Cell and Tissue Research (2018) 371:395–397
https://doi.org/10.1007/s00441-018-2802-5

EDITORIAL

Neutrophils: multitasking first responders of immunity and tissue homeostasis

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Published online: 1 February 2018

From an evolutionary perspective, neutrophils are one of oldest immune cell types and represent a key first responder to infection and tissue injury (Leiding 2017). These early immune components first appear in simple invertebrates, such as cnidarians, as cells called amebocytes. In higher invertebrates, these primordial neutrophils take the form of hemocytes, cells that possess many of the functions of both neutrophils (phagocytosis, degranulation) and platelets (ability to initiate clotting of hemolymph). In vertebrates, these frontline immune cells take the form of the classic neutrophil, a granular phagocyte that is rapidly recruited to sites of infection or injury. Diverging from its evolutionary roots, the vertebrate neutrophil has lost much of its hemostatic function and appears to be dedicated to the host response to infection/injury.

In many ways, the rapid and robust response of neutrophils to infection has placed this leukocyte in the spotlight as the prototypical cell of the innate immune response. Upon infection or injury, neutrophils are recruited en masse, migrating from the bloodstream, crossing the endothelium, and entering the tissue interstitium where these cells then home to the specific site of challenge. Over the past century, these foot soldiers of the innate immune system have been studied in detail, providing great insight as to how the host recognizes pathogens, how cells are recruited to specific tissue beds, how immune cells are able to directly kill a variety of pathogens (lysosomes, proteases, reactive-oxygen species), and how immune cells inflict the collateral damage associated with inflammation. These studies began to define a clear role for the neutrophil as a short lived, non-discriminating killer that, while key to controlling infectious agents, often resulted in significant harm to self-tissues in an effort to ensure the clearance of the pathogen. For decades, this view of neutrophils as an unsophisticated "thug" of the innate immune system predominated, and, for the most part, limited efforts to search for, and understand, other functions of the neutrophil.

Despite the common view that we had already fully mapped the function of the neutrophil, research persisted and, with the advent of new techniques and technology (conditional genetic knock-out animals, blocking and depleting antibodies, multi-color flow cytometry, etc.), our understanding of these prototypical innate immune cells has changed dramatically over the last two decades. In particular, perhaps no single technique has advanced our understanding of neutrophils biology better than intravital imaging. What began with Julius Cohnheim nearly 150 years ago, using a simple white-light microscope to study blood flow and leukocyte behavior in a frog's tongue, has evolved to embrace cutting-edge technology allowing for the visualization multiple cell types, pathogens, and effector functions in real-time, in the living animal with resolution never believed to be possible. With this approach we have mapped cell recruitment, adhesion, endothelial transmigration, and migration. We have discovered and characterized effector mechanisms such as phagocytosis and neutrophil extracellular trap production, and we have mapped interactions between neutrophils, other leukocytes, platelets, tissues, and pathogens. Intravital imaging has literally "opened our eyes" to the true role of neutrophils in infection, inflammation and repair.

Importantly, we now know that neutrophils play key roles in the initiation, modulation, and resolution of the host immune response. Neutrophils interact with other leukocytes, modifying the ability of these other cells to respond to infections and injury. Neutrophils are also key players in the clearance of cellular debris and the initiation of tissue repair

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processes making these cells central to the maintenance of tissue homeostasis. In this special edition of *Cell and Tissue Research*, we present a collection of works that provide insight into this diverse spectrum of neutrophil activities within the host immune and tissue repair responses.

To provide an overall view of neutrophils in health and disease, Dr. Paul Kubes has contributed a review that highlights our changing views on the role of these cells within the host immune response (Kubes 2018). Dr. Kubes has been at the forefront of neutrophil research for more than 25 years and been instrumental in driving studies that have shed light on the "non-classical" functions of neutrophils. This review serves as an excellent introduction to this special edition of *Cell and Tissue Research*, providing perspective on where the field of neutrophil research started, how it has evolved and what issues remain to be solved.

Following this overview, we next address the origin and development of neutrophils. In particular, we focus on the activities of early, primordial, neutrophil-like cells known as coelomocytes in invertebrates (Homa 2018). These coelomocytes possess many of the same effector mechanisms as vertebrate neutrophils including, in particular, the ability to generate extracellular traps (ET). ETs in many ways resemble the neutrophil extracellular traps (NETs) generated by mammalian neutrophils and provides important insight into mechanisms regulating the generation of these immune effector structures and the function of these traps within the organism. Building upon our understanding of these primordial neutrophils, Phillipson and Christoffersson review the literature indicating that specific neutrophil subsets exist within the mammalian immune system (Christoffersson and Phillipson 2018). This has long been a question within neutrophil research; specifically, if each neutrophil is capable of a diverse array of activities or if specialized subsets of neutrophils exist, each able to provide a unique response to a given situation. Understanding this issue will be key to our ability to regulate the host immune response and to design therapies that limit collateral damage and improve resolution of tissue damage or injury.

