Phagocytosis and neutrophil extracellular traps

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Abstract

Neutrophils are recruited rapidly to sites of infection in response to host- and/or microbe-derived proinflammatory molecules. At such sites, neutrophils phagocytose microbes and are activated to produce superoxide and other reactive oxygen species (ROS). In addition, neutrophils contain stores of antimicrobial peptides and enzymes that work in concert with ROS to kill ingested microbes. Neutrophils can also release chromosomal DNA bound with antimicrobial peptides and enzymes to form web-like structures known as extracellular traps. Neutrophil extracellular traps (NETs) have been reported to ensnare and kill microbes and are commonly considered to be an important component of innate host defense. Notably, the formation of NETs is most often reported as a cytolytic process. Whereas intraphagosomal killing of microbes sequesters cytotoxic antimicrobial molecules that would otherwise damage host tissues, the formation of NETs and associated extracellular release of these molecules can contribute to host tissue destruction and disease. Here we compare and contrast phagocytosis and NETs in host defense, with emphasis on recent studies of NETs that ultimately underscore the importance of phagocytosis as the primary means by which neutrophils eliminate microbes.

Keywords

Neutrophil, neutrophil extracellular trap, NETs, phagocytosis

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**Introduction**

Neutrophils are the most abundant leukocytes in human blood, and their central role in innate defense against infection is unequivocal. The processes that recruit neutrophils to sites of microbe invasion, phagocytosis, and coupling of the engulfment process to rapid deployment of oxygen-dependent and oxygen-independent mechanisms for efficient microbe killing and digestion have been studied extensively. Many fundamental insights into these neutrophil processes have arisen from studies of human patients and bacterial and fungal pathogens to inhibit or coopt these defense processes to evade elimination while also causing tissue destruction and disease.

**Phagocytosis, phagocytic killing, and neutrophil extracellular traps**

Phagocytosis is a specialized form of receptor-mediated endocytosis that is utilized by neutrophils and macrophages to ingest particles and microbes that are at least 0.5 microns in size\(^1\). The list of phagocytic receptors continues to grow and includes molecules that bind directly to microbes such as CEACAMs, lectins, and integrins as well as receptors that engage microbes opsonized with IgG or complement fragments\(^2\). In all cases, signaling downstream of these receptors triggers local actin polymerization that is essential for extension of membrane pseudopodia around the microbe and its internalization.

A distinguishing feature of neutrophils is the fact that phagocytic receptor signaling also elicits rapid deployment of oxidative and non-oxidative host defense mechanisms via simultaneous assembly and activation of the Nox2-containing NADPH oxidase complex and mobilization of specific and azurophilic granules. As a result, phagosome–granule fusion and the production of superoxide anions and other toxic ROS is typically apparent within 60 seconds of particle or microbe binding\(^3,4\). The speed and efficiency of this process creates a highly lethal milieu in the phagosome lumen that consists of oxidants, cationic antimicrobial peptides, iron binding proteins, and enzymes such as elastase and myeloperoxidase (MPO). The formation of such an environment is in keeping with the ability of neutrophils to kill the majority of ingested microbes within 30 minutes\(^5,6\). By contrast, phagosome maturation in macrophages is relatively slow and consists of incremental modification of nascent phagosomes via sequential interaction with early endosomes, late endosomes, and lysosomes\(^8\).

The importance of NADPH oxidase-derived ROS to microbe killing is exemplified by the life-threatening infections that arise in patients who have inherited mutations in genes that encode subunits of this enzyme complex\(^9\). Pathogens that evade killing by neutrophils inhibit or evade toxic ROS and achieve this by inhibiting NADPH oxidase targeting, assembly, or activity\(^10,11\). Less is known about the mechanisms that control oxygen-independent defense mechanisms, including granule targeting and fusion, but recent data indicate that distinct Rab27-independent and -dependent mechanisms control azurophilic granule fusion with phagosomes and the plasma membrane, respectively\(^12\). Additional insight will likely be gleaned from further studies of pathogens that manipulate phagosome fusion with specific and/or azurophilic granules as part of their virulence strategies\(^13\).

