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Review

Macrophage-targeted delivery systems for nucleic acid therapy of inflammatory diseases

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ABSTRACT

Inflammation is an immune response that marks several pathophysiological conditions in our body. Though adaptive immune cells play a major role in the progression of the disease, components of innate immune system, mainly monocytes and macrophages play the central role in onset of inflammation. Tissue-associated macrophages are widely distributed in the body showing tremendous anatomical and functional diversity and are actively involved in maintaining the homeostasis. They exhibit different phenotypes depending on their residing tissue microenvironment and the two major functional phenotypes are *classically activated* M1 phenotype showing pro-inflammatory characteristics and *alternatively activated* M2 phenotype demonstrating anti-inflammatory nature. Several cytokines, chemokines and other regulatory mediators delicately govern the balance of the two phenotypes in a tissue. This balance, however, is subverted during infection, injury or autoimmune response leading to increased population of M1 phenotype and subsequent chronic inflammatory disease states. This review underlines the role of macrophages in inflammatory diseases with an insight into potential molecular targets for nucleic acid therapy. Finally, some recent nanotechnology-based approaches to devise macrophage-specific targeted therapy have been highlighted.

Contents

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1. Introduction

Inflammation is a stimuli-activated adaptive response of the body that initiates a coordinated cascade of complex regulatory network upon tissue injury, microbial infection or autoimmune response [1]. The pathological implication of inflammatory response of the body is very well understood especially during microbial infection though its physiological function is yet to be characterized. Macrophages, the bone marrow derived leucocytes, are widely distributed cell population in the body that exhibit different phenotypic characteristics depending on their location and function (Fig. 1) [2]. They serve an important role in maintaining homeostasis in the body and are also key regulators of the inflammatory process. They along with dendritic cells are key members of the innate immune system responsible for recognizing "non-self" through membrane bound or intracellular pattern-recognition receptors (PRRs) and initiating the production of inflammatory cytokines and chemokines and subsequent involvement of adaptive immune system.

Macrophages are derived from monocyte precursor under tissue specific differentiation and infiltrate the site of infection or injury to produce inflammatory mediators including chemokines, cytokines vasoactive amines, eicosanoids and other products of proteolytic cascades. They can be *classically polarized* to pro-inflammatory M1 phenotype and function as an effector of T_H1 and T_H17 mediated immune response upon stimulation by lipopolysaccharide (LPS), toll like receptor (TLR) activation, granulocyte monocyte colony stimulating factor (GM-CSF) or interferon-γ (IFN-γ) produced from pathogenic invasion. The M1 phenotype macrophages produce abundant amounts of tumor necrosis factor (TNF) and interleukins (IL-12, IL-23) that attract tissue specific T_H1 and T_H17 to the site of infection, thereby increasing the inflammatory response. The clearance of parasite infection however can also result in non-specific tissue damage and enhanced inflammatory response that can cause inflammatory diseases. Instead, macrophages can be *alternatively polarized* to anti-inflammatory M2 phenotype by T_H2 specific cytokine, IL-4 and result in higher expression of IL-10 and IL-1RA and lower the production of IL-12. M2 polarized macrophages have immunosuppressive function and are involved in pathogen clearance, alleviating inflammation, tissue repair and remodeling as well as tumor progression. The two phenotypes of macrophages show diversity in function-specific surface markers as well as secreted chemokine profile that differentiates the two populations [3]. Macrophages therefore play a pivotal role in maintaining homeostasis and regulating the inflammatory response of the body and thus, their phenotypic balance is an important parameter in defining the initiation, progression and resolution of inflammatory conditions (Fig. 1).

