Preface

Our appreciation of the complex biology of the phagocyte has its roots in the last two decades of the 19th century, when Ilya Ilyich Mechnikov made his extraordinary observations on starfish larvae. He watched some highly motile cells in dissected larvae clustering around, and internalizing, particulate material he had added to the cell suspension. From these basic observations he hypothesized that these cells constituted a key arm in the protection of a multicelled organism against infection. At that time the "humoralist" theory of serum-dependent immunity held sway, and the heavyweights of infection biology—Louis Pasteur, Emil Von Behring, and Robert Koch—were extremely skeptical of this cellular theory. Fortunately, however, the seminal nature of Mechnikov's hypothesis was eventually recognized and he was awarded the 1908 Nobel Prize for Medicine, jointly with Paul Ehrlich, a pioneer of humoral immunity. Pasteur recruited him to the Pasteur Institute in Paris, where he remained for the rest of his career.

In multicelled organisms, cells that indulge in phagocytosis have since been recognized to be a specialized cell type, and the term "professional phagocytes" was coined by Michel Rabinovitch to be applied to cells for which phagocytosis is their primary function (Rabinovitch, 1995). To accomplish this task, these cells have a broad range of adhesion receptors capable of recognizing and binding a wide variety of ligands, both self and foreign. Once engaged, these phagocytic receptors trigger rapid rearrangement of the subtending cytoskeleton, which leads to engulfment and internalization of the bound particle. In single-celled organisms such as amoebae, this type of behavior is a means of nutrient acquisition. However, in multicelled animals the roles fulfilled by this behavior are many, and vary with the nature of the professional phagocyte and its tissue environment.

Cells of this phagocyte lineage are derived from hemapoietic stem cells in the bone marrow. These stem cells give rise to a variety of distinct lineages capable of fulfilling a broad range of roles linked to homeostasis as well as defense. The phagocyte lineages that fulfill housekeeping functions include *osteoclasts*, which remodel bone, *Kupffer cells*, which remove damaged erythrocytes from circulation, and *macrophages*, which are responsible for a wide range of homeostatic functions from removing cellular debris from tissues to the regulation of cholesterol levels in the serum. Cells of the *polymorphonuclear leukocyte* lineage, including *neutrophils*, *granulocytes*, and *eosinophils*, are the advance guard to any foreign invasion. They have a hair-trigger to any microbial insult, are readily recruited to the site of infection, and have a battery of antimicrobial weapons such as a robust superoxide burst and a range of hydrolase-containing secretory granules. Their response is a knee-jerk reaction to infection and can be highly destructive to the surrounding tissue unless downregulated rapidly. The next phagocytes to arrive at the scene are the *blood monocyte-derived macrophages*, which clean up the damaged tissue, and the *dendritic cells*, whose role it is to sample antigen and ferry it back to the nearest draining lymph node to present to T cells. Antigen sampling and presentation to lymphocytes is hard-wired into the developmental cycle of the dendritic cell to maximize the efficiency of the process. The subsequent acquired immune response dampens the neutrophil activity and upregulates the capacity of the macrophage to kill microbes and to present antigen, thus transforming it from a degradative cell to an antimicrobial cell that is now also capable of stimulating lymphocytes.

The different phagocyte lineages act as a team, communicating with one another and developing the tissue response from a relatively nonspecific inflammatory response to one that is antigen specific. These evolving behaviors are orchestrated by a range of receptors and chemical messengers produced by the different phagocytes. With respect to the initial response, recent advances in innate immunity have led to the identification of a range of highly conserved pattern recognition receptors capable of reacting to a wide gamut of molecular patterns that are conserved, or recurring, in the microbial kingdom. These receptors are found both on the cell surface and endocytic pathway (Toll-like receptors [TLRs] and non-TLRs) and within the cell's cytoplasm (nucleotide oligomerization domain [NOD] and retinoic acid-induced gene 1 [RIG-1]-like proteins). Engagement of these receptors initiates a proinflammatory and subsequent anti-inflammatory response through the release of chemokines responsible for the recruitment of mononuclear leukocytes, macrophages, and cytokines, such as tumor necrosis factor-α (which amplifies the response) and interleukin-10 (which downregulates it). This inflammatory reaction continues to build until one starts to see lymphocytes appearing at the tissue site, at which point the inflammation becomes more regulated and the neutro-

phils are usually supplanted by macrophages. This transition is orchestrated predominantly by cytokines, such as interferon-γ, produced by natural killer cells and T lymphocytes. It is this environment that induces a functional shift in the macrophage, transforming it from a noninflammatory, degradative cell responsible for tissue homeostasis into an antimicrobial cell with the ability to generate reactive oxygen and nitrogen intermediates and to process and present antigen.

This volume contains chapters from recognized experts in phagocyte behavior that explore and explain the complex biology behind the roles fulfilled by these different phagocyte lineages. The chapters discuss the different cell types and how they sense and respond to their environment. They also explore the properties and function of the phagosome itself, which is linked intimately with the divergent roles fulfilled by the professional phagocyte lineages. These chapters include discussion of the link between innate immunity and the development of specific cellular and humoral immune responses. Finally, the volume includes chapters that explore a variety of different infection models and how the phagocytes respond to control the infection and bolster protective immunity. The present volume therefore complements the earlier pathogen-centered volume edited by Cossart et al. (2005).

The volume is not encyclopedic; we have been selec tive, and the contents are a reflection of the interests o the two editors and their love of the macrophage and it cellular biology. Of all the phagocytes, we feel the macro phage is the most versatile, and yet the least celebrated Most of the phagocyte lineages are specialized, reminiscen of the fragment attributed to the Greek philosopher Ar chilocus and popularized by Isaiah Berlin, among others "The fox knows many things, but the hedgehog knows one big thing" (Berlin, 1953). To our minds, the macrophage is "the fox," and the dendritic cell and other leukocytes are "hedgehogs."

DAVID G. RUSSELL
SIAMON GORDON

REFERENCES

Berlin, I. 1953. The hedgehog and the fox: an essay on Tol stoy's view of history. Weidenfeld and Nicolson, London United Kingdom.

Cossart, P., P. Boquet, S. Normark, and R. Rappuoli (ed.) 2005. *Cellular Biology*, 2nd ed. ASM Press, Washington, DC

Rabinovitch, M. 1995. Professional and non-professiona phagocytes: an introduction. *Trends Cell Biol.* 5:85–87.