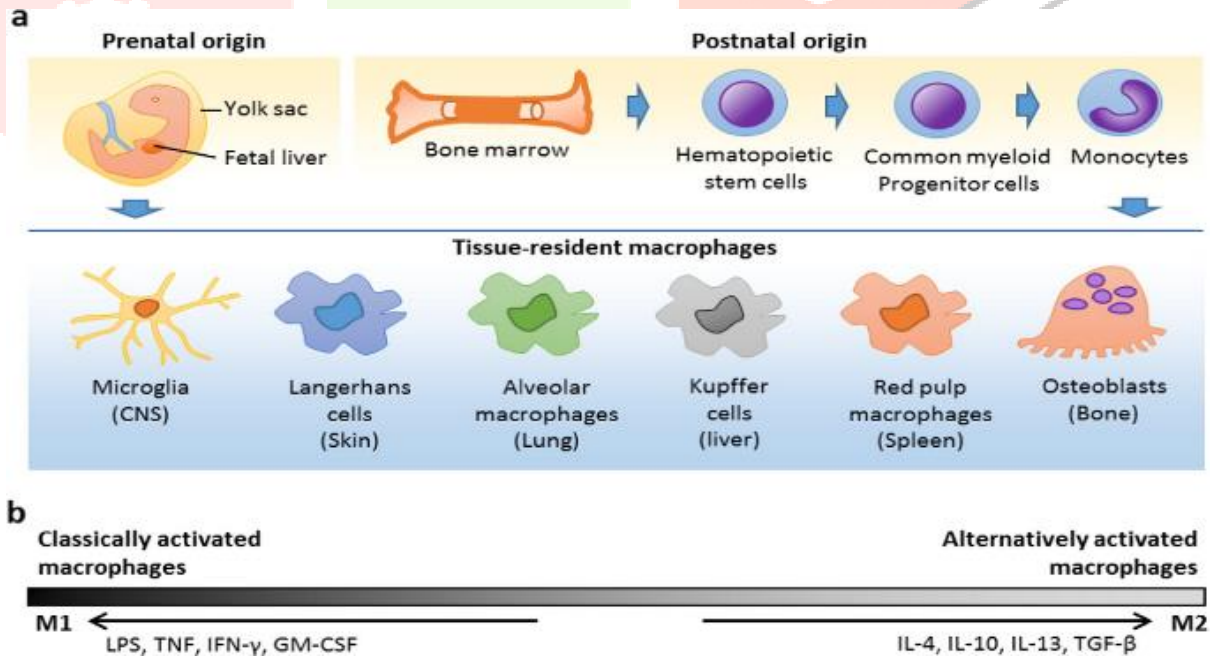

Fig. 2.(a)Tissue-resident macrophage origins include the most well-known, foetal liver-derived monocytes, as well as yolk sac-derived macrophages[21]. (b) A linear scale identifying the two macrophage activation states, M1 and M2, as well as the stimuli . Adapted figures from.[20].

Macrophages and tumor-associated macrophages (TAMs)tumor-enriched niches or tumours themselves, have made great progress. cancer therapy field of interest.[24-26].TAMs are a noticeable part of solid tumours, frequently making up a significant portion of the cell mass.[24].TAMs are produced from monocytes that the tumour attracts. via soluble mediators such as chemokine (C-C) ligand 2. (CCL2).[27].When monocytes are subjected to anti-inflammatory substances such TGF-β and prostaglandin E2, IL-4, and IL-10, they become polarised into M2-like macrophages.[24,27].TAMs(Tumor-associated macrophages) can also increase tumour spread through non-immune mechanisms, such as by releasing a significant amount of (VEGF), which encourages angiogenesis and vasculogenesis.[28]

Monocytes are blood cells that may overcome endothelial barriers. barrier for tissue macrophages to differentiate. known as mononuclear macrophages.Primary macrophages taken from animals, which mostly contain bone marrow-derived macrophages, are one of two main groups of macrophages that have been examined.[34,35],alveolar macrophages[36].human acute mononuclear leukemia cells (THP-1).[37]

1.2.Development of Macrophage-Mediated Delivery Systems Drug:-

The first report on a macrophage-mediated anti-retroviral medication delivery system using nanoparticles was made in 2006.[29].additionally to distribute medication for the care of Parkinson's disease.[30]Based on positive results, macrophages have been used as carriers for the delivery of medications with various qualities. substantially increased in order to research and treat different illnesses like cancer.[31],inflammation[32],and HIV infection[33]