We next focus on the ability of the neutrophil to traffic from the bloodstream to specific sites of infection or injury (Petri and Sanz 2018; Ivetic 2018). Perhaps one of the best studied cells from the perspective of the leukocyte recruitment cascade, neutrophils have, in a large part, provided the very basis of our understanding of cellular recruitment and trafficking. Neutrophils participate in a multi-step process to move from the circulation to the intersititum of a given tissue, utilizing a broad spectrum of adhesion molecules, ligands, and chemokine receptors. By studying neutrophils, we have gained a fundamental understanding of how adhesion molecules function and are regulated. Additionally, we have mapped how cells are able to "decide" between two different and competing chemotactic gradients. In many ways, the neutrophil itself has been our laboratory, allowing us to systematically map the overall functions of, and specific domains within, individual adhesion molecules and chemokine receptors. Overall, we have been able to use neutrophils as a bellweather in our understanding of cellular recruitment to different tissue beds or in response to various types of challenge (infection vs. sterile injury).

The next two articles address the various effector functions of neutrophils (Yin and Heit 2018; Ortmann and Kolaczkowska 2018). Neutrophils possess a diverse array of "tools" with which they can use to deal with infectious agents or injured tissue. Many of these "tools" consist of preformed mediators that are stored in granules, ready for immediate release into either the extracellular environment or into intracellular vesicles such as phagosomes. The ability of the neutrophil to generate these highly toxic mediators, to efficiently shunt these molecules to newly forming granules and the ability to traffic these granules within the cell represents a highly coordinated and carefully orchestrated series of events. Further complicating this process are the other effector functions of neutrophils including the generation reactive oxygen species (ROS), reactive nitrogen species (RNS) and the production of NETs. Since their discovery a little more than a decade ago, NETs have catapulted to the forefront of neutrophil research (Brinkmann et al. 2004). Studies examining these extracellular DNA structures have implicated this immune effector in key roles in pathogen clearance, collateral tissue damage, and even in the generation of autoimmunity. The included reviews address these issues in detail, summarizing our current knowledge and illustrating the remaining gaps in our understanding of these structures.

Following review of neutrophil effector functions, articles in this special edition of *Cell and Tissue Research* shift to address the response of neutrophils to various infections and disease conditions. Specifically, the role of neutrophils in response to *Staphylococcus aureus* infection (Lewis and Surewaard 2018), viral infection (Naumenko et al. 2018), the cancer microenvironment (Rakic et al. 2018), sterile tissue injury (Wang 2018), and equine laminitis (Leise 2018) is addressed. These works highlight the diverse spectrum of neutrophil responses possible and illustrate the ability of these cells to react to both infectious and sterile injury stimuli. Importantly, these reviews demonstrate the often discussed duel-role of neutrophils: where these cells are responsible for both the clearance of a pathogen and for tissue pathology in the absence of (or following) infection. It is this duel enigma that places the neutrophil at the forefront of both disease resolution and induction.

Building on this diverse spectrum of neutrophil responses, we next focus on how neutrophils interact with other cells of the immune and hemostasis systems. Specifically, reviews will provide insight regarding our understanding of how neutrophils interact with, and modulate

the behavior of monocytes and macrophages within health and disease (Kumar et al. 2018). These interactions have proven to be centrally important with respect to the development of an inflammatory vs. a reparative tissue environment. Additionally, we focus on the interactions between neutrophils and platelets (Lisman 2018). Again recent research has demonstrated that platelets represent key immune modulators, inducing neutrophil recruitment, activation, and effector functions such as the generation of NETs. We continue to expand upon this concept of specific neutrophil interactions by looking at the role of neutrophils in response to infection and injury in various tissue beds. Specifically, articles address the role of neutrophils within the lung (Aulakh 2018), within the liver (Alvarenga et al. 2018) and within the lymphatic system (Stephens and Liao 2018). Comparison of differences in neutrophil responses within specific tissue microenvironments provides important insights into the function of these cells with respect to both infection and tissue homeostasis.

Finally, we present a series of articles that address our understanding of the role of neutrophils in clinical disease. These works span the spectrum, ranging from human critical care medicine (McDonald 2018) to bovine health and disease (Bassel and Caswell 2018), to the role of neutrophils in equine lung inflammation and ischemia reperfusion injury (Anderson and Singh 2018). These works bring our understanding of the neutrophil full circle, from mapping of specific effector functions and cell recruitment pathways to the role these cells play in the generation, and resolution, of disease. Importantly, understanding how the neutrophil fits into the bigger picture of organ dysfunction and disease in general will allow for the development of neutrophil-targeting therapies with the goal of improving patient outcomes.

Over the past 20 years, our understanding of the role of the neutrophil has evolved from that of an unrefined cell that is recruited en masse to inflict widespread, non-specific damage within a tissue to an emerging belief that the neutrophil occupies a central position in the initiation and modulation of the host immune and inflammatory responses. By better understanding the specific activities and interactions between neutrophils, tissues, and other immune cells, we will gain knowledge regarding the specific mechanisms leading to pathogen clearance, host tissue damage, and, perhaps most importantly, the appropriate induction of tissue repair, helping to return the organism to a disease-free state. As this understanding improves, we will see the neutrophil assume a role as a key therapeutic target for a wide range of disease conditions including infection, cancer, sterile injury and autoimmunity. It is clear that the days of categorizing the neutrophil as a simple immune "thug" are gone, and this most basic of immune cells is now becoming appreciated for the central role it plays in regulating and controlling the whole of the host immune response.

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