DOI: 10.1111/imr.13188

Immunological Reviews WILEY

INTRODUCTION

# Neutrophils and their friends

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**Funding information**
Associazione Italiana per la Ricerca sul Cancro, Grant/Award Number: AIRC IG-20339; Ministero dell'Università e della Ricerca, Grant/Award Number: MIUR-PRIN 20177J4E75_004; Fondazione Cassa di Risparmio di Verona Vicenza Belluno e Ancona; National Institute of Allergy and Infectious Diseases, Grant/Award Number: AI132335

## 1 | FIRST AN HOMAGE

To organize this volume, *Neutrophils and their friends*, we solicited contributions from a diverse group of exceptional and productive members of the community of scientists engaged in the study of neutrophil biology, namely the Neutrophil Community. Given the abundance of outstanding contributors from which to choose, the decisions were difficult, but it was difficult as well to err in whomever we selected. Our intention for this volume is to present an accurate representation of contemporary understanding of neutrophil biology in all its glory and diversity, and to demonstrate thereby the position of neutrophils as critical collaborators in inflammation and in immune response. Before highlighting the science in the volume and how these two dozen manuscripts meet our goal, we want to focus attention on another issue.

Over time, authentic communities cultivate a historical memory that recognizes its origins and reveres those critical thinkers whose observations guide the paths of those who follow. These pioneers, in person or in the principles that their work revealed, serve as mentors: they orient investigators new to the field by providing fundamental principles on which to build and by illuminating questions that merit pursuing. Our memories of those pioneers and their contributions provide the meshwork that unites us as a community and creates the ethos that guides our pursuits and interactions. With that spirit, we, as members of the Neutrophil Community, begin this volume by honoring Professor Filippo Rossi, the Italian neutrophil biologist whose seminal studies identified fundamental biochemical features of the phagocyte oxidase, which underlies the production of microbicidal reactive oxygen species (Figure 1a). Filippo Rossi died on October 23, 2022.

Rossi was Emeritus Professor of the Verona University, where he taught General Pathology at the Medical School, and established and directed the General Pathology Institute from 1980 to 2003. Among his professional initiatives, Filippo promoted the establishment of two new Faculties at Verona University, namely Bioinformatics and Agro-Industrial Biotechnology. As a charismatic personality, Filippo Rossi has been a prominent figure in the discipline of General Pathology in Italy, contributing to its development with great passion and dedication. His studies and scientific results have earned him international recognition as one of the preeminent scientists in the field of inflammation and phagocyte biology. It was his seminal discovery that the phagocyte respiratory burst enzyme is an NADPH oxidase, and not an NADH-dependent enzyme, that set exploration of the biochemical basis for oxidase activation on the right path. An appreciation of the significance of this discovery of Rossi was celebrated a few years ago in the *Journal of Leukocyte Biology*.[1] The complementary attributes of an insatiable scientific curiosity and a remarkable spirit of innovation have driven Filippo Rossi's research. His commitment to education extended well beyond the borders of Italy. He initiated programs in Ngozi, Burundi,

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This article introduces a series of reviews covering Neutrophils and Friends appearing in Volume 314 of *Immunological Reviews*.

