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Review

When two is better than one: macrophages and neutrophils work in concert in innate immunity as complementary and cooperative partners of a myeloid phagocyte system

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RECEIVED AUGUST 12, 2009; REVISED SEPTEMBER 6, 2009; ACCEPTED SEPTEMBER 21, 2009. DOI: 10.1189/jlb.0809549

ABSTRACT

The antimicrobial effector activity of phagocytes is crucial in the host innate defense against infection, and the classic view is that the phagocytes operating against intracellular and extracellular microbial pathogens are, respectively, macrophages and neutrophils. As a result of the common origin of the two phagocytes, they share several functionalities, including avid phagocytosis, similar kinetic behavior under inflammatory/infectious conditions, and antimicrobial and immunomodulatory activities. However, consequent to specialization during their differentiation, macrophages and neutrophils acquire distinctive, complementary features that originate different levels of antimicrobial capacities and cytotoxicity and different tissue localization and lifespan. This review highlights data suggesting the perspective that the combination of overlapping and complementary characteristics of the two professional phagocytes promotes their cooperative participation as effectors and modulators in innate immunity against infection and as orchestrators of adaptive immunity. In the concerted activities operating in antimicrobial innate immunity, macrophages and neutrophils are not able to replace each other. The common and complementary developmental, kinetic, and functional properties of neutrophils and macrophages make them the effector arms of a myeloid phagocyte system that groups neutrophils with members of the old mononuclear phagocyte system. The use by mammals of a system with two dedicated phagocytic cells working cooperatively represents an advantageous innate immune attack strategy that allows the efficient and safe use of powerful but dangerous microbicidal molecules. This crucial strategy is a target of key virulence mechanisms of successful pathogens. *J. Leukoc. Biol.* 87: 93–106; 2010.

Introduction

The outcome of the presence of a microbe within a host is dependent on the nature of the host-microbe interaction [1]. When such an interaction progresses with advantage to the microbe, as the pathogenicity factors of the microbe overcome the immune defenses of the host, an infectious disease ensues. On the contrary, when the host is capable of mounting an immune response that provides a balanced protection, infection is prevented or controlled.

When infectious agents pass the defenses of epithelia and invade normally sterile body territories, they encounter innate antimicrobial mechanisms. When protective, these mechanisms involve the efficient intervention of several immune and nonimmune cells but are crucially centered on the activities of the dedicated phagocytes, monocytes/macrophages, and neutrophils. This concept is in line with the seminal studies by Metchnikoff [2], who created the theory of phagocytosis and highlighted the phagocytic and antimicrobial abilities of macrophages and microphages (neutrophils).

However, in the following years, neutrophils were largely underestimated, and macrophages acquired the status of the essential phagocytes. This view was reflected in the exclusion of the neutrophil in the initial attribution in 1967 of the label "professional phagocytes" to macrophages [3] and in the creation in 1969 of the mononuclear phagocyte system that grouped macrophages and their precursors (monocytes and bone marrow precursors) [4].

About 20 years later, neutrophils started to emerge as archetypical immune cells with rich effector and immunomodulatory functions [5], which led to the addition of neutrophils to monocytes/macrophages in the updated version of the concept of professional phagocytes [6].

Besides being precursors of macrophages [7–9], monocytes have progressively being recognized as relevant, direct effectors of antibacterial innate immunity [10, 11].

Abbreviations: DC=dendritic cell, HNP-1=human neutrophil peptide 1, MPO=myeloperoxidase, PRR=pattern recognition receptor, PS=phosphatidylserine, RNS=reactive nitrogen species, ROS=reactive oxygen species

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DCs [12] were added later to the mononuclear phagocyte system [13]. They are a group of primarily APCs and immunomodulatory macrophagic cells that display heterogeneous phagocytic activity [14]. However, DCs have a limited capacity for lysosomal degradation of phagocytosed material [15], and in contrast to neutrophils and macrophages, they are not involved in direct pathogen clearance [16].

This review is centered on the participation of phagocytes in the antimicrobial mechanisms of innate immunity in mammals. Detailed reviews are available about neutrophils [17–19] and monocytes/macrophages [10, 20, 21].

SPECIALIZED FEATURES COMPLEMENT THE COMMONALITIES OF MACROPHAGES AND NEUTROPHILS

The initial view that neutrophils and macrophages arise from a common late bone marrow precursor [22, 23] has been confirmed by results showing that these phagocytes originate from stem cells that differentiate through common myeloid progenitors and granulocyte/macrophage progenitors [24–26]. This common origin explains that the same functional defects can affect neutrophils and macrophages simultaneously [27] and that neutropenia and monocytopenia can occur concomitantly in several hematological disorders [28]. Their common origin also explains that these two professional phagocytes share several characteristics: (i) Like macrophages, neutrophils are avidly phagocytic, and both phagocytes use a large array of antimicrobial mechanisms that involve oxidants, granule proteins, and iron-withholding molecules (reviewed in refs. [18, 29, 30]). ROS are produced by a NADPH oxidase complex. Phagocytes can also produce RNS, and induced NO synthase is involved in the production of the microbicidal NO. The ROS member superoxide combines with the RNS NO to form a product—peroxynitrite—which is more bactericidal and cytotoxic than either of its precursors [31]. (ii) Macrophages and neutrophils have similar transcriptional profiles and coexpression of several genes [25, 32, 33] with common secretion of some cytokines and chemokines [34–36]; this explains why monocytes/macrophages and neutrophils recruit inflammatory phagocytes (see below). (iii) Macrophages and neutrophils have overlapping expression of cell surface receptors for Igs and complement [37] and for several chemokines [34, 35], which explains that under infectious/inflammatory situations, neutrophils and monocytes are concomitantly recruited (see below). (iv) The two phagocytes have overlapping expression of some antigens [8, 38], which explains the difficulty in selectively depleting neutrophils or monocytes/macrophages with antibodies (see below