Immunobiology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Immunobiology

journal homepage: www.elsevier.com/locate/imbio

Review Article

Macrophages: Their role, activation and polarization in pulmonary diseases

Shweta Arora[a], Kapil Dev[a], Beamon Agarwal[b], Pragnya Das[c], Mansoor Ali Syed[a,*]

[a] Translational Research Laboratory, Department of Biotechnology, Jamia Millia Islamia, New Delhi, India
[b] Department of Hematopathology, Montefiore Medical Center, 111 East 210th Street, Bronx, NY 10467-2401, United States
[c] Drexel University College of Medicine, Philadelphia, PA 19134, United States

ARTICLE INFO

Keywords:
M1/M2 macrophages
Classical activation
Alternative activation
Lung inflammation
COPD
BPD
Asthma

ABSTRACT

Macrophages, circulating in the blood or concatenated into different organs and tissues constitute the first barrier against any disease. They are foremost controllers of both innate and acquired immunity, healthy tissue homeostasis, vasculogenesis and congenital metabolism. Two hallmarks of macrophages are diversity and plasticity due to which they acquire a wobbling array of phenotypes. These phenotypes are appropriately synchronized responses to a variety of different stimuli from either the tissue microenvironment or – microbes or their products. Based on the phenotype, macrophages are classified into classically activated/(M1) and alternatively activated/(M2) which are further sub-categorized into M2a, M2b, M2c and M2d based upon gene expression profiles. Macrophage phenotype metamorphosis is the regulating factor in initiation, progression, and termination of numerous inflammatory diseases. Several transcriptional factors and other factors controlling gene expression such as miRNAs contribute to the transformation of macrophages at different points in different diseases. Understanding the mechanisms of macrophage polarization and modulation of their phenotypes to adjust to the micro environmental conditions might provide us a great prospective for designing novel therapeutic strategy. In view of the above, this review summarises the activation of macrophages, the factors intricated in activation along with benefaction of macrophage polarization in response to microbial infections, pulmonary toxicity, lung injury and other inflammatory diseases such as chronic obstructive pulmonary dysplasia (COPD), bronchopulmonary dysplasia (BPD), asthma and sepsis, along with the existing efforts to develop therapies targeting this facet of macrophage biology.

1. Background

Macrophages are the ultimate cells of differentiation of the mononuclear phagocyte system. The system further embraces dendritic cells, blood monocytes in circulation and committed myeloid lineage cells in the bone marrow. A marked heterogeneity is displayed by monocytes and dendritic cells in response to environmental stimuli. However, in case of human macrophages, some apprehensions with respect to marked expression motifs of surface markers that delineate different macrophage subsets still persist (Cassetta et al., 2011). They form an important component of immunity, playing indispensable characters in innate as well as acquired immunity. Macrophages residing in the tissues are the first barriers of defense against extrinsic invaders and coordinate leukocyte penetration in innate immunity. They subscribe equilibrium between antigen removal by phagocytosis and degradation of microbes, apoptotic cells, and neoplastic cells (Gordon, 2003). They are able to acquire well defined phenotypes via phenotypic polarization in response to variegated environmental signals (which could be

Abbreviations: ROI, reactive oxygen intermediates; VEGF, vascular endothelial growth factor; Arg-1, Arginase-1; HO-1, Heme Oxygenase-1; SRXN1, Sulphiredoxin-1; iNOS, inducible nitric oxide synthase; Th1, T-helper cells1; IFN-γ, interferon gamma; IL-4, interleukin-4; Th-2, T-helper cells 2; LPS, lipopolysaccharide; TNF-, αtumor necrosis factor alpha; GM-CSF, granulocyte monocyte colony stimulating factor; NK, natural killer cells; APC, antigen presenting cells; IFNGR, interferon gamma receptor; PAMPs, pathogen associated molecular patterns; TLR, toll like receptor; TAM, tumor associated macrophages; MMP, metalloproteinase; STATs, signal transducer and activator of transcription; IRFs, interferon regulatory factor; PPARγ, peroxisome proliferator activated receptor gamma; CREB, cAMP-responsive element binding protein; NF-κβ, nuclear factor kappa beta; AP, activator protein; UTR, untranslated region; miR, micro RNA; PPP, pentose phosphate pathway; CARKL, carbohydrate kinase like protein; GSH, glutathione; ETC, electron transport chain; γ-GCE, gamma glutamylcysteinylethyl ester; NO, nitric oxide; TCA, tricarboxylic acid; ARDS, acute respiratory distress syndrome; ALI, acute lung injury; RIG-I, retinoic acid inducible gene; NODs, NOD like receptors; AEC, alveolar epithelial cells; PMN, polymorphonuclear leukocytes; MARCO, macrophage receptor with a collagenous structure; SARS, severe acquired respiratory syndrome; RSV, respiratory syncitial virus; COPD, chronic obstructive pulmonary disorder; LMP, low molecular mass protein; Mtb, *Mycobacterium tuberculosis*; BPD, broncho pulmonary dysplasia; AEC, alveolar epithelial cells; GSH-C4, *n*-butanoyl GSH derivative; NAC, *N*-acetyl cysteine; GSH-OEt, GSH-monoethyl ester; TREM, triggering receptor expressed on myeloid cells; Bcl-2, B-cell lymphoma 2; SOCS-1, suppressor of cytokine signalling-1

