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Let us not Forget Macrophages: The Role of M1 and M2 Macrophages in the Human Body

Max Molina Ayala and Edwin Roger Parra*

Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, USA

***Corresponding author:** Edwin Roger Parra, Department of Translational Molecular Pathology, Unit 951, The University of Texas, USA

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ABSTRACT

Macrophages and their roles and interactions have been greatly studied over the past 30 years. Their classification into M1 and M2 and the M2 subtypes makes their study approachable because each of classification or subtype has its own function. More importantly, macrophages polarize into each of these roles by direct stimuli that are independent of other immune cells, making them vital in organizing innate immunity as well as the coordinated response for recovery after injury. In this mini review, we briefly dive into macrophages' classification, their roles in disease, and the missing pieces to our understanding the complete picture required to use them as targets for therapy.

Keywords: M1 Macrophages; M2 Macrophages; Immune; Innate; Role

Introduction

Macrophages are an essential component of the immune system and play important roles in regulating the cellular environment in response to injury. They are one of the most flexible components of the innate immune system, with a high plasticity that enables them to change their phenotype in response to their microenvironment [1]. The nomenclature for the continuum of phenotypes for macrophages was coined to distinguish between two populations according to their activation pathway: the classical way or an alternative pathway dominated by cytokines [2], resulting in the M1 and M2 classifications, respectively, which roughly correspond to the previously existing nomenclatures of Th1 and Th2. An M1 or M2 classification represents not only a distinct pathway of macrophage activation but function as well, with distinct cytokine production activity. Although M2 macrophages are activated in an alternative way, distinctions in stimuli give these cells unique phenotypes and roles, leading to further classifications of M2a, M2b, M2c, and M2d. This mini review dives into the most used terms, macrophages' interactions with disease, and the opportunities that lie ahead.

Macrophages Across Diseases

After finding their place within human tissues and organs, macrophages, and their organ-specific counterparts, such as dust cells, Kupffer cells, microglia, and Langerhans cells respond to their microenvironment stimuli, usually after injury or infection [3]. The activation of macrophages happens in two distinct pathways, the so-called classical activation, resulting in M1 macrophages, and alternative activation, resulting in M2 macrophages [4]. Stimulation of Toll-like receptors by agonists such as bacterial lipopolysaccharides lead to M1 differentiation, a phenotype that has intense proinflammatory capabilities, favors the expansion of Th1 lymphocytes, and produces nitric oxide and cytokines in large quantities [3]. This makes M1 macrophages an invaluable tool for fighting invading microorganisms such as bacteria, while being responsible for damage to the host when this proinflammatory response is modulated or modified by the invading microorganisms; however, in other cases M1 macrophages aid in the replication of certain viral infections [5,6].

M2 macrophages, in contrast, are activated by exposure to specific cytokines: IL-4, IL-10, or IL-13 [7]. M2 macrophages will then acquire a high phagocytic capacity, produce extracellular matrix, and stimulate collagen production, and produce angiogenic and anti-inflammatory responses, thus aiding wound healing to the point of being considered the benign counterpart of the M1 macrophages [8]. M2 macrophages, however, have been studied and further categorized into subgroups with well-defined tasks [9]. M2 macrophages are polarized by IL-4 or IL-13 and promote endocytic activity, cell growth, and tissue repair. When exposed to immune complexes, Toll-like receptor ligands, or IL-1β, M2a macrophages turn into M2b macrophages with pro- and anti-inflammatory cytokine production, effectively regulating the immune response of their environment. Inactivated macrophages, classified as M2c, are mainly created by exposure to glucocorticoids and IL-10 and mostly perform apoptotic cell phagocytosis. Finally, M2d macrophages are created by Toll-like receptor antagonists, such as some angiotensin receptor blockers, and produce IL-10 and vascular endothelial growth factors [10]. However, as with M1, M2 macrophages can have their response hijacked either by invading microorganisms or malignant cells in the process of modifying their tumor microenvironment and be detrimental to the host [11].

The distinction and relationship between M1 and M2 macrophages have traditionally been regarded as the "fight or fix" response, regarding M1 and M2 macrophages respectively [12], and thus the responses are understood as opposing activities. It remains of biological significance that the activity of macrophages and their organ-specific counterparts does not require T cell or B cell signaling, and as such is part of the first response to injury. However, constant macrophage function is necessary, and thus a default state of the macrophage is needed, which has been demonstrated to be either M2 or a state closely resembling this activation pathway [13,14]. Another important property is that macrophages present enough plasticity to change their polarization if presented with the correct signaling [15].

