

Macrophages as a target for drug delivery: a boon to nano-therapeutics

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Introduction

Although macrophages are the primary cells involved in the normal immune response however their phenotype and imbalance in the ratio dysregulate the immune response, therefore leading to inflammation. Because of their active role in immunological disorders, macrophages may be exploited in the early stage of diseases via targeted therapy. The advancement in nanotechnology has made adequate possibilities in receptor-mediated targeted drug delivery. Moreover, macrophage-targeted drug delivery takes into consideration their plasticity and modulation. A cost-effective intervention in clinical trials and implementation of ethical guidelines can facilitate translating this approach from lab to bench (Pei and Yeo 2016).

Frequently expressed receptors on the surface of Macrophage: target sites

Mannose receptor (MR) comprises of a carbohydrate recognition domain, cysteine-rich zone, fibronectin region, and carboxyl-terminal part; that allow MR binding to sugars and Sulphur rich compounds. The same receptor facilitates the recognition of pathogens and endocytosis.

Folate receptor (FR) is a protein-linked glycosylphosphatidylinositol receptor that can bind efficiently to folic acid-based structures. FR is adequately expressed in activated synovial macrophages and tumor-associated macrophages (TAMs), particularly in epithelial cancers.

Glucan receptor (Dectin-1) is overexpressed in myeloid cells. As glucan is abundantly present in fungal

cell wall, hence Dectin-1 is used to identify pathogenic fungi and can be targeted for inhibiting fungal infections.

Macrophage scavenger receptor (SR) is highly rich in cationic collagen and shows an affinity for anionic drug moieties. SR is highly selective to polysaccharides as well as it can bind to dextran sulfate but not to chondroitin sulfate. SR can be a target for human serum albumin-based probes.

Materials and Methods

Databases; PubMed, Medline, Scopus, and Web of Science, were searched thoroughly. Keywords such as macrophages AND nanotechnology, and receptor targeting AND macrophages were used for the search.

Results and Discussion

Nano-therapeutics for targeting macrophages in diseases

Inflammatory bowel disease is a chronic inflammatory disorder in which the regulation of macrophage is disrupted due to an imbalance between the anti-inflammatory and pro-inflammatory cytokines. Due to the ongoing cascade of events around the intestinal epithelial tissues, the levels of pro-inflammatory cytokines such as interleukins (IL-12, IL-23, and IL-16) are elevated causing severe inflammation. This can be prevented by targeting macrophages at an earlier stage to modulate their role using various approaches such as anti-TNF- α targeted therapy, corticosteroid targeted therapy, or anti-inflammatory peptide such as lysine-proline-valine therapy, through the interaction of nanoparticles with various surface receptors (Mukhtar et al. 2020a). Different moieties can be encapsulated in the nanostructures such as polymeric

nanoparticles, liposomes, dendrimers, niosomes, etc. as shown in Fig. 1.

Leishmaniasis is a pathogenic parasitic infection that begins on entry of promastigote in humans where it attaches to phagocytes. After a series of events, promastigotes transform into amastigotes inside the infected macrophages. This intracellular form of parasite resides in macrophages and stimulates inflammation. Various research rationales have been designed to kill this obligatory parasitic form which otherwise may pose serious health risks such as coma. Mannosylated nanocarriers have an affinity for MR; the main receptor domain used for gaining access inside macrophages by the promastigotes. Mannosylated polymeric nanoparticles loaded with amphotericin B, paromomycin, and other anti-parasitic agents are being studied for therapeutic outcomes.

Tuberculosis is caused by *M. tuberculosis* which infects the alveolar macrophages, resides, and replicates there. Different drugs such as isoniazid, rifampicin, and other antibacterial agents like selenium or gallium can be loaded inside the nanoparticles by exploiting the surface modification approach (Mukhtar et al. 2022b). Such strategies not only improve intracellular therapy but also promote phagolysosomal destruction of bacterial load effectively. Macrophages also play a role in the pathophysiology of other diseases including HIV infection, rheumatoid arthritis, and Salmonellosis, and can hence be targeted by the surface modification of nanoparticles, either by chemical (polymer derivatization) reaction or by physical anchorage and functionalization of ligand.

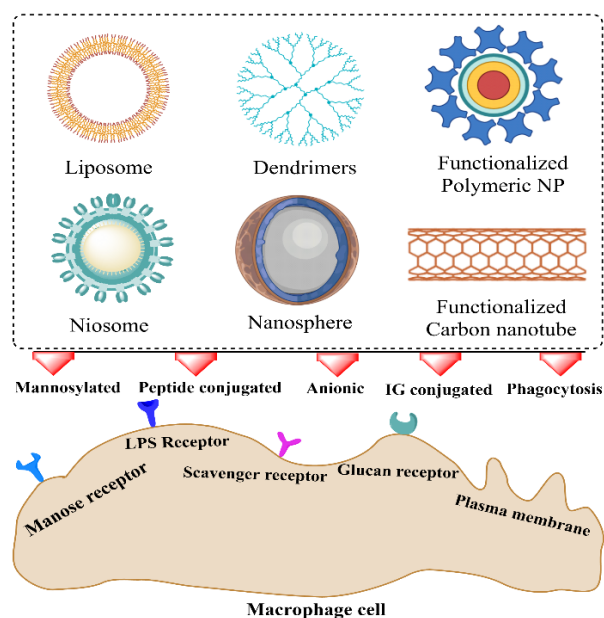


Fig. 1. Macrophage surface receptors as targets for nanotherapeutics

TAMs as therapeutic targets

M2-polarized TAMs are involved in the progression of cancer and therefore can be targeted using nanotherapeutics. Strategies that can inhibit polarization of M1 TAMs (anti-tumor) to M2 TAMs, or lead to reeducation of M2 phenotype to M1 are being studied for cancer therapy (Cai et al. 2022). It has been established that immunomodulatory nanocarriers promoting inhibition of interleukins such as IL-10 can facilitate the M2 polarization to M1. Also, pro-IL-12 therapy reverses M2 to M1 TAMs. The nano-therapy which targets the infiltrated macrophages, mainly aims at either downregulating the pro-inflammatory cytokines produced by M1 macrophages or re-polarizing the macrophages from M1 to M2 phenotype facilitating the resolution of inflammation. The levels of certain chemokines and cytokines if quantified might provide the estimated time to target the macrophages for resolving the inflammatory disorders and cancer.

Conclusion

The role of macrophages in immune disorders and tumors is well established now. As macrophages are natural targets and therefore can be exploited for delivering drugs using nanocarriers. Albeit, the physiological parameters influencing the macrophage's phenotypes must be taken into account before designing a drug delivery vehicle. Hence, insight is needed to understand the dynamics of differentiation and polarization of macrophages as long-term therapy can interfere with the innate immune response.

References

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