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Review

A stratified myeloid system, the challenge of understanding macrophage diversity

F. Geissmann[a,b,*], E. Mass[a,b]

[a] Memorial Sloan Kettering Cancer Center, 417 E 68th St New York, NY 10065, USA
[b] Weill Cornell Graduate School of Medical Sciences, Weill Cornell Medicine, 1300 York Avenue New York, NY 10065, USA

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ABSTRACT

The present issue of 'Seminars in Immunology' addresses the topic of macrophage biology, 100 years after the death of Elie Metchnikoff (May 1845–July 1916). As foreseen by Metchnikoff, the roles of macrophages in the maintenance of homeostasis and immunity against pathogens have become a broad and active area of investigation. We now start to realize that the myeloid system includes a multiplicity of cell types with diverse developmental origins and functions. Therefore, the textbook picture of a plastic and multifunctional macrophage does not meet the requirements of our current knowledge anymore. Further development toward a quantitative and molecular understanding of myeloid cell biology *in vivo* and their roles in tissue homeostasis and remodeling will benefit from taking this complexity into account. A tentative model to help in this pursuit and account for myeloid cell and macrophage diversity is discussed below.

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1. Introduction

Over the past few years, a better knowledge of the developmental biology of macrophages, monocytes, and dendritic cells has emerged, which should lead to a molecular understanding of their functions within tissues *in vivo*, and guide comprehensive and efficient therapeutic interventions. In this issue, Gold and Brückner summarize their view of macrophage development and function in the fruit fly *Drosophila melanogaster*. McGrath and Palis, as well as Kierdorf et al. critically review the experimental work that recently transformed our view on the development of tissue-resident macrophages in mice, and Puhr et al. review the current understanding of dendritic cell differentiation. Ulland et al. review the functions of microglia in the brain with a focus on growth factors and activating receptors. Lauvau et al. give a detailed and comprehensive review of the mechanisms by which monocytes promote microbial clearance. Finally, Schultze and Schmidt review recent studies exploring transcriptional and epigenetic regulation in monocytes/macrophages under homeostatic and stress conditions.

2. Metchnikoff's macrophage

Phagocytosis of microbes and foreign particles was observed and described by pathologists in the second half of the 19th century [1]. The unique contribution of Elie Metchnikoff, formulated in the 1880s, stemmed from his adhesion to the new theory of

* Corresponding author.
E-mail address: geissmaf@mskcc.org (F. Geissmann).

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evolution proposed by Darwin. Metchnikoff hypothesized that phagocytosis was a physiological mechanism selected by evolution in metazoans for the purpose of removing unfit cells and microbes. This led him to study 'intracellular digestion' across the animal kingdom from unicellular organisms such as Amoebae to invertebrates and vertebrates during embryogenesis as well as in adult animals [2]. Applying his comparative, experimental, systematic, and quantitative approach to vertebrates, Metchnikoff collected large amounts of data on phagocytosis by mesodermal cells during embryogenesis, tissue homeostasis, and the defense against infectious pathogens [3,4]. From these observations, he proposed a 'Theory of cellular immunity' that featured a central role for phagocytosis in the inflammatory response against pathogens. Against the long-held idea that inflammation was a local tissue degeneration, Metchnikoff wrote "*Inflammation generally must be regarded as a phagocytic reaction on the part of the organism against irritants. This reaction is carried out by the mobile phagocytes, sometimes alone, sometimes with the aid of the vascular phagocytes* (via diapedesis) *or of the nervous system*" [2].

After Metchnikoff, macrophages have been considered as the phagocyte 'par excellence', and numerous researchers have confirmed that macrophages are mesodermal cells, present as a distinct cell type across ontogeny, from embryo to adults, and across the animal kingdom from insects to vertebrates (see article by Gold et al., in this issue). Macrophages sense, scavenge, and whenever possible, digest dying and unfit cells, protein and lipid deposits, crystals, and microorganisms [5–7]. Macrophages also produce a large spectrum of bioactive molecules such as cytokines and growth factors in response to signals from their environment. From an immunological perspective, their ability to present peptides from foreign protein to T-lymphocytes in many vertebrates is important for the mounting of an antigen specific immune memory [6,7].