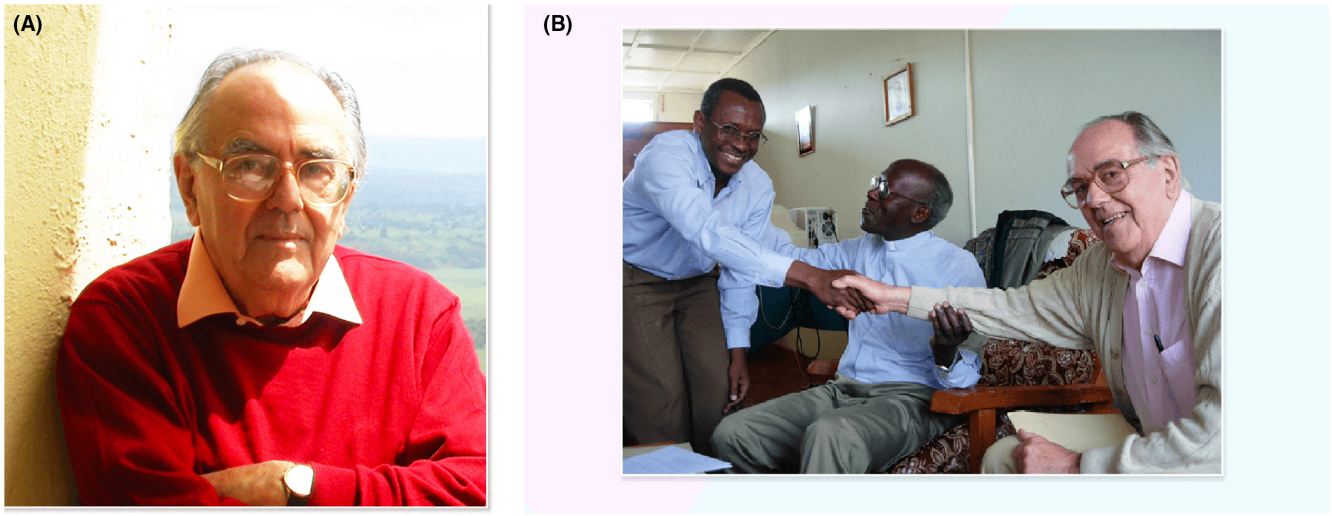


FIGURE 1 Professor Filippo Rossi. (A) Professor Filippo Rossi, a preeminent investigator in the field of leukocyte biology and inflammation, made the seminal observation that the phagocyte oxidase depended on NADPH, not NADH, a critical advance in understanding the biochemistry of oxidant production in stimulated neutrophils. (B) Not only an exceptional scientist and teacher, Rossi was also an enthusiastic and generous humanitarian, shown here with colleagues at Amahoro Proafrica in Burundi

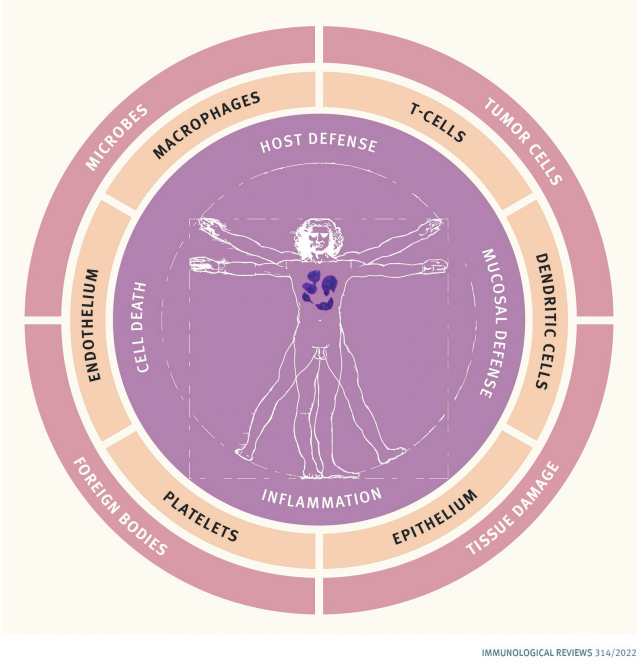


FIGURE 2 The Neutrophil: a *polyvalent* cell. The manuscripts in this review chronicle the many ways in which neutrophils, remarkably versatile and agile, collaborate with other cells, both immune and otherwise, and soluble factors to drive a wide range of biological activities. They mediate antimicrobial host defense; initiate, sustain, and terminate inflammatory events; uphold the integrity of mucosal surfaces; and contribute to the death of themselves and malignant cells. By direct contact or secreted biomolecules, neutrophils communicate with macrophages, T-cells, epithelium, platelets, dendritic cells, and endothelium to engage and resolve threats from microbes, tumor cells, foreign bodies, and tissue damage

to train health care professionals and participated in the humanitarian activities of Amahoro Proafrica in Burundi (Figure 1b). In the final years of his academic career, his endless pursuit of knowledge drove him to pioneer investigations into the role of inflammation in the pathogenesis of Alzheimer's disease, pursuits that culminated in the publications of original observations in high impact journals, including *Nature*. Last, but not least, Filippo Rossi directly trained and indirectly inspired more than one generation of scientists, always leading first by example. Vibrant to the end, his passion, self-sacrifice, and study will continue to instruct over time, well beyond the passing of his physical presence.

