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Editorial Open Access

# Macrophage Polarization-Introduction

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## Editorial

Macrophages (MΦ) are phagocytic cells of the innate immune system that are present in virtually all tissues. Macrophages differentiate from circulating peripheral-blood mononuclear cells (PBMCs), which migrate from the bloodstream into tissue in the steady state or in response to trauma or infection [1]. Mononuclear cells develop from myeloid progenitor cells in the bone marrow that serve as the precursor for a variety of different cell types, including neutrophils, eosinophils, basophils, MΦ, dendritic cells (DCs) and mast cells. During monocyte development, myeloid progenitor cells sequentially give rise to monoblasts, pro-monocytes and finally monocytes, which are released from the bone marrow into the bloodstream [1]. Monocytes migrate from the blood into tissues to become tissue-specific MΦ of the bone (osteoclasts), alveoli (alveolar), central nervous system (microglial cells), connective tissue (histiocytes), gastrointestinal tract, liver (Kupffer cells), spleen, and reproductive tract [2,3]. Monocytes that migrate into these tissues are influenced by the local environment where exposure to local growth factors, proinflammatory cytokines, and microbial components promote differentiation into MΦ [4]. The function of the MΦ within that local environment is linked to the type of receptor interaction and the cytokine composition that is encountered [5]. For example, exposure to human granulocyte-macrophage colony stimulating factor can polarize monocytes towards the M1 subtype with a proinflammatory cytokine profile typified by secretion of TNF, IL-1, IL-23 etc. In contrast, treatment with macrophage colony stimulating factor or IL-4 produces an anti-inflammatory cytokine profile similar to the M2 subtype which is exemplified by IL-10 and IL-1RA secretion [6,7]. Classically activated (M1) macrophages have an effector role in TH1 immune responses and M2 macrophages appear to have immunosuppressive and tissue repair functions.

Tissue resident MΦ participate in protection, tissue integrity, repair and surveillance from harmful microorganisms and materials. In mucosal surfaces such as the respiratory, reproductive and gastrointestinal tracts, the MΦ is the primary means and first line of defense in the capture and clearance of noxious material and microorganisms [8]. These noxious materials can be external such as bacteria and viruses or they can be internal such as hemoglobin, apoptotic debris and cancer cells. For example, every day MΦ process and clear hemoglobin from approximately $2 \times 10^{11}$ red blood cells via the cell surface receptor CD163. Free hemoglobin is bound to the acute phase protein haptoglobin and is then internalized by CD163. This clearance process is of vital importance without which humans could not survive. In fact, extracellular hemoglobin has been shown to polarize the macrophage proteome toward Hb-clearance, enhanced antioxidant capacity and suppressed HLA class 2 expression [9]. Macrophages are likewise engaged in the removal of the cellular debris that is generated by normal apoptosis and tissue remodeling. When cells die the MΦ will investigate the nature of the remodeling or apoptosis. If the remodeling is a result of normal physiologic processes, the material is phagocytized but does not elicit the production of immune modulators [10].

When MΦ detect danger signals such as necrosis or infection, an alternate pathway is engaged where the MΦ undergo dramatic changes to their physiology. Alterations include modified expression of cell surface receptors, production of proinflammatory mediators, and secretion of cytokines [11]. Macrophages detect danger signals through pattern-recognition receptors such as CD206, Toll-Like receptors such as TLR-2 or TLR-4 and IL-1R [12,13]. The response to endogenous danger signals is one example of how macrophage activation can occur in tissues. Macrophages have an incredible ability to efficiently respond to their environment and change their phenotype as a result of innate and adaptive immune responses. Environmental signals, however, do not always induce changes that increase MΦ activation and function. In fact, both innate and adaptive responses can give rise to MΦ that are less equipped to provide adequate cytokine secretion and are more susceptible to infections.

Danger can also come as a result of tumorigenesis. Studies have demonstrated that a distinct population of MΦ participates in the dispersal of malignant cells [14-16]. Macrophages are one of the major cell populations infiltrating solid tumors. Tumor associated macrophages (TAMs) play an important role in tumor immunity and demonstrated functions similar to M2. TAMs appear to be a polarized M2 population of cells with potent immunosuppressive properties [17]. The presence and expression of the M2 macrophages often reflect a poor prognosis. Interestingly, the CD163 receptor is often used as a marker for TAMs. CD163 is associated with Hodgkin's lymphoma, non-small cell lung cancer, breast carcinoma, endometrial carcinoma, colon carcinoma, and T cell lymphoma [18-21].