* Corresponding author.
E-mail addresses: shweta169213@st.jmi.ac.in (S. Arora), kdev@jmi.ac.in (K. Dev), bagarwal@montefiore.org (B. Agarwal), pd427@drexel.edu (P. Das), smansoor@jmi.ac.in (M.A. Syed).

https://doi.org/10.1016/j.imbio.2017.11.001
Received 13 April 2017; Received in revised form 10 November 2017; Accepted 10 November 2017

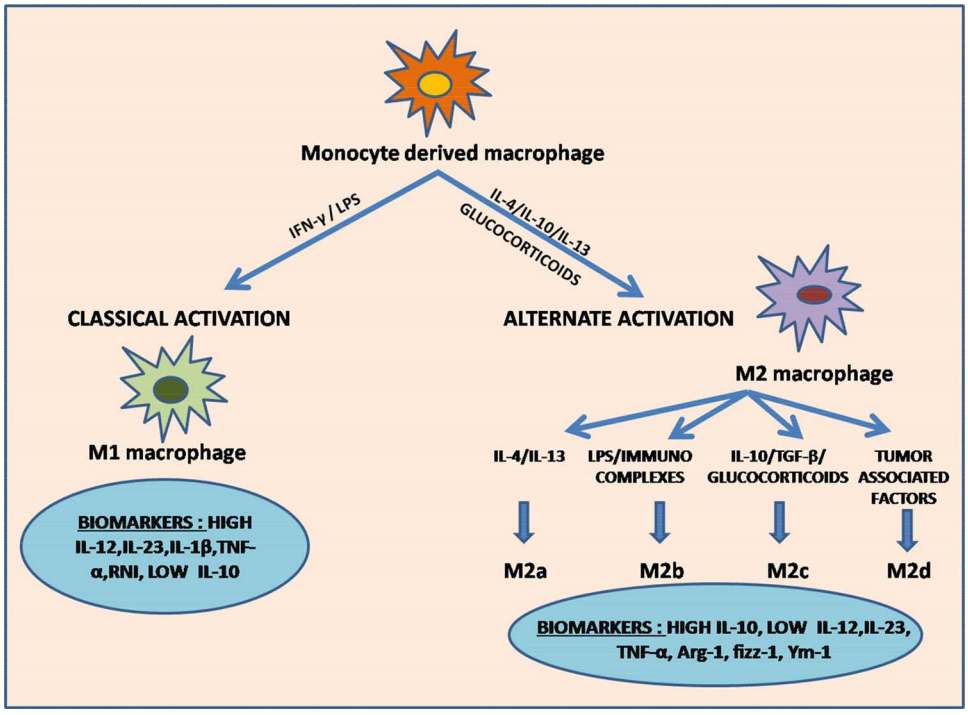

Fig. 1. Classical and Alternate pathway of Macrophage polarization.
The figure depicts the pathways involved in macrophage polarization in response to signals received from micro-environment. Classical activation of M1 macrophages is induced by LPS/IFN-γ exposure. Activated M1 macrophages promote enhanced secretion of M1 chemokines, Th1 response elements, i-NOS (inducible nitric oxide synthase) dependent reactive nitrogen intermediates (RNI), high levels of IL-12, IL-23 IL-1β and TNF-α, and low levels of IL-10, which exert pro-inflammatory and cytotoxic effects. They are also involved in tumor suppression and immunostimulation. Alternately activated M2 macrophages are stimulated by IL-4, IL-10, IL-13 and glucocorticoids. IL-4 and IL-13 activates M2a subtype. Presence of immunocomplexes and LPS activates M2b subtype. M2c subtype is induced by IL-10, TGF-β and glucocorticoids. Presence of tumor associated factors triggers the activation of M2d subtype. Activated M2 macrophages enhance the secretion of IL-10 and reduces the secretion of IL-12 and IL-23 due to which they exert anti-inflammatory effects and roles in tissue repair and wound healing. M2d subtype is the prime constituent of TAMs (tumor associated macrophages) and hence promote tumor growth.

pathogenic parts or products, injured cells, cellular debris or initiated lymphocytes);and during divergent states of disease (O'Shea and Paul, 2010).