## 2 | GOALS FOR THIS VOLUME

Our goals for *Neutrophils and their Friends* are two-fold. First, the information presented in these collected reviews should replace the longstanding view of neutrophils as lone wolves that in unmeasured fashion unleash a storm of oxidants and antimicrobial agents to kill and eradicate threatening microbes, frequently, thanks to their exuberant and seemingly unregulated responses, with unintended collateral damage to the host. To counter that view, articles in this volume offer a more contemporary and informed profile of neutrophils as cells that are remarkably agile in their ability to interpret a wide variety of different signals and in their celerity to adapt to the needs of the situation (Figure 2). In a word, and a French word at that, neutrophils are *polyvalent*: they have multiple competences that allow them to meet all needs and purposes, just as a *homme polyvalent* is a versatile, multi-faceted man who can meet any challenge.

In addition to illustrating the extensive repertoire of neutrophil functional attributes, articles in this volume detail the many collaborations that neutrophils form with other cells and soluble factors to mount and then resolve inflammatory responses. Finely regulated, neutrophils maintain communications with cellular colleagues, local and distant, to protect the host from threats, internal and external, and to restore homeostasis.

## 3 | COLLABORATION AND ACTIVATION

Recruited to sites of infection and tissue damage, neutrophils engage with tissue-based cells, including endothelial and epithelial cells, as well as other circulating cells such as platelets and T-cells.[2,3] Depending on the magnitude of the provocation, neutrophils can sustain or terminate tissue damage secondary to inflammation. Interactions with T-cells, either directly or indirectly via dendritic cells, extend the sphere of influence of neutrophils beyond the acute inflammatory response and serve as a gateway to shaping adaptive immunity and to contributing to the development and maintenance of immune tolerance, as discussed in detail by Bert and colleagues.[3] Furthermore, in the tumor microenvironment (TME), neutrophil-mediated responses can dampen or promote tumor progression, and communication in this setting is bidirectional, with neutrophils and malignant cells signaling reciprocally to modulate the inflammatory tone in the tumor bed.

Neutrophil actions are not unbridled, as suggested by a term such as *respiratory burst*, but rather finely tuned, whether acting alone or with others. The diverse set of receptors on the surface of neutrophils enables the recognition of a seemingly infinite variety of ligands. Mechanisms for regulating the threshold to activation provide a way to tune responses to meet demand, as achieved by interruption of intracellular activation pathways by engagement of inhibitory receptors. Using the C-lectin inhibitory receptor CLEC12A as a model, Fernandes and McLeish discuss its cell biology to illustrate how inhibitory receptors contribute to the regulation of neutrophil responsiveness.[4] Many neutrophil receptors are members of the family of G protein-coupled receptors, which participate in the full spectrum of responses, from activation to inhibition. Dahlgren et al. critically review the varied activities of these receptors with a focus on those that participate in pattern recognition, a critical element in host defense pathways.[5]

Taken together, the recognition that neutrophils have a functional repertoire far more expansive than previously appreciated, brings us closer to a view of the immune system that is more inclusive and integrated, acknowledging that innate responses also demonstrate an immunologic memory. However, unlike the gene rearrangements at the basis of lymphocyte recognition, epigenetic modulation informs innate cells. As discussed by Kalafati et al., epigenetic and immunometabolic factors train myeloid precursors in the bone marrow, sometimes to the benefit and other times to the detriment of the host.[6] For example, trained immunity may link the sterile inflammation related to dietary customs in the Western hemisphere to the cardiac and metabolic diseases commonly seen in those populations. The complex series of events that occur in the bone marrow during neutropoiesis remain incompletely understood, in part due to a lack of unambiguous identification of very immature neutrophil progenitor cells along the differentiation pathway. Calzetti et al.[7] analytically discuss the shortcomings in current understanding and identify technical advances that may advance our knowledge of events essential for normal as well as emergency neutropoiesis.