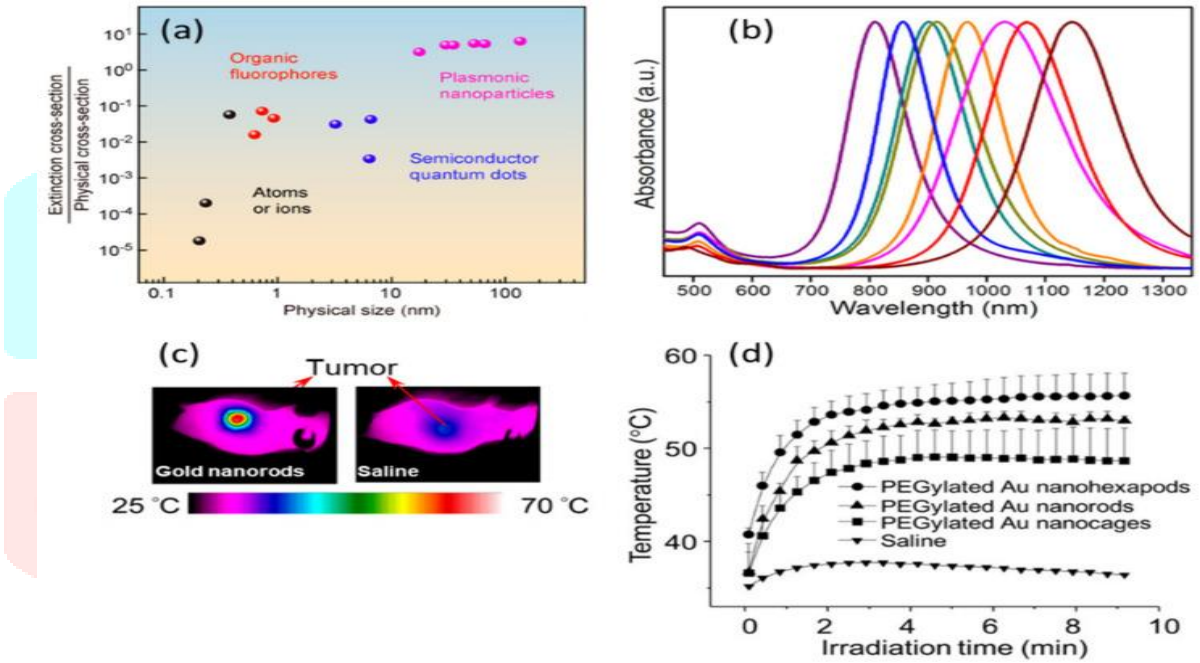

Fig 3. (a) all the different kinds of NPs, metallic plasmonic NPs have the highest extinction cross-section to physical cross-section ratio. (b) During the synthesis, the longitudinal absorption of gold nanorods can be accurately controlled and can even reach the near infrared range. As AuNR aspect ratios rise from 3.8 to 7.5, AuNR longitudinal absorptions change from 780 nm to 1200 nm. (c) Thermographs of mice getting photothermal therapy who were carrying tumours. (d) A rise in temperature in the tumour area as a function of the radiation exposure period. For these investigations, a diode laser (808 nm) with a power density of 1.2 W/cm2 was used. American Chemical Society permission granted for reproduction.[38,39,40]

Auto immune Deficiency Syndrome (AIDS)

macrophages have a distinct role in HIV infection. The HIV can enter the macrophage when gp120 binds to CD4 and the chemokine receptor CCR5 second membrane receptor[43]. In fact, productive HIV-1 infection in macrophages happens independently of cellular DNA synthesis.[44]the creation and development of viral In macrophages, cytoplasmic vacuoles contain particles.[45]Macro pinocytosis is another entrance point that has been proven to be necessary for the transmission of HIV-1 to macrophages[46].