The discovery of neutrophil extracellular traps (NETs) suggested the existence of an additional mechanism that allows neutrophils to trap and/or kill extracellular microbes\(^14\). In a landmark study, Brinkmann et al. reported that some activated neutrophils release decondensed chromatin fibers as web-like structures to which cationic neutrophil proteins such as elastase, histones, and MPO are bound\(^15\). These structures—aptly named NETs—can ensnare and kill microorganisms. Subsequent work by the same group of researchers reported a mechanism for the formation of NETs that requires ROS and, more notably, is a cytoplastic process\(^16\). The formation of NETs that results from neutrophil lysis was proposed as a novel cell death program ultimately termed NETosis\(^17,18\). The formation of NETs and NETosis have often been used as synonymous terms for years, but whether the formation of NETs is always a result of the cytoplastic process described as NETosis has been called into question\(^19,20\). Indeed, NETs can form from viable neutrophils\(^21-23\) or from neutrophils that have undergone non-specific lysis\(^24\). Thus, there is reasonable agreement in the field that the term “NETosis” should not be used to describe the formation of NETs unless a specific cell death mechanism is known\(^25,26\).

NETs have been studied extensively since the report by Brinkmann et al., and it is clear they can contribute to host defense. For example, Urban et al.\(^27\) and Branzk et al.\(^28\) reported that NETs are important for host defense against microbes that cannot be phagocytosed, such as fungi in hyphal form. More recently, Thanabalasuriar et al. demonstrated that NETs prevent dissemination of Pseudomonas aeruginosa from biofilms in a mouse infection model\(^29\). These roles for NETs in host defense are important and complementary to those of phagocytosis. However, the misconception that NETs are a primary means by which neutrophils kill microorganisms has become seemingly pervasive outside of the field of phagocyte biology. Here we compare and contrast phagocytosis and the formation of NETs (and outcomes associated with each process) as components of host defense.

**Physical sequestration of microbes following phagocytosis**

There is no question that the ability of neutrophils to sequester microbes within an enclosed phagocytic vacuole (phagosome) is important for host defense. Ingested microbes can no longer disseminate freely, and molecules normally shed or secreted from pathogenic microbes are contained within phagosomes and thus unable to contribute to disease. By comparison, NETs ensnare microorganisms, but surface binding to a DNA scaffold is not likely to prevent dissemination fully. Moreover, NET-bound microbes are still able to release molecules such as bacterial endotoxins that can be detrimental. These latter points notwithstanding, studies by Branzk et al. and
Nonphlogistic removal of apoptotic neutrophils

ROS and antimicrobial enzymes contained within neutrophil granules are not microbe specific and can also cause non-specific damage to host cells and tissues if they are released by exocytosis or following cell lysis. Extracellular release of these toxic agents by neutrophils contributes significantly to many human inflammatory diseases. Therefore, it is not surprising that neutrophil lifespan and antimicrobial functions are highly regulated. Human neutrophils are terminally differentiated cells that undergo apoptosis constitutively at the end of their lifespan. As neutrophils undergo apoptosis, they lose functional capacity, as indicated by defects in chemotaxis, phagocytosis, degranulation, and the ability to produce superoxide in response to certain stimuli. Importantly, apoptotic neutrophils remain intact and are ingested by mononuclear phagocytes in a non-inflammatory process known as effecroycytosis. Removal of apoptotic neutrophils helps maintain immune system homeostasis and is key to resolution of the inflammatory response. This highly regulated process prevents host exposure to components of lysed neutrophils. Therefore, it could be argued that the formation of NETs by cytology is an incidental phenomenon that results from necrotic lysis rather than a unique type of cell death. This notion is gaining support among neutrophil biologists and cell death experts.

