Macrophages
Much More Than Big Eaters!

Ann Marie Schmidt

Macrophage Polarization

The Russian bacteriologist Metchnikov described the macrophage for the first time in the late 19th century.¹ For his extraordinary contributions to the then burgeoning field of immunology, he was one of the recipients of the 1908 Nobel Prize in Medicine or Physiology. The etymology of the word macrophage, built from the roots makros and phagein, lends insights into the earliest understanding of the function of these cells, that is, the devouring of large structures. We now understand that these big eater cells engulf invading pathogens, as well as debris and dead and dying cells. However, beyond roles for these cells in phagocytosis, research has uncovered seminal functions for macrophages in diverse processes, such as development,² metabolism,³ and reproduction.⁴ Once monocytes are recruited from the circulation into the target tissues, they are transformed into macrophages; these cells are both modulated by and modulate the fundamental phenotypes of the tissues into which they are drawn and then reside. Far from innocent bystanders, macrophages influence major gene programs and functions of the target tissues, for better or for worse.

Six contributions have been assembled in this ATVB Miniseries to review how macrophage responses transform the function of diverse tissues in health and disease. Although the traditional term macrophage polarization has been applied to suggest seemingly opposed expression of classical antigenic markers and functions in these cells,⁵ the concept of the extremes of M1 versus M2 polarization, which broadly refers to proinflammatory versus anti/tissue repair functions, respectively, is evolving to a much more comprehensive and dynamic classification in which plasticity and tissue-specific expression and functional patterns are unveiled.

In this Miniseries, Leitinger and Schulman⁶ explore how macrophage heterogeneity contributes to atherosclerotic lesion development and plaque stability. Bolego et al⁷ explore the intriguing connection between the molecular designation of macrophage phenotypes in cardiovascular disease and modulatory roles for estrogen signaling. Might macrophages, in part, explain the protection of premenopausal women to cardiovascular disease? Tugal et al⁸ tackle the discussion of the major transcriptional regulatory pathways for macrophage polarization. They review the mechanisms by which complex cross-talk among fundamental biological networks, such as signal transducers and activators of transcription, nuclear factor-kB, interferon regulatory factors, hypoxia-inducible factors, peroxisome proliferator-activated receptors, glucocorticoid receptors, Krüppel-like factors, microRNAs, and CCAAT/enhancer-binding proteins, orchestrate adaptive and adverse responses to stress.

Finally, this Miniseries departs, a bit, from the journal’s classical focus on atherosclerosis, thrombosis, and vascular biology to explore how macrophage polarization responses elegantly modulate the host response to HIV-1 infection and cancer by Alfano et al.⁹ In future issues, Mantovani and Locati examine macrophage responses in cancer, and Ferrante reviews the current status of the role of macrophages in excess energy balance and the impact on adiposity, obesity, and metabolic dysfunction. From these salient reviews, we learn that not only are adipose tissue macrophages, alveolar macrophages in the lungs, Kupffer cells in the liver, macrophages in foci of infection, and tumor-associated macrophages, for example, quite different from circulating monocytes but indeed they also differ greatly from each another. Influenced by their target tissues they have evolved unique characteristics and functional mandates in these highly specialized sites.

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⁵ Arterioscler Thromb Vasc Biol is available at http://atvb.ahajournals.org
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⁸ The Russian bacteriologist Metchnikov described the macrophage.
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Taken together, these compendia regaling the reader with the rich roles of macrophage polarization and plasticity in health and disease will hopefully serve to spur new research to uncover the means to harness the benefits of macrophage activity in these settings. The Merriam-Webster online dictionary supplies multiple definitions for the word polarization. Among these, of course, is the classical concept of the concentration about opposing extremes of groups or interests formerly ranged on a continuum. Sprung from Mechnikov’s original description of this intriguing cell type to our emerging understanding of its complex roles in homeostasis and pathology, perhaps the more appropriate definition of polarization vis-à-vis the macrophage may be deduced from one of numerous Merriam-Webster entries for the word from the world of physical science, that is, the action or process of affecting radiation and especially light so that the vibrations of the wave assume a definite form. We hope that the readers of ATVB enjoy this series as we consider how macrophages assume definite forms within the unique host depots to which they are attracted and in which they reside, prosper, benefit or antagonize, and eventually succumb.

Disclosures

None.

References


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