Tuberculosis

TuberculosisVarious pathogens are stored in macrophages. InCases of mycobacterium tuberculosis and tubercle bacillusAn aerial cause of tuberculosis calledfor a very long time in lung alveolar macrophages.[47]

Gaucher Disease

Gaucher disease is a rare hereditary condition that is connected to functioning b-glucocerebrosidase activity deficit and characterised by the presence of macrophages that are lipid-rich. the liver, spleen, bone, and lungs all include (gaucher cells). In order for this disease's enzyme replacement therapy to be effective, the capacity to provide macrophages with b-glucocerebrosidase,when these cells build up glycolipids when there is an enzyme shortage.[48,49]

Skin Cancer

MIF (migration inhibitory factor) is a potent inhibitor of macrophages and an in vivo activator. The skin displays MIF through the keratinocytes and fibroblasts of the epidermis.[50,51]Both the development of tumours and inflammation are directly influenced by the MIF.Chronic UV radiation (280–320 nm) exposure improves MIF synthesis, which could reduce the p53-dependent apoptotic mechanisms, resulting in the photocarcinogenesis in the skin This recently discovered mechanism might be involved. Towards a general comprehension of photoinduced skin damage,This ultimately leads to cancer development.[52]

1.3.Macrophages in drug delivery system:-

i .macrophage in targeted site for cancer therapy:-

Macrophage residence and polarisation are highly linked with the advancement of cancer. Numerous studies have demonstrated that the Tumor-associated macrophages (TAMs) can control the course of solid malignancies.[53] capable of stimulating tumour cell extravasation, formation, and subsequent progression of metastatic lesions, hence establishing favoured locations for metastatic cell seeding.[54]. It Having a mostly concentrated on controlling adaptive immune reactions.

There is still a clear possibility to target innate immune cells in order to eradicate cancer given the crucial role that macrophages and monocytes play in the aetiology of the disease. In order to treat cancer, macrophages are primarily targeted using three strategies:(i)block the invasion of monocytes into solid tumours, (ii) repolarize TAMs to destroy the solid tumours TAMs from the tumour microenvironment.[55]

This section will go over the major developments, restrictions, and potential future Possibilities for medication delivery to macrophages and monocytes methods for treating cancer. Macrophages have traditionally been avoided during circulation in cancer therapy because they are thought to be an unfavourable mechanism for the early clearance of drug delivery systems.

However, macrophages are being reconsidered as a potential target in cancer therapy due to the growing understanding of the complicated involvement of TAMs in tumour growth.[57-59].In cancer therapy, TAMs have been addressed in two different ways: first, by depleting TAMs and preventing its tumor-promoting actions, and second, by reprogramming TAMs into more M1-like pro-inflammatory phenotypes and enhancing their immunostimulatory characteristics. Chemotherapeutic drugs are used in these strategies.[58,60-62]particular signalling pathway blockers.[63]According to Germanoetal, trabectedin selectively reduced angiogenesis and reduced monocytes and macrophages in tumours, spleens, and blood, indicating that TAM inhibition may be the primary mechanism behind its anticancer effects.[62]Similar to this, local administration of IL-21 caused TAM to polarise from the M2 phenotype to the M1 phenotype, activating their anticancer potential.[64]Due to their affinity toward hypoxia and capacity to move and infiltrate into tumours, macrophages and monocytes have been investigated as potential carriers of anticancer medications and imaging agents.[65,66].

An essential cytokine with anti-proliferation properties is transmembrane TNF. In one experiment, TNF-expressing macrophages' membranes were used to enclose empty chitosan nanoparticles, and the resulting particles greatly reduced the growth of cancer cells.[67]

The targeting tumour site are shown in fig.[56]

