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Review Article

Biopolymer Mediated Macrophage Polarization: A Method of ALS (Amyotropic Lateral Sclerosis) Control

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Abstract

Amyotrophic lateral sclerosis (ALS) is a motor neuron disease (MND) with the worst prognosis with 4-5 years. Both upper and lower motor neurons in the cortex and in the brainstem spinal cord are affected. No effective treatments are available yet. Furthermore, in 10-14% ALS cases are involved with genetic defects, while about 90% cases are reported as sporadic. In fact, immune dysregulation causes the activation of inflammatory cells that augment the ALS disease progression. M2 macrophages have immunosuppressive activity, produces high level of anti-inflammatory cytokine IL-10 and mediates tissue repair, noticed in diabetic and nephrotic mice. The M1-type of macrophages (MΦs), are pro-inflammatory and causes lung disease, like ALI (acute lung injury) and ARDS (acute respiratory distress syndrome). Recently, it was demonstrated that M2-type of MΦs are immunosuppressive, can induce boost Tregs (Regulatory T cells), and serves as a candidate for immune-cell-based therapy for ALS.

In this review we drew a hypothetical connection, supported by evidence, between nanoparticles medicated MΦs polarization to M2 type and targeting to deliver in the brain for ALS control.

Keywords: ALS Disease; Motor Neuron Defects; MQ Polarization; Nanobiopolymer

Introduction

The task of understanding the molecular and cellular relationships to detect the pathways of ALS disease formation is complex. Amyotrophic lateral sclerosis (ALS), also called Lou Gehrig disease, is a fatal neurodegenerative disease generally affects the aged persons. Immune dysregulation followed by loss of upper and lower motor neuron functions are the characteristics of ALS. Presence of M1 type of macrophages (MΦs) which is pro-inflammatory and lymphocytes are noticed in the central nervous system (CNS) of ALS patients [1-6]. Increased levels of cytokines, IL-6, IL-1β, and tumor necrosis factor-a (TNF-α) were also found in the blood of ALS patients [7]. Similar observations with CNS and peripheral inflammatory responses were reported in ALS transgenic animal model [8,9]. However, no such curative treatments of this disease are still available.

The plasticity of MΦs are their unique property, can adopt different phenotypes under the influence of particular cytokines presents in their surroundings. During chronic neuro-inflammation, macrophages infiltrated in the CNS region polarizes to an inflammatory M1 phenotype and secretes various pro-inflammatory cytokines (e.g., IL-6, IL-12 and TNF-α), inducible nitric oxide synthase (iNOS), cyclooxygenase (COX)-2, and reactive oxygen species [10-13]. In contrast, the other type, M2-MΦs are anti-inflammatory and can be established by repolarization of M1-type by treating with IL-4/IL-10/IL-13, TGF-β, or glucocorticoids [14-16]. M2 cells have been reported to have high endocytic clearance capacities and also enhance tissue repair [17,18].

The unique plasticity of this, M1 and M2, two different forms of MΦs and their balance in between different phenotypes maintain the immune homeostasis in the healthy conditions, and similarly

abnormal imbalance can cause disease like acute lung injury (ALI), acute respiratory distress syndrome (ARDS) [14,19,20], and tumor aggressiveness [21-24], and the genesis of ALS [6].

Here we will highlight the involvement of nanomaterials in the polarization of MΦs to its beneficiary form, M1 type, as well as its delivery to neural area to fight against the ALS symptoms.

Mechanisms of MΦs Polarization

- MΦ s-M1 polarization can be done by the activated STAT1 and IRF5, while STAT6/STAT3 and IRF4 can polarize M2-MΦs [19,25]
- LPS and IFN-γ can induce M1 type [27,28] while IL-4 or IL-4 and IL-13 together can polarize to M2-type [26]
- NF-κB inhibition in MΦs could lead to the polarization toward M2 phenotype [29]
- In an activated T cells, low concentration of G-CSF down-regulates the M1 driving cytokine IFN-γ, while high concentration of G-CSF up-regulates the M2 driving cytokine IL-4 [30].

Nanoparticles (NPs) mediated MΦ s polarization

Medical applications of NPs are increasing due to their physicochemical properties, e.g., chemical composition and structure, shape, size, and surface properties, etc. Their surfaces could be hydrophilic or hydrophobic and exhibit specific ligands and surface charges which specifies them for using to treat different clinical diseases [31]. Synthetic NPs with various structures are now-a-days produced from liposomes [32,33], chitosan [34], poly (lactic-coglycolic acid) (PLGA) [35,36], dextran [37], silica [38], and metals such as iron oxide or gold [39]. These NPs polarizes MΦs from an M1 to an M2 phenotype which down-regulates the pro-inflammatory cytokines, such as, IL-6, IL-1β, and TNF-α which prevents the inflammation in arthritic rat models [40]. Similarly, the Gold nanoparticles (GNPs) were shown to inhibit NF-κB and IRFs activation and drives the MΦs polarization towards the anti-inflammatory M2 phenotype which contributes to the reduction of lung inflammation in ALI [41].