Tumor-associated macrophages have been documented to promote tumor growth, despite having phagocytic activity, and have active metabolic pathways that are like M2 macrophages; thus tumor-associated macrophages create an environment that promotes tumor growth and are associated with poor prognosis [4]. Studies have attempted to determine the dominant polarization in specific diseases. M1-predominant diseases include bacterial infections and autoimmune mechanisms with accumulation of oxidative damage, such as atherosclerosis [16] and inflammatory bowel disease [17,18]. M2-predominant diseases prominently include cancer [19] and several infectious diseases, such as leishmania, tuberculosis (Figure 1), and HIV [20, 21]. These responses, as we have said before, can be co-opted by the disease to favor it, whether it be viral replication, bacterial survival, or tumor growth [12].

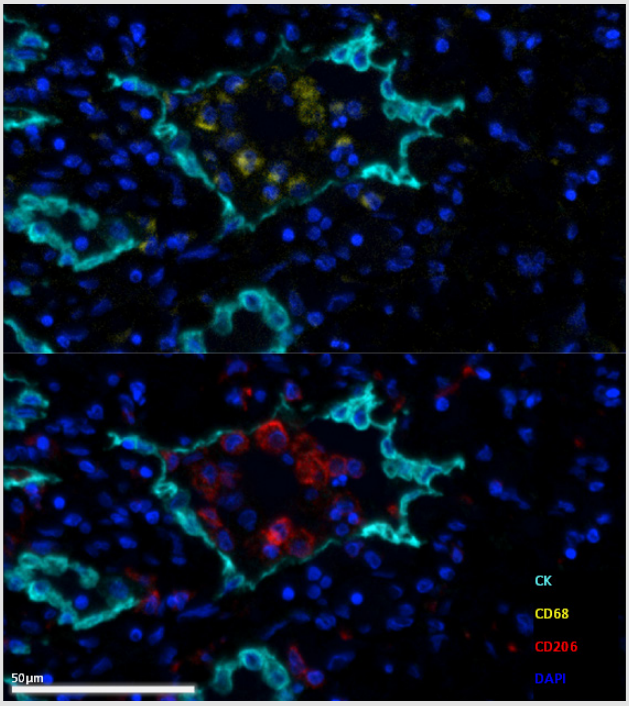

Figure 1: Multiplex immunofluorescence image of alveoli in a patient with active tuberculosis. The alveolar space is full of macrophages that are positive for both CD68 (yellow, top) and CD206 (Red, bottom), indicating the predominant M2 response to tuberculosis, even outside of granulomas.

It is apparent that macrophages polarize into either of these roles during disease [4], and the question is whether modern human civilization benefits from our current levels of M1 and M2 responses. Our lifestyles have continuously changed over the past two hundred years, such that most people now live in long-lived and low-germ environments while our lifestyles and diet create proinflammatory states [16]. These changes have led to an increase in M1 responses that promote or worsen disease and an increase of M2 responses that are not beneficial for several modern diseases, such as cancer. Another modern example is the M1 response to SARS-CoV-2 infection, in which recruited macrophages in the lungs upregulate and prolong the inflammatory response to the virus with T cell activation, causing a pathological inflammatory response that can lead to acute respiratory distress syndrome [22,23]. This inappropriate level of response from our innate immune system, and the roles that M1 and M2 macrophages play in modern disease, make them interesting targets for study and development of therapeutic strategies such as creating microRNA carriers that deliver the necessary signaling to regulate macrophages in diseases where they play important roles [15].

Studying Macrophages

Discovering, mapping, and understanding the interactions of macrophages in our current environment is a work in progress. Steady progress in the fields of oncology and autoimmune diseases has been made by studying the interactions of tumor-associated macrophages and their phenotypes during treatment and its outcomes [24] or the interactions of macrophage populations in site-specific pathologies such as rheumatoid arthritis [25], in which resident macrophages favor the inflammatory state of disease. However, systemic suppression of macrophage activity has severe side effects that make this approach unfeasible for most of these conditions [26] and finding treatments specific enough to target distinct macrophage subtypes is a challenge we have yet to overcome. Further study of macrophages may yield the specific markers or targets that can be exploited to create therapies that are both specific and effective. As new platforms for research emerge, such as spatial transcriptomics [27], protein analysis [28], and even multi-omic platforms [29], and as more robust and widespread platforms such as multiplex immunofluorescence with digital image analysis [30] become available in more countries, we can pave the way to study every facet of disease and the interactions of macrophages in such conditions [31].

Conclusion

The traditional role of macrophages as cleaners and sweepers in the body, as well as antigen presenting cells, is limited in scope to their actual role and importance in both homeostasis and injury. With our current technology, we have a need to further understand how to take advantage of the unique plasticity of macrophages and their abilities. M1 and M2 macrophages function in opposing and self-regulatory roles, polarize according to stimuli and their environment, and can be modified to better suit response to injury in the human body. As we have gained understanding of the importance of macrophages, they have become desirable targets of study, as promoting either an M1 or M2 response-or suppressing both in a selective manner-can finally put a leash on the masters of inflammation that macrophages are in our bodies.

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Conflicts of Interest

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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