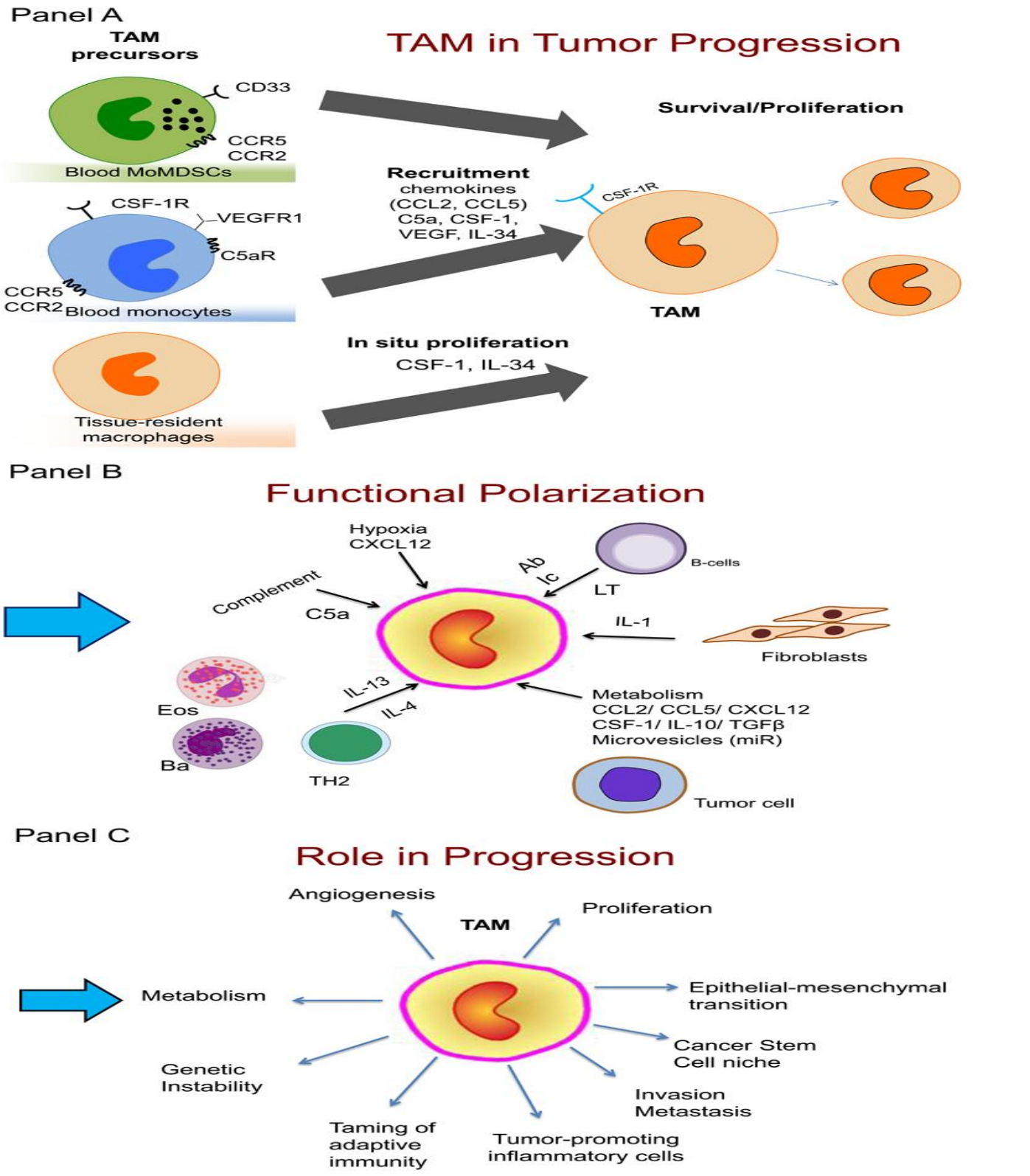

Fig. 4. A schematic representation of the role of tumor-associated macrophages intumor progression

Panel A. Monocytes and MoMDSCare recruited in tumors in response to diverse chemoattractants including CSF1, chemokines and complement components. In tumors, monocytes differentiate into macrophages (Tumor-associated macrophages, TAM). In some tumors, in situ proliferation may occur and local tissue resident macrophages of embryonic origin may contribute to TAM. Signals in the tumor microenvironment skew the function of TAM.

Panel B. Pathways and molecules polarizing TAM differ in different tumors. These include: IL-4 and IL-13 derived from TH2 cells, eosinophils (Eos) and basophils (Bas); cytokines and metabolites from tumor cells; antibodies (Ab) from B cells and immune complexes (Ic); stromal cell-derived factors (IL-1, LT).

Panel C. TAM affect virtually all aspects of tumor cell biology, including provision of a niche for cancer stem cells (CSC); angiogenesis; epithelial to mesenchymal transition (EMT); invasion and metastasis; proliferation; genetic instability.[56]

ii.Macrophages in targeted drug delivery to cardiovascular disease(cvd):-

Nearly all CVDs, including myocarditis, atherosclerosis (AS), pulmonary artery hypertension (PAH), stroke, and cardiac disease, are accompanied by macrophage-induced inflammation. Targeting malfunctioning macrophages is thus a promising CVD treatment method. In order to treat cardiovascular disease, this section will cover current developments employing DDS to target vascular macrophages.

ii.(a). Atherosclerosis (AS)