## 4 | CROSSTALK WITH PROKARYOTES AT MUCOSAL SURFACES

Neutrophils not only patrol the vasculature and tissue spaces but also serve as sentinels at the interface between the host and the outside world. At the mucosa of the alimentary and respiratory tracts, neutrophils communicate with commensal microbes to maintain mucosal homeostasis and tissue health. Discussed in detail by Silva et al.,[8] neutrophils must maintain host integrity at these sites, blocking the establishment of infection and minimizing signs of inflammation. When neutrophil function, number, or both is compromised, disintegration of mucosal defenses becomes manifested in serious clinical disease, as seen in the varied pathologies of the gastrointestinal and respiratory tracts experienced by individuals with chronic granulomatous disease.[8]

The maintenance of periodontal health illustrates the importance of neutrophil crosstalk with commensal organisms. When neutrophils are normal in number and functional capacity, homeostasis and good health reign in the oral cavity. However, excessive populations or activity of neutrophils disrupt the balance and promote dysbiosis, tissue degradation, or both. Uriarte and Hajishengallis describe how organisms that have adapted to the periodontal environment, such as *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Filifactor alocis and Peptoanaerobacter stomatis*, can exacerbate the imbalance between host and microbe, and compromise the integrity of oral health and promote periodontal disease.[9]

## 5 | LIFE AND DEATH IN THE PHAGOSOME

Historically, phagocytosis represents the defining activity of neutrophils and the focus of longstanding investigation, dating back to the studies of leukocyte phagocytosis by Cohn, Hirsch, and others at Rockefeller University in the 1950s. Probing the intricacies of the phagosome persists, as clearly chronicled by Lodge and Chilvers.[10] In our mind, there are three predominant challenges to understanding fully events in the phagosome: (1) the complex and interacting agents within the phagosomal lumen; (2) the varied responses of microbes to attack; and (3) the heterogeneity among phagosomes.

The phagosome represents a specialized intracellular compartment created de novo as neutrophils ingest susceptible targets. Therein, the mix of granule contents, delivered to the phagosome lumen by degranulation, oxidants, produced on site by the assembled

and active NADPH oxidase, and ions, shuttled from cytoplasm or the extracellular space, collaborate to create an environment that kills or extensively damages vulnerable microbes. Ironically, the same complexity of intraphagosomal events and products that enable neutrophils to damage a remarkably diverse range of microbes has likewise thwarted investigations in search of ***the*** precise agent and mechanism of antimicrobial action. Lodge and Chilvers critically assess our current understanding of events in neutrophil phagosomes, delineate shortcomings in our knowledge, and discuss issues that merit exploration.[10]

For certain, many of our notions as to the biochemical events that transpire within neutrophil phagosomes need revision, starting with the actions of oxidants generated therein. Kettle and colleagues in Christchurch revisit the role of superoxide, the most proximate product of the NADPH oxidase-catalyzed electron transfer to molecular oxygen, in antimicrobial activity and in the overall economy of reactive oxygen species within the phagosome.[11] Although itself not microbicidal, superoxide reacts with myeloperoxidase (MPO) to sustain the generation of the potent microbicide, hypochlorous acid (HOCl). Given the prominent contribution of MPO-catalyzed HOCl production to overall oxidant-dependent antimicrobial action in neutrophils, superoxide is, at least in one respect, *super*.

Adding to the challenge of decoding the antimicrobial events that culminate in killing intraphagosomal prey are the myriad responses of microbes to attack. Capitalizing on skills refined by their adaptations to threats from competing organisms in environmental settings, microbes are not passive victims trapped in phagosomes but rather targets that sense and react to the hostile conditions encountered. Hampton and Dickerhof[12] discuss how microbes can actively undermine neutrophil responses, change surface charge to rebuff attack by cationic antimicrobial peptides, release agents that bind and inactivate antimicrobial mediators (as occurs with MPO inactivation by the staphylococcal peroxidase inhibitor, SPIN), degrade or neutralize oxidants, and repair damage exerted by phagosomal contents. The speed with which organisms adapt to their new environments can be remarkable and, when successful, allow ingested bacteria to persist, alive, within neutrophils.