This Special Issue of the Journal of Clinical and Cellular Immunology is devoted to "Macrophage Polarization". The collection of original reviews and research articles critically evaluate and expand upon our understanding of macrophage polarization. For example, Foey presents a succinct review of the research evidence for the manipulation of macrophage polarization to provide a therapeutic intervention for chronic inflammatory disorders such as Crohn's disease and periodontal disease [22]. Macrophages exhibit a wide range of functional properties ranging from pro-inflammatory to anti-inflammatory, from anti-tumoral to pro-tumoral. Given this broad functional capacity, the potential for macrophage reprogramming is at hand.

Mortara et al. [23] discuss the polarization of infiltrating leukocytes and their role in pro-angiogenesis of non-small cell lung cancer (NSCLC). Lung cancer is the most common cancer in the developed world. NSCLC is the most common type comprising approximately

80% of all lung cancers. NSCLC can be divided into two subtypes: squamous cell and adenocarcinoma both of which can be treated with surgical intervention if caught early. Unfortunately, lung cancer is more often not diagnosed until after the patient becomes symptomatic. The late stage diagnosis, severely limits the therapeutic options available to the patient. Chemotherapy is typically a difficult course of treatment with only partial effectiveness and only 20% of patients surviving 5 years beyond diagnosis. As a result of the dim outlook for patients with NSCLC, innovative and alternative therapies are in desperate need. In this review, Mortara et al. [23] describe the functionality of tumor infiltrating and tumor associated NK cells in producing pro-tumor properties that provide for angiogenesis, stromal support and rather than being killers of tumor, these cells promote tumor expansion and progression. By evaluating these cell populations in NSCLC, it is postulated that a more precise knowledge of these cells and their properties can open avenues for diagnosis, therapeutics, and perhaps prevention.

Three reviews provide insight on MΦ polarization in infectious disease. Decote-Ricardo et al. [24] provide a review of the mechanisms of macrophage polarization in response to infections. A significant degree of cell signalling and communication occurs continually as a reaction to environmental sampling and host defense. Macrophages have a role in innate and adaptive responses to virtually all-infectious agents. Through the association of pattern recognition molecules, Toll-like receptors and pathogen recognition receptors, the MΦ is continuously sampling the environment for signs of invasion. Once engaged, these MΦ molecules can promote microbicidal activity against the pathogen. Several pathogens have evolved strategies to evade and defeat these mechanisms by altering the M1 and M2 phenotype in their favor. Various species of Salmonella and Mycobacterium have adapted the means to avoid, alter and subvert activated M1 cells. Viruses such as HIV and herpes can likewise alter the phenotype and take advantage of the M2 cells. M2 cells can serve as an important reservoir for virus replication. Intracellular parasites such as Trypanosoma cruzi can also utilize the M2 macrophages as a reservoir for evasion and to promote an anti-inflammatory environment favorable to parasite replication. Sang et al. [25] discuss the involvement of macrophages in viral replication and anti-viral activity. The MΦ cellular response if complex, resulting in changes to the differential process of the macrophage. The role of Type I and III interferon's is discussed as it pertains to viral infection and what impacts it can have to MΦ polarization. An incorporation of interferon mediated antiviral states into the framework of MΦ polarization is supported by view that interferon can regulate M1 and M2 phenotypes. Finally, a discussion of MΦ polarization is presented in the context of Chaga's disease [25]. The control of the T. cruzi infections is dependent on cytokine-mediated macrophage activation leading to intracellular killing of the parasite. Data suggests that M1 polarization is closely linked to the elimination of parasites, and M2 polarization could be effective in preventing the progression of oxidative and inflammatory pathology that is seen in Chaga's disease [26].

Thomsen and Rosendahl present a review on polarization of MΦ in metabolic disease describing some of the current ideas and trends in the progression of diabetes [27]. Inflammation is a recurrent trend in metabolic disease and cardiovascular disease. Medbury et al. present a review on cholesterol and MΦ polarization towards an understanding of the bidirectional interplay that exists between cholesterol and macrophage phenotype [28]. Both of these reviews provide thoughtful insight into key pathways that may be targeted for the development of novel therapeutics.

The remaining articles in this special issue pertain to original research into the mechanisms of polarized MΦ. The different pathways to MΦ differentiation and activation bring about insight into influenza virus replication in M1 versus M2 macrophages. Greater susceptibility to influenza A was seen in the M2 phenotype [29]. Venter et al. investigate the rate of glycolysis in RAW 264.7 and Mafb/C-Maf deficient cell lines. These results confirm the idea that macrophages prefer a rapid glycolytic metabolism because it provides the energy required for immune function [30]. Oka et al. explore multiple emulsion formulation to deliver microRNA into TAMs to achieve M1 repolarization. Motility, morphology and apoptotic profile of cancer cells was determined. Treated cells had a greater cellular interaction [31].

These studies and reviews collectively broaden our understanding of macrophage polarization and further our efforts to improve therapeutics and develop interventions that can capitalize on function. I commend each of the authors for their hard work, scientific effort and contribution to macrophage biology.

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