AS is an inflammatory condition of the artery wall caused by lipids and characterised by plaque accumulation. This happens as a result of the buildup of sick cells, including monocytes, macrophages, endothelial cells (ECs), smooth muscle cells (SMCs), and neutrophils, as well as lipids and elements of the extracellular matrix (ECM), with the typical buildup of cholesteryl ester (oxLDL).[68,69]

Although the pathophysiology of AS is not entirely understood, mounting evidence indicates that the presence of macrophages and the pro-inflammatory cytokines produced by macrophages, such as IL-1, IL-18, and macrophage inflammatory protein-1 (MIP-1), play a significant role.[70]

Targeting macrophages in AS:-

In the clinic, delaying the onset of AS is frequently accomplished by enhancing cholesterol efflux from macrophages or lowering lipid uptake into macrophages. 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) inhibitors, also referred to as statins (e.g., lovastatin, and atorvastatin), are one class of medications that are utilised to elicit these responses. However, statins are typically given as a capsule or tablet, which could be hazardous to the liver because of their restricted ability to target. A number of DDS, including NPs that resemble HDL, were addressed in an effort to increase statin administration.[71,72]

In order to deliver the miR-33 mimic to naive macrophages, chitosan NPs with a diameter of 150–200 nm were created. This led to a 5% increase in cholesterol efflux and a general decrease in reverse cholesterol transport to the plasma, liver, and faeces.[73]

Beta -CD, which is frequently employed in pharmaceutical applications to distribute hydrophobic medicines, is another method to encourage cholesterol efflux. According to Zimmer et al., treatment of beta -CD dramatically increased cholesterol efflux by encouraging plaque macrophage LXR activation and amplifying anti-inflammatory effects.[74,75]Follow-up research have been prompted by these findings, which point to the possibility that improving the solubility and removing cholesterol crystals could be an efficient and potentially applicable technique for treating AS.[74,75]

Plaque rupture can be avoided and inflammation can be reduced by modifying the polarity of monocytes and macrophages toward anti-inflammatory phenotypes.[76-79].

There is evidence that the LyP-1 peptide can penetrate tumours. LyP-1 was shown by She et al. to target atherosclerotic plaques, enter the inside of the plaques, aggregate in macrophages, and cause their death, which significantly decreased the loads brought on by advanced hypoxic plaques.[80]

Overall, DDS-delivered biologics and small molecule medications regulate macrophage activity and prevent AS plaque rupture. Small molecule medications must be administered repeatedly to maintain blood concentration, although toxicity frequently occurs and reduces efficacy. Due to their high efficacy and specificity, biological medications like IL-1 antibody, TRAF6i, and CD47 antibody display excellent anti-AS effects and represent a new approach to treating AS. It is difficult for DDS to accumulate at the plaque site because of dispersed intravascular plaque and changed blood flow. HDL-based NPs efficiently undergo cytosolic transport and naturally target plaque, allowing the cargo to enter cells without being stopped by endosomes.[78,79].

ii.(b).Pulmonary arterial hypertension (PAH)

Precapillary pulmonary arteries in PAH undergo vascular remodelling as a result of SMC overgrowth, apoptosis-resistant ECs, fibroblasts, macrophages, increased ECM deposition, and persistent inflammation.[81-83].
PAH is classified into thefollowing categories:
(i) idiopathic PAH,
(ii) heritable PAH (HPAH),
(iii) drug- and toxin-induced PAH,
(iv) associated PAH (APAH), and
(v) persistent pulmonary hypertension of the newborn (PPHN).[84]

One distinct feature of PAH is the increased recruitment of monocytes and macrophages in the perivascular region.[85,86]

Techniques for PAH macrophage targeting :-

In numerous models, including those with experimentally generated hypoxia and portopulmonary hypertension, depletion or inactivation of such macrophages has showed promise in the treatment of PAH.[86-88]In example, inhaled cerivastatin-liposomes displayed sustained release profiles over a period of 12 hours, prevented PASMC proliferation, and markedly decreased CD68+ macrophages, which are common in advanced obliterative plexiform lesions. This had the impact of reducing small artery blockage and decreasing pulmonary alveolar proteinosis.[89]

Macrophages work together to cause PAH inflammation, although the precise process by which this happens is unknown. Because macrophages are mostly found in the perivascular area and there aren't many products being tested in clinical settings, targeting them can be difficult.