Whereas the complex mix of interacting agents within phagosomes and the capacity of ingested microbes to counter the attack together make deciphering how neutrophils kill microbes nearly impossible, the heterogeneity among phagosomes compounds the challenge even further. As reviewed by Hampton and Dickerhof,[12] not all neutrophils in circulation exhibit the same capacity for phagocytosis and, even within the same neutrophil, phagosomes differ with respect to their capacity to generate oxidants. The challenges to understanding fully the most fundamental aspect of phagocyte biology, i.e., killing ingested microbes, seem insurmountable.

## 6 | MICROBES TURN THE TABLE ON NEUTROPHILS

Not only can neutrophils influence the fate of ingested microbes, but also some bacteria confined within phagosomes can reciprocate and accelerate programmed cell death pathways in neutrophils. The process of phagocytosis itself promotes neutrophil apoptosis as an early step in the nonphlogistic clearance of neutrophils by macrophages. However, certain organisms interrupt the normal sequence of events that drive phagocytosis-induced apoptosis to accelerate or delay the process or, in some cases, to redirect neutrophil destiny to a necrotic cell death. The DeLeo laboratory made seminal contributions to the recognition of that ingested microbes impact neutrophil fate, and Kobyashi et al.[13] chronicle the varied roles that apoptosis plays in the life and death of neutrophils and how microbes can modulate neutrophil fate, often to benefit the organism and disadvantage the host. The authors reflect as well on the consequences of neutrophil cytolysis, a process overlapping with or identical to neutrophil extracellular trap (NET) formation, in catalyzing tissue damage during overwhelming infection.

In addition to influences originating in the phagosome that dictate neutrophil behavior, cytoplasmic complexes can initiate functional responses. For example, the inflammasome is a cytoplasmic platform that supports secretion of the potent proinflammatory cytokine IL-1β and initiates pyroptosis, a form of lytic cell death. A growing appreciation of inflammasomes in immunology and inflammation has flourished in the two decades since their identification by Tschopp two decades ago,[14] with both novel nomenclature and complex signaling pathways filling the literature. Dubyak and colleagues[15] provide a lucid overview of this exciting and rapidly expanding area, elegantly comparing and contrasting inflammasome-related events in macrophages and in neutrophils. The authors introduce readers to the family of gasdermins and their central role in the pore formation that allows efflux of IL-1β and pyroptotic lysis. Especially interesting is the authors' analysis of neutrophil-specific events that differ from those of macrophages. It is clear that despite the relatively little amount of IL-1β released on a per cell basis, neutrophils serve as a major source of its production at inflammatory sites simply because of the abundance of neutrophils that accumulate.

## 7 | NEUTROPHILS IN THE SETTING OF MALIGNANCY

Evidence for significant and complicated roles for neutrophils in tumor biology continues to amass. Driven by repeatedly documented infiltration of tumors by neutrophils, investigators are exploring the identity and fundamental biology of tumor-associated neutrophils (TAN) and their clinical relevance. One of the challenges central to the discussion of TAN relates to myeloid-derived suppressor cells and the characterization of neutrophils alternatively as tumor-promoting (N2) or anti-tumor (N1). Antuamine et al.[16] discuss the history of these concepts and nomenclature and offer critical analyses of their merits and shortcomings.

Uncertainty of the relevance of observations from studies in murine experimental systems to human oncology limits confidence that interventions based on such studies will be effective in a clinical setting. Nonetheless, it is certain that the tumor microenvironment

(TME) exists as a complex setting where inflammatory cells, including neutrophils, coexist with fibroblasts, extracellular matrix, and vessels to promote signs and signals of persistent tissue injury. Segal et al.[2] detail the reciprocal crosstalk in the TME that occurs among neutrophils, platelets, T-lymphocytes, and malignant cells to sculpt the local environment and modulate tumor behavior. The N1 and N2 nomenclature surfaces again, as in the review by Antuamine et al.[16] and once more the authors encourage caution in extrapolating neutrophil subtypes identified in murine systems to the human condition.