In the event of infection or injury in body tissues, circulating monocytes are recruited and transformed primarily to pro-inflammatory M1 polarized macrophage phenotype under the influence of local tissue environment. The M1 polarization of macrophages is regulated by nuclear factor (NF)-κb, activator protein 1 (AP1), interferon regulatory factor (IRF) and mineralocorticoid receptor (MR) [4]. The pro-inflammatory macrophages exhibit enhanced endocytic activity and antigen presentation to initiate immunogenic response against the microbial infection. They also secrete inflammatory mediators such as TNF, nitric oxide, reactive oxygen intermediates, hydrolytic enzymes and cytokines such as IL-1 that in turn activate the anti-microbial defense mechanism involving a highly oxidative environment that results in killing the invading organisms. Furthermore, M1 polarized macrophages produce T_H1 attracting chemokines such as C-X-C motif chemokine CXCL9 and CXCL10. The inflammatory process that commences due to the

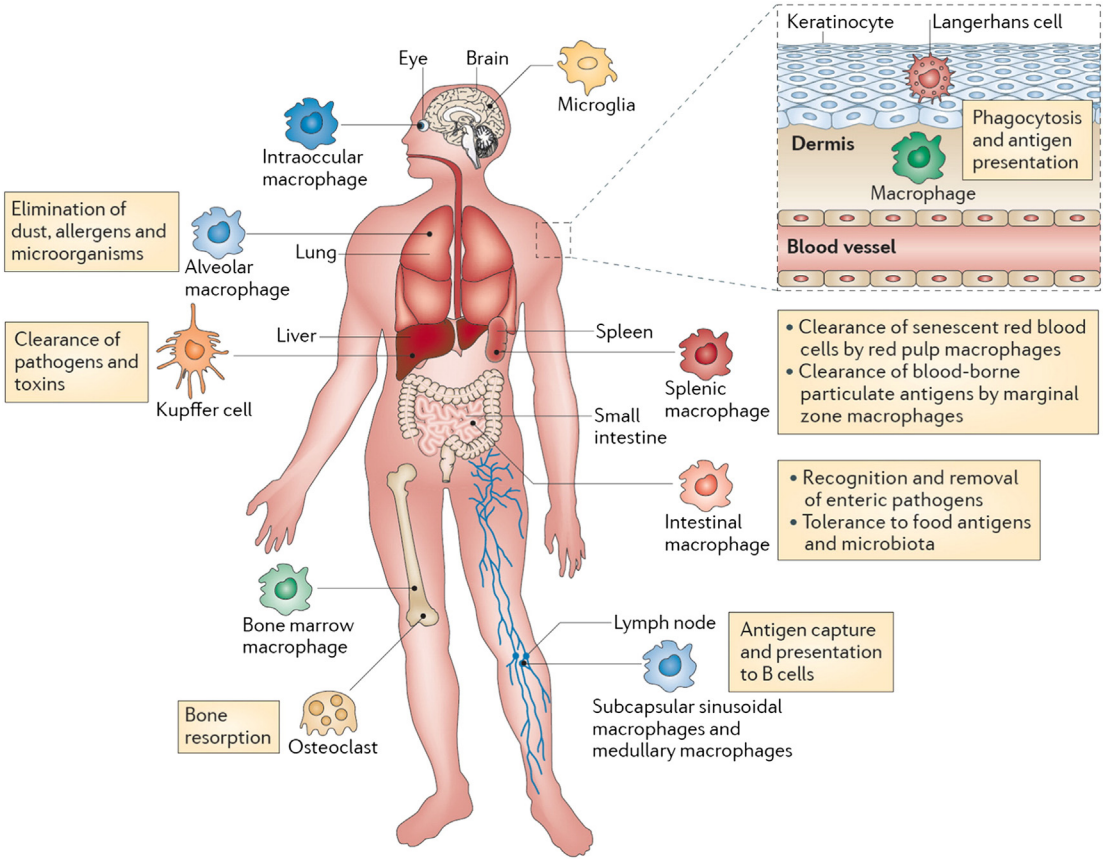

Fig. 1. Tissue macrophages perform important homeostatic functions. Mononuclear phagocytes are generated from committed hematopoietic stem cells located in the bone marrow. Macrophage precursors are released into the circulation as monocytes and quickly migrate into nearly all tissues of the body, where they differentiate into mature macrophages. Various populations of mature tissue macrophages are strategically located throughout the body and perform important immune surveillance activities, including phagocytosis, antigen presentation and immunosuppression. Reprinted with permission from NPG [2].

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