Since the proliferation of SMCs and the malfunction of ECs are directly related to remodelling of the pulmonary arteries, concurrently targeting macrophages and SMCs or ECs presents a promising PAH therapy strategy.

iii.Targeting on the other specified diseases:-

Catalase has been delivered by macrophages, which successfully crosses the blood-brain barrier and achieves active targeted therapy by drastically reducing neuroinflammation and substantia nigra degeneration in rats with Parkinson's disease.[90-92]

The macrophage's bacterial recognition receptorsmembrane is capable of identifying pathogen-related molecularbacteria's patterns Macrophages have so been cocultured.to substantially boost the expression with bacteriaa macrophage's recognition receptorsmembrane.[93]By taking advantage of the precise recognition between integrin 41 on the macrophage membrane and the atherosclerotic vascular adhesion molecule VCAM-1, atherosclerotic lesions can be targeted for medication delivery via macrophages. One study used this technique to remove more than 90% of reactive oxygen species from endothelial cells.[94]

This formulation demonstrated great biocompatibility, decreased the drug's inherent toxicity, and permitted the use of a lower dose to have the same therapeutic benefit.

2.Review of literature:-

1. **.Patra JK,et al.(2018)**
   Nanomedicine and nano delivery systems are a relatively new but rapidly developing science where materials in the nanoscale range are employed to serve as means of diagnostic tools or to deliver therapeutic agents to specific targeted sites in a controlled manner. Nanotechnology offers multiple benefits in treating chronic human diseases by site-specific, and target-oriented delivery of precise medicines.
2. **García KP,et al.(2014)**
   Nanoparticles represent highly promising platforms for the development of imaging and therapeutic agents, including those that can either be detected *via* more than one imaging technique (multi-modal imaging agents) or used for both diagnosis and therapy (theranostics).
3. **T.A. Wynn, et al. (2013)**
   In this Review, we discuss how macrophages regulate normal physiology and development, and provide several examples of their pathophysiological roles in disease.
4. **J. Godsell, et al. (2016)**
   Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by the development of autoantibodies to nuclear antigens and inflammatory responses mediated by multiple cytokines.
5. **D.M. Mosser, et al. (2008)**
   In this Review we suggest a new grouping of macrophage populations based on three different homeostatic activities — host defence, wound healing and immune regulation. We propose that similarly to primary colours, these three basic macrophage populations can blend into various other 'shades' of activation.
6. **Li R., et al.(2019)**
   the targeted delivery of therapeutics to sites of rheumatoid arthritis (RA) has been a long-standing challenge. Inspired by the intrinsic inflammation-targeting capacity of macrophages, a macrophage-derived microvesicle (MMV)-coated nanoparticle (MNP) was developed for targeting RA. The MMV was efficiently produced through a novel method.
7. **Schett G., et al. (2008)**
   Cytokine expression in the inflamed synovial membrane of patients with rheumatoid arthritis and other forms of chronic inflammatory arthritis and other forms of chronic inflammatory arthritis leads to formation of osteoclasts.

8. **Kumar PV, et al. (2006)**
The present study was aimed at developing and exploring the use of mannosylated dendritic architecture for the selective delivery of an anti-tuberculosis drug, rifampicin (RIF) to alveolar macrophages (AM).
9. **R. Ostuni,et al.(2015)**
Infiltration by immune cells is a hallmark of most forms of malignancy. In this context, tumor-associated macrophages (TAMs) represent key regulators of the complex interplay between the immune system and cancer.
10. **G. Germano,et al.(2013)**
There is widespread interest in macrophages as a therapeutic target in cancer. Here, we demonstrate that trabectedin, a recently approved chemotherapeutic agent, induces rapid apoptosis exclusively in mononuclear phagocytes.

3.Future:-

As our understanding of molecular and cellular pathways advances quickly, it will be crucial to keep in mind how they are integrated into more complex functions. This may be best accomplished by combining in vitro and whole animal studies and by paying closer attention to the biology of macrophage cells. Amazing advancements in imaging inside a living host.[95]