The ability to harness the activity of neutrophils to halt tumor progression, promote elimination of cancer cells, or both could provide clinicians with potent therapies with fewer toxicities than those associated with current interventions. Behrens et al.[17] review how neutrophils and monoclonal antibodies can support antibody-directed cellular cytotoxicity. With tumor cells covered by tumor-specific monoclonal antibodies, neutrophils can drive tumor killing. Critical for this intervention to yield results is formation of the neutrophil cytotoxic synapse: a tight cellular structure dependent on conformational changes that follow binding by Mac-1 (aka complement receptor 3, $\alpha_m\beta_2$, CD11b CD18). Firmly associated with antibody-targeted tumor cells, neutrophils exert tumor cytotoxicity in a variety of different ways, including trogocytosis, as discussed in detail.[17]

## 8 | NEITHER MICROBES NOR TUMOR CELLS AS TARGETS

In certain settings and under specific circumstances, activated neutrophils direct their proinflammatory effector mechanisms against targets that are neither microbes nor tumor cells. For example, activated neutrophils mediate, directly or indirectly, much of the pathology seen in sickle cell disease (SCD) by initiating and propagating vascular occlusions by virtue of their interaction with damaged endothelium, sickled erythrocytes, and activated platelets. Torres and Hidalgo[18] summarize findings that elucidate the complex behavior of activated neutrophils and their interactions that culminate in the vascular injury and end organ damage seen in SCD.

Neutrophil-mediated attack of vascular elements extends beyond the context of SCD. Evidence suggests that in some settings, such as systemic lupus erythematosus (SLE), a subpopulation of circulating neutrophils, namely the low-density granulocytes (LDG), drives the pathogenesis of the systemic autoinflammatory syndrome. Carmona-Rivera and Kaplan[19] review the evidence that LDG exist as a unique subpopulation of neutrophils that figure prominently not only in SLE but also in other inflammatory diseases, including psoriasis, rheumatoid arthritis, idiopathic inflammatory myopathies, and anti-neutrophil cytoplasmic vasculitis (ANCA).

Ayomonnier et al.[20] provide a comprehensive and thought-provoking overview of how the extraordinary versatility of neutrophils influences the behavior of other cells in the vessel wall and contributes to the initiation, maintenance, or both of inflammatory diseases in small, medium, or large vessels. The remarkable functional repertoire of neutrophils enables them to adapt to situations and modulate proinflammatory cells to suppress responses, drive fibrosis, promote thrombosis, or influence local vascular biology in other ways.

Van Avondt et al.[21] explore the process of immunosenescence, the muting of the immune system by the accumulated consequences of unresolved chronic inflammatory processes accumulated during aging. Like other elements of the immune system, neutrophils incur changes as hosts age, culminating in diminished functional capacity and untoward clinical outcomes for the elderly. For example, elderly humans experience greater morbidity and mortality from infection and respond less well to vaccinations than do younger individuals. But beyond the obvious implications that reduced neutrophil functional capacity would have for host defense, the impact of the aging process is more pervasive. The authors discuss in detail the contribution of aged neutrophils, both acting alone and in critical interactions with macrophages, to atherosclerosis, myocardial infarction, cerebral vascular insufficiency, neurodegenerative disease, and cancer—a spectrum both daunting and sobering.

Even when their integrity is compromised, neutrophil contents support a variety of biological phenomena. Van Bruggen and Martinod[22] review how the extracellular aggregation of neutrophil DNA, histones, and several cationic granule proteins contribute to host defense and to significant elements of sterile inflammation. Alone or in association with platelets, NETs directly contribute to thrombosis and can trigger other immune cells as well as endothelial cells to promote additional thrombosis.

These interactions contribute to the morbidity and mortality seen in infections with SARS-CoV-2. Castanheira and Kubes[23] discuss how NET formation figures in the pathogenesis of COVID-19 and of the thrombosis, disseminated intravascular coagulation, and respiratory failure that frequently complicate severe disease. Their discussion focuses attention on neutrophil heterogeneity both in general and in the specific context of COVID-19. A better understanding of the mechanistic underpinnings and functional implications of neutrophil heterogeneity in circulation and in inflamed airways is prerequisite to creating new therapeutic approaches.

## 9 | ABANDONED TOPICS NEWLY EXPLORED

Two reviews in this volume revisit subjects long abandoned because they were judged unimportant for or unrelated to neutrophil activities in biological settings—namely the roles of mitochondria and of metabolism in neutrophil biology. With respect to the first issue, mitochondria, most investigators consider neutrophils to have few, if any, functionally normal mitochondria and to have little reliance on mitochondria as an energy source. Peng et al.[24] dispel both notions and catalogue an array of neutrophil functions in which mitochondria participate, including neutrophil development, chemotaxis, oxidant

production, degranulation, and cell death. The release of mitochondria and mitochondrial DNA contributes to the antimicrobial response of neutrophils and can modulate the local inflammatory tone.

Just as mitochondria have long been overlooked as meaningful participants in neutrophil biology, recognition that metabolic pathways other than glycolysis have a significant role in neutrophil function is only recent. Neutrophils exhibit more metabolic versatility than previously appreciated, and Morrison et al.[25] describe in detail the metabolic programs involved in cellular energetics, neutropoiesis in the bone marrow, antimicrobial action, and engagement of cell death pathways. Exploration of such pathways in normal neutrophils may provide the foundation for novel therapeutic interventions in settings where neutrophil-driven inflammation is dysfunctional or dysregulated.

## 10 | CONCLUSION: CAVEAT LECTOR

As intimated at the outset of this overview of the volume, assembling these manuscripts was an effort both informative and joyful: informative in that we both learned a great deal in the process of editing the submissions and joyful in seeing the wealth of new information and new directions embodied in the assembled volume.

One recurrent disclaimer appears in several manuscripts, namely the caution that the observed phenomena, although true in murine systems, may not apply to the human condition. One of us (WMN) addresses the basis for this concern in a review that delineates the differences in structure and function of murine and human neutrophils and identifies situations where extrapolation from murine experimental systems to humans may be misleading or simply incorrect.[26] With those concerns in mind, it is essential that investigators who capitalize on the power of in vivo murine systems make a good faith effort to test their conclusions in experimental conditions that use human cells, where possible. Of course, it is simply not always possible to recapitulate complex in vivo studies performed in mice by using human cells in vitro, in which case investigators should be cautious in claiming that they have insight into how human neutrophils might behave. At the very least, when investigators report their findings in manuscripts, book chapters, or oral presentations, they should be accurate and qualify their conclusions by explicitly identifying the species studied. That is, the title of manuscripts describing work done exclusively in murine experimental systems should be "Murine neutrophils do X", not "Neutrophils do X"; in the absence of data using human cells, the latter is only a speculation, is not supported by data, and may not be true.

Given that a groundswell of support for these suggestions from investigators and journal editors seems unlikely, the best advice for now is *reader beware*.

### ACKNOWLEDGEMENTS

Work in the MAC lab is supported by grants from AIRC IG-20339; MIUR-PRIN 20177J4E75_004; and Fondazione Cassa di Risparmio di Verona Vicenza Belluno e Ancona. Work in the WMN lab is supported by a grant from the National Institute of Allergy and Infectious Diseases AI132335. MAC and WMN express thanks to the patience and sustained support from the *Immunological Reviews* editorial office. We extend special thanks to Leena Sharon Rajasekaran who has been a constant and trusty guide throughout the process. Thanks as well to Arthi Riya, Production Editor, Claudia Bentley for applying her artistic skills to create Figure 2, and to Professor John Cambier, Editor-in-Chief, for allowing us to undertake this initiative. We thank Robert A. Clark (UTHSA, San Antonio, TX) for a helpful modification of Figure 2.

### CONFLICT OF INTEREST

Neither author has conflicts of interests to report.

### DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study

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**How to cite this article:** Cassatella MA, Nauseef WM. Neutrophils and their friends. *Immunol Rev*. 2023;00:1-7. doi:10.1111/imr.13188