3. The 'umbrella' macrophage

Altogether, a century of work on macrophages has established the idea that this evolutionary conserved cell type plays important roles in phagocytosis and production of bioactive molecules, immune and non-immune functions in embryogenesis, tissue homeostasis, protection against infectious diseases, and more recently in tumor growth [8–10]. Yet, the role of macrophages in disease remains complex and not well understood. This is primarily due to our limited knowledge of the developmental and molecular mechanisms that underlie macrophage diversity across tissues and the poorly defined nature of macrophages [11,12]. For comparison, the study of lymphoid cells in diseases has benefited tremendously from being rooted into a detailed knowledge of thymic and bone marrow lymphopoiesis. Metchnikoff discussed in evolutionary terms the heterogeneity of phagocytes, from tissue phagocytes already present in invertebrates to blood leukocytes that appear with the circulatory system and extravasate into inflamed tissues [13]. This work was carried forward into the 20th century and resulted in distinction between dendritic cells and macrophages by Steinman and Cohn [14]. However, the term macrophage is still an 'umbrella' for very different phagocytic cells types. The 'mononuclear phagocyte system' model (MPS), initially proposed by Van Furth and Cohn [15,16], held that monocytes were the precursors of all tissue macrophages. It followed that resident phagocytes such as Kupffer cells in the liver, brain microglia, or alveolar macrophages, as well as blood inflammatory monocytes that enter tissues via diapedesis during inflammation, and myeloid cells that populate the lamina propria of the gut are all called macrophages and are frequently defined by a set of common markers, despite their developmental, molecular, and functional heterogeneity.

The *in vitro* models that have been developed to study macrophages have accordingly relied on the cultivation of blood monocytes or bone marrow progenitors, without always trying to recapitulate the biology and diversity of macrophages resulting from their different developmental origins. It is also the case that we frequently lack unique marker(s) to distinguish monocytes from macrophages in a given tissue, even more so when the tissue is the site of an inflammatory response, *e.g.* an atherosclerotic plaque. Likewise, current transgenic mouse models in use to target 'macrophages' and study their biology *in vivo* do not reliably distinguish distinct types of myeloid cells, in contrast to equivalent models useful for example for the study of B- and T-lymphocytes. To account for macrophage diversity, the MPS model was augmented by a differentiation/activation process of monocytes called 'polarization' and defined *in vitro* [17], where external cues such as interferon gamma or interleukin-4 direct monocyte differentiation towards classical M1 and alternative M2 macrophages respectively [17–19]. This paradigm was proposed to account for the diversity of macrophage phenotypes and functions in a given healthy or diseased tissue, and logically suggests that 're- or de- polarizing' tissue macrophages may help restore homeostasis [17]. However, this paradigm does not reflect the developmental origin of macrophages and how it may contribute to the observed phenotypic and functional diversity.

4. A stratified myeloid system

Although many investigators from the basic sciences, clinical sciences, and pharmaceutical industry 'see' macrophages through the MPS framework, numerous observations and experimental results from different laboratories do not fit into the aforementioned model, and strategies to target the 'right' macrophage represent a challenge. As it will be discussed below, it has become apparent that plasticity of monocytes do not solely account for macrophage diversity. Several layers of 'hard wired' macrophage diversity result from developmental processes that take place in the developing embryo and the post natal bone marrow to govern myeloid cell function *in vivo* (Fig. 1A). This would be better referred to as a 'stratified myeloid system' (SMS) than a 'mononuclear' phagocyte system.

It is interesting to note in this regard that phagocyte diversity in *Drosophila* may also result from a layered developmental process (see Gold et al.).

The first layer of diversity is due to the two distinct developmental lineages that contribute to myeloid cells in an adult mouse. On one hand, there are the hematopoietic stem cell (HSC)-derived myeloid cells and on the other there are Yolk Sac (YS)-derived adult resident tissue macrophages. These cells arise from distinct hematopoietic lineages and likely exert different functions (see McGrath and Palis, as well as Kierdorf et al., in the present issue).

A second level of diversity is observed within each of these two compartments and can be largely attributed to specification of the cells within each compartment. Bone marrow HSCs differentiate in a steady state along several lineages to generate a number of distinct cells types, including conventional dendritic cells, plasmacytoid dendritic cells, several monocyte subsets, and cells such as gut lamina propria 'macrophages/DCs' (see Puhr et al.). A common feature of HSC-derived cells is a short lifespan and constant renewal from the bone marrow HSCs. YS-derived resident tissue macrophages also undergo specification into different cell types, such as microglia and Kupffer cells, but this process is likely to take place during embryogenesis as tissue resident macrophages self-maintain after birth (Fig. 1A).