Macrophages amalgamate with B and T cells through systems grounded on the secretion of enzymes, reactive radicals, cytokines, chemokines and metabolites of arachidonic acid (fluid phase mediated mechanism); and through cell to cell communication (Gordon, 2003; Stout and Suttles, 2005; Duffield, 2003). Their activation is dependent upon the signals they receive from their microenvironment which can potentially promote or suppress inflammation leading to smashing of tissue or resuscitation and wound repair, respectively. Thus, the functional phenotype of macrophages acquired in sequel to signals derived from tissues finally trigger, instruct and adjourn the adaptive immune response (Mantovani et al., 2005). Moreover, these cells also bestow themselves in homoeostatic functions such as reconstruction of tissues in ontogenesis and metabolic function symphonization (Gordon, 2003; Biswas and Mantovani, 2010; Sica and Bronte, 2007).

Monocytes migrating from blood stream to the peripheral tissues are the progenitor cells of macrophages. The demarcation (differentiation) of these monocytes into macrophages and dendritic cells occurs on exposition to microbial compounds, cytokines favouring inflammation and local growth factors (Tacke et al., 2006). Different regulatory levels and attainment of enhanced resistance to microbes has been achieved by intercellular communication between activated T and B lymphocytes and macrophages. A broader range of trophic functions such as the job of Th2- derived interleukin-4 (IL-4) against extracellular parasitic infection and Th1-derived interferon-gamma (IFN-g) against intracellular infection in acquired immunity and several immunomodulatory agents are responsible for the emergence of the concept of the two correspondents: M1 and M2 macrophages (Martinez and Gordon, 2014). The multiple properties of different phenotypic variants of macrophages possess substantial effects on the residing tissues under different diseased conditions. A specific subset can be either defensive during disease or homeostasis or can be modified in order to complement disease pathogenesis and progression.

2. Heterogeneity in macrophage activation and polarization

Two hallmarks of macrophages are diversity and plasticity. Classically activated M1 and alternatively activated M2 phenotypes of macrophages portray two zestful changing states of macrophage activation. M1/M2 macrophage polarization is a tightly coordinated process involving numerous pathways of signal transduction, transcriptional and post-transcriptional networks of regulation. M1 macrophages release pro-inflammatory cytokines which retard cellular proliferation surrounding the tissue leading to tissue damage. In contrast, M2 macrophages release anti-inflammatory cytokines which aids in cellular proliferation and promotes wound healing and tissue repair. Any imbalance in macrophage M1/M2 polarization may have detrimental effects resulting in varied diseases or states of inflammation (Wang et al., 2014).

2.1. Macrophage polarization: classical and alternate activation

IFN-γ or a combination of IFN-γ with microbial stimuli like lipopolysaccharide (LPS present in the exterior membrane of Gram-negative bacteria) or other cytokines such as GM-CSF (granulocyte-macrophage colony stimulating factor) and TNF-α is responsible for the differentiation of classically activated M1 macrophage (Martinez and Gordon, 2014; Murray et al., 2014). Lipopolysaccharide (LPS), is carried to the cell surface receptor complex via an LPS-binding protein (Guha and Mackman, 2001). Th1, CD8+ cytotoxic lymphocytes, natural killer (NK) cells, antigen-presenting cells (APC) and B cells, all secrete IFN-γ. IFN-γ is then recognized by IFN-γ receptor (IFNGR), and binding of IFN-γ to IFNGR triggers a series of signal cascades leading to activation and differentiation of M1 macrophages. M1 macrophages possess a specific set of characteristics determined on the basis of tissue location. These characteristics are: a. enhanced secretion of pro-inflammatory cytokines like TNF-α, IL-15, IL-23, IL-1β; b. amplified antigen presenting capacity; c. increased production of iNOS-dependent reactive nitrogen intermediates (RNI) and reactive oxygen intermediates (ROI) and d. aggravated release of IL-12. M1 macrophages, being the first shield to safeguard against intracellular pathogens, display enhanced endocytic functions. Moreover, they secrete high