blood® Editorial



# Introduction to a review series on human neutrophils

We have been fascinated by neutrophils ever since Metchnikoff's discovery of phagocytosis in starfish larvae in 1883, work that ultimately led to his winning the Nobel Prize in 1908. Humans produce about $1 \times 10^{10}$ neutrophils per day in the bone marrow. These professional phagocytes set out daily on a search-and-destroy mission as part of the innate immune system to eliminate bacterial invaders and protect us from overwhelming infection. We knew that these cells were important because patients who did not have them suffered from fatal infections resulting from organisms in their own bodies. In the late 1960s, largely from studies of chronic granulomatous disease, first clinically described as "a syndrome of recurrent infection and infiltration of viscera by pigmented lipid histiocytes" in 1957, it became clear that neutrophil functional defects, and in particular impaired bacterial killing reflecting an inability to make superoxide, could also put patients at risk for severe, overwhelming infection. This ushered in a decade or two of intense study of neutrophil physiology that was greatly facilitated by the examination of other genetic experiments of nature that led to increased propensity to infection. Leukocyte adhesion deficiency, neutrophil actin dysfunction, Chediak-Higashi syndrome, and Rac2 deficiency, among others, greatly enhanced our understanding of the important role of adhesion in motility, transmigration, and phagocytosis as well as the roles of the cytoskeleton, oxidative metabolism, and granule release in neutrophil function.

During this time, the neutrophil was thought of as a terminally differentiated cell on a one-way suicide mission from bone marrow to tissue with a life expectancy of about 3 days. Neutrophils seemed not to interact a lot with other cells and were thought not to do much in terms of protein synthesis. However, some signs of the future came from attempts to study neutrophils in these infected patients. The quest to prepare cells from humans in a truly quiescent state was very difficult, and we learned that cells from infected patients came off at different densities on Ficoll gradients and infinitesimal levels of lipopolysaccharide (LPS) on labware could dramatically alter the activation state of neutrophils. In fact, just allowing blood to cool to room temperature and bringing it back to 37°C would upregulate CD11b and activate the cells. It became clear that priming by agents like granulocyte colony-stimulating factor (GCSF), LPS, or tumor necrosis factor (TNF) that otherwise do not attract or activate neutrophils would dramatically alter their response to a second stimulus. Clearly, neutrophils could be put into various activation states by interaction with their environment.

Fast forward to 2019, and the picture has changed quite a bit. Neutrophil heterogeneity is a hot topic, although the debate on whether there are preset populations of neutrophils or simply various states of activation is not resolved. The life span of neutrophils is probably a lot longer than previously surmised, the factors that modulate their egress from the marrow, including autonomic nervous system control, are better understood, and we know that neutrophils return to the marrow in a different activation state than when they left. They still are not major synthetic powerhouses, but through their sheer numbers, they secrete sufficient substances to modulate lymphocyte function and play a role in wound healing, upregulation and downregulation of inflammation, and perhaps tumor control. Certainly, they play a much more important role in immunity than simply as storm troopers attacking bacteria.

In this issue of *Blood*, we present a series of articles that review the current status of knowledge on several aspects of the secret lives of neutrophils.

- Mary C. Dinauer will set the stage by discussing "Inflammatory consequences of inherited disorders affecting neutrophil function." She will discuss chronic granulomatous disease (CGD) and leukocyte adhesion deficiency (LAD), 2 disorders that were instrumental in starting detailed molecular research into neutrophil function and now have led in part to our understanding of the role of these cells in immune regulation.

- Itziar Cossío, Daniel Lucas, and Andrés Hidalgo discuss "Neutrophils as regulators of the hematopoietic niche" and how neutrophils play a significant role in nonimmune homeostasis, including the fascinating circadian movement of neutrophils regulated by the autonomic nervous system and cross talk between immune cells and stem cells.

- Marie-Dominique Filippi will discuss "Neutrophil transendothelial migration: updates and new perspectives." Although LAD helped us understand adhesion to endothelium, the process of transmigration between endothelial junctions and through the middle of endothelial cells is now understood in great detail and contributes to movement of neutrophils to and from the marrow as well as the vascular space.

- Morgan A. Giese, Laurel E. Hind, and Anna Huttenlocher will discuss "Neutrophil plasticity in the tumor microenvironment." The authors point out that the response to cancer is similar to wound healing and that neutrophils can play a role in this inflammatory process. The fact that neutrophils can migrate back to the marrow from liver and lung raises

Submitted 29 January 2019; accepted 30 January 2019. Prepublished online as *Blood* First Edition paper, 21 March 2019; DOI 10.1182/blood-2019-01-891770.

interesting questions about the role of reverse migration in cancer.

- Dachuan Zhang and Paul S. Frenette will review the bidirectional "Cross talk between neutrophils and the microbiota." As implied by early studies, neutrophils can be primed by exposure to substances from microorganisms. However, these interactions have now been studied in great detail and are organism specific. The authors will tell us how the microbiome can alter neutrophil activation and how neutrophils can alter the microbiome.

- Fernanda V. S. Castanheira and Paul Kubes review "Neutrophils and NETs in modulating acute and chronic inflammation." Neutrophil extracellular traps (NETs) are web-like structures of DNA that are extruded from neutrophils under various conditions and, although they were initially thought to trap bacteria, they are now known to also modulate inflammation during infection, immune disease, and tissue repair.

- Denis F. Noubouossie, Brandi N. Reeves, Brian D. Strahl, and Nigel S. Key discuss the role of neutrophil interactions in thrombosis in their review, "Neutrophils: back in the thrombosis spotlight." Neutrophils, in part through release of NETs, may act to localize coagulation components and may promote vessel occlusion independently from fibrin formation.

So, contrary to the notions of several decades ago, it seems that neutrophils are not just the suicidal foot soldiers of the innate immune system destined to attack and destroy invading bacteria; they are also immune diplomats that interact with many parts of the host immune system to turn down the inflammatory response and repair the damage.

**Nancy Berliner**
Deputy Editor, *Blood*

**Thomas D. Coates**
Associate Editor, *Blood*