where TAM can both influence and promote cancermigration and metastasis of tumour cells. Consideration should also be given to the idea that surface contact-dependent interactions, independent of antibodies or phagocytosis, may directly contribute to cellular and antimicrobial cytoxicity. Despite recent advancements in our understanding of the diversity of surface receptors, the ability of macrophages to distinguish between changed host components, such as virus-infected cells and tumours, and normal physiologic constituents is still poorly understood. Compared to research on lymphocytes and epithelial cells, investigations on the functions of macrophage membrane receptors and transporters have received comparatively little attention. By utilising modern genetic, cellular, and molecular approaches, traceable experimental models are available to investigate the mechanisms of macrophage membrane activities during cell-cell fusion, phagocytosis, adhesion, and infection.[96]both in vitro and in vivo, in controlled gene expression. Although there has already been significant advancement in the experimental ability to conditionally and selectively remove undesirable or enhance macrophage function in vivo, antibodies directed against particular surface receptors and regulatory plasma membrane molecules also support enhanced molecular engineering. Overall, maintaining host tolerance to infection while selectively modulating macrophage sub - groups inside the living host remains a key treatment objective.

4.Outlook for macrophages:-

One strategy to address the lack of specificity of traditional chemotherapeutic drugs is molecularly targeted therapy. Site-specific targeted drug delivery negotiates an exclusive distribution to a predetermined compartment with the maximal intrinsic therapeutic activity of the bioactive, which concurrently minimises the access of the drug to irrelevant non-target cells and provides distinct therapeutic effects. The distinctive characteristic of targeting is the controlled pace and mechanism of drug delivery to pharmacological receptors and precise interaction with target cells. An ideal targeted drug delivery strategy would not only increase the therapeutic effectiveness of medications but would also reduce the toxicity of the drug so that smaller dosages of the drug may be used in therapy. Utilizing ligand-anchored carrier systems, targeted medication delivery may be accomplished.

Despite the potential advantages of targeted nanocarriers, there are still several hurdles to be cleared, including low oral bioavailability, instability in circulation, insufficient tissue dispersion, toxicity, and expense. The targeting moiety needs to be unique to the targeted macrophages. Additional research should examine internalisation using several cell types to confirm specificity as well as surface modification utilising different target molecules to improve macrophage internalisation selectivity. However, circulatory instability and hemolytic as well as cytotoxic toxicity are likely to significantly hinder the desired translation from bench to clinics.

Many of these innovative nanoarchitectures currently lack safety information; therefore, long-term toxicity studies that go beyond proof-of-concept studies should be conducted.

There should be more preclinical and clinical research on pertinent animal models and disease states. It is important to overcome problems with the manufacture and scaling up of these nanocarriers. Another need when considering these systems for clinical application is long-term storage stability.Finally, the price of these nanomedicines must be within a reasonable low range in order for them to be successful in the clinic.It may be able to realise the idea of comprehensive targeting by chronologically developing the drug delivery system from a simple drug carrier to a designed nanocarrier. We think a multidisciplinary approach is necessary to understand the function of numerous, as-yet-unknown elements in the targeting of medications and nanocarriers to this critical immune system cell, the macrophage.It's crucial to note that further research is required to produce the mechanistic information needed to understand how and why receptor-based drug delivery systems considerably maximise (or optimise) their therapeutic efficacies.

5.Need of macrophages:

Overall, macrophages are good and play a critical role in the human body. They protect our body from bacterial and viral infections by secreting antimicrobial mediators and pro-inflammatory cytokines, while also mediating repair through an anti-inflammatory response. They also allow for protection from neuronal damage in the brain, and regulate iron and bilirubin levels in the liver.

They attract anti-inflammatory cytokines, which mediate vascular growth and have microcidal properties, to the wound site. Macrophages have very positive effects and maintain tissue homeostasis within humans, however they can also contribute to disease. This can be the case when tumor-associated macrophages evade suppression by the immune system and promote tumor growth, or when atherosclerosis is promoted within arteries by the action of macrophages.

6.Conclusion :

Macrophages are phagocytic cells that play an important part in inflammation, cancer, and injury in the human immune system. Compared to conventional drug delivery approaches, macrophage-mediated drug delivery has several benefits, but the variability of the macrophages used to create these delivery systems has restricted their usage in clinical settings. Furthermore, it is uncertain how macrophages interact with drug cargo, making it challenging to anticipate whether the medication would be metabolised by endolysin. More study is required to determine how to safeguard membrane surface proteins during extraction of the macrophage membrane in order to ensure that delivery systems mediated by macrophages maintain the natural functions of macrophages. Macrophage storage that maintains biological activity is still a significant barrier to large-scale production. Future research addressing these issues might advance the clinical use of macrophage-mediated medication delivery.

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