Importantly, selective binding of the NPs on the cell surface depends on the sufficient amounts of the receptor expression by the cell as well as enough ligand expression by the NPs either by themselves or to be added on their surface. Jain., *et al*. have already developed such a vehicle to transport IL-10 into an inflammatory area to repolarize pro-inflammatory M1- MΦs to an anti-inflammatory M2-type. The results turn out as a novel therapeutic strategy for many inflammatory diseases including ALS [40].

NPs Acts as a safe cargo to deliver cytokines in the brain for polarizing M1- to M2-MΦ$_s$

NPs can penetrate the blood-brain barrier [42] and maintain their stability in circulation from proteases or other enzymes in the blood stream and the highly acidic environment in the stomach [43]. Polymeric NPs can carry engineered antibodies or aptamers based on the target, which enables them to recognize specific cells. All these features support the use of NPs for targeted drug delivery [35,44,45]. Furthermore, nanomaterials can be enriched with different drugs together and/or can be combined to carry different medications to overcome multidrug resistance challenges [31,46]. With the technological development of drug-carrying NPs and by the pharmacokinetics and bioavailability analyses one can upgrade the nanodrugs for their vascular permeability, mononuclear phagocyte uptake, and slowed excretion of the drug molecules which are important for the disease treatment [47].

NPs can deliver pre-polarized M2-MΦ $_s$

Transplantation of macrophages at the site, has proven as a valid technology to restore kidney function or fibrosis [48]. However, in some environments *in vivo,* transplanted macrophages may lose their properties [49,50]. Therefore, delivery of encapsulated M2-macropahges will allow a sustained delivery of the anti-inflammatory molecule(s) secreted by M2- type [51-53]. Pre-polarization of MΦs to its M2-type can be done *in vitro* by adding IL-10 on the cell suspension within the alginate or in the culture media before encapsulation [54]. This could be then used for cell transplantation *in vivo*, and also can be used as an anti-fibrosis to prevent epithelial to mesenchymal transformation [54].

Discussion

Macrophages (MΦs) are derived from monocytes and are important for an innate as well as an adaptive immune response. The main scavenger cells of the body is the macrophages as they maintain the cellular homeostasis as well as immune surveillance within the innate immune system. MΦs can also present antigen, and subsequently can do the priming of the T lymphocyte [55]. MΦs are heterogeneous and can be polarized to its two forms

interchangeably which signifies their various functional capabilities in regulating tissue inflammation and phagocytic clearance [56].

Pro-inflammatory M1-MΦs can be formed by the exposure to specific microbial stimuli such as lipopolysaccharide (LPS) and the formation of anti-inflammatory M2-type depends on the exposure with cytokines such as interleukin-4 (IL-4), interleukin-10 (IL-10) or interferon-γ (IFNγ) [57,58]. Functionally, these MΦs are distinct in their membrane expression of opsonic receptor CD16 and mannose receptor; and in their ability to produce chemokines/cytokines. Further, their abilities to support or suppress inflammation, scavenging debris and promoting tissue repair are unique to their types [58].

The nanotechnology-based therapeutic approach described here-in though hold some promises for fatal ALS therapies, it should counted that this therapeutic model may have some intrinsic limitations, for example, the long-term effectiveness of such method is highly dependent on the stability/plasticity of the polarized MΦs, which may affect its therapeutic efficacy (Figure 1).

Figure 1: Schematic presentation of ALS development by M1-type of macrophages and its rescue by nanoparticles (NPs) loaded with polarizing cytokines. Nanopolymer encapsulated the M1 polarizing cytokines IL-4, IL-10, etc. can polarize M1 to its antii-inflammatory M2 form and can rescue the ALS disease.

Conclusions and Future Perspectives

- In general, M2-type MΦs anti-inflammatory while M1-type MΦs is pro-inflammatory.
- Nanoparticle can polarize MΦs to its different types but a standardized conditions are needed to measure the results.
- MΦs -polarizing drug-loaded nanoparticles may also demonstrate synergistic effects with their therapeutic payload.
- The literature suggests that polymeric nanoparticles and liposomes can cause M2-type polarization following MΦs treatment, while other types of nanoparticles can cause M1-type polarization.
- Overall, nanoparticles are a promising treatment approach to modulate MΦs polarization in the ALS treatment, and the methods should consider the MΦs-polarizing potential of nanoparticles to M2-type in order to maximize their therapeutic efficacy against ALS disease.

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Author Contributions

Both of the authors contributed equally to preparing this article, reading and approving the final manuscript.

Conflict of Interest

Both of the authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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