High intraphagosomal concentration of microbicides

Few microorganisms have the ability to survive following phagocytosis by neutrophils. This is because intraphagosomal concentrations of neutrophil ROS and antimicrobial peptides are extraordinarily high, as intraphagosomal volume is limited (estimated at 1.2 µm³ for bacterial phagosomes). For example, Winterbourn et al. estimated the initial rate of superoxide generation as 5.2 mM/second and the intraphagosomal concentration of MPO as ~1 mM. Based on these estimates, hypochlorous acid (HOCI), commonly known as the active ingredient in household bleach, is produced at 134 mM/minute. The granule protein concentration in the neutrophil phagosome has been estimated to be as high as 200 mg/mL. Although MPO and elastase, components of neutrophil azurophilic granules, are hallmark features of NETs, the amount present on an extracellular DNA scaffold is likely far less than that present in phagosomes. Moreover, the concentration of ROS produced within phagosomes is simply not possible on or near NETs, as intact and viable neutrophils are needed to produce ROS; the half-life of these molecules is limited, and they diffuse readily. Therefore, compared with the microbialidal processes that occur within phagosomes (following phagocytosis), NETs have far less capacity to kill microorganisms.

Noncytolytic versus cytolytic processes for the formation of NETs

The formation of NETs was described initially as a cytolytic process that culminates in the loss of plasma membrane integrity and release of cellular contents, most notably nuclear DNA, histones, and components of cytoplasmic granules, into the extracellular milieu. Indeed, the majority of studies of NETs or their components either directly demonstrate or infer lysis of neutrophils. By comparison, Yousefi and colleagues first reported that extracellular traps form from mitochondrial DNA released from viable eosinophils. This finding has since been extended to include neutrophils and basophils. The formation of NETs from viable neutrophils is a noncytolytic process and is therefore compatible with the regulated turnover of neutrophils described above. More notably, such a process has the potential to function in concert with phagocytosis, as described above for microbes that cannot be ingested.

NETs and human disease

Inasmuch as neutrophils are abundant leukocytes and have tremendous capacity for cytotoxicity, it is not unexpected that many diseases are associated with NETs. Although there are caveats with associating NETs and human disease, the sheer number of recent findings in this area underscores the importance of strictly regulated neutrophil activation and turnover (safe removal) to health and homeostasis. For example, NETs have been associated with multiple types of cancer and cancer metastasis, including breast cancer, hepatocellular carcinoma, lung cancer, ovarian cancer, oral squamous cell carcinoma, pancreatic cancer, and thyroid cancer. NETs have been implicated in autoimmune disorders such as lupus erythematosus and in the development of thrombosis and can contribute to the severity of sepsis. Cell-free or extracellular DNA associated with elastase, MPO, and/or citrullinated histones has been associated with numerous respiratory diseases. NETs or NET components have been found in sputum from individuals with chronic obstructive pulmonary disease and severe asthma, plasma from patients with severe influenza A virus infection, bronchoalveolar lavage fluid from patients with ventilator-associated pneumonia, and in plasma from patients with acute respiratory distress syndrome. Most recently, NETs have been associated with severe COVID-19.

Collectively, these data further support the idea that nonphlogistic turnover of neutrophils is essential to human health. In contrast to NETs, neutrophil phagocytosis is not associated directly with severe pathologies or disease.

Conclusion

The idea that neutrophils utilize NETs extensively to eradicate microbes or that NETs are employed for host defense more prominently than phagocytosis has become increasingly pervasive outside of the field of phagocyte biology. Although a significant body of work supports the notion that NETs can contribute to host defense, the relative contribution of NETs to human host defense in vivo remains largely unknown. This
issue is difficult to address, in part because the formation of NETs and neutrophil lysis can be synonymous. Identification of cell-free/extracellular DNA associated with citrullinated histones and/or neutrophil granule proteins is consistent with neutrophil lysis in vivo, a phenomenon linked to tissue destruction and disease. Indeed, the vast majority of studies published on the topic of NETs within the past two years underscore the role of NETs in disease. These data are consistent with the long-held tenet that uncontrolled release of neutrophil components, as occurs in cytolysis, is detrimental to health and exacerbates disease. Notably, the host immune system has evolved numerous tightly controlled mechanisms to prevent cytolysis, which implies that the formation of NETs via cell lysis is incidental, as is the contribution of such NETs to host defense.

Here we considered phagocytosis and NETs as components of host defense. Based on an assessment of historic and recently published studies and established paradigms, it seems clear that phagocytosis coupled to rapid phagosome–granule fusion and ROS production remains the primary means by which neutrophils eliminate invading microbes. More work is needed to determine the relative contribution of NETs and other lytic cell death mechanisms to host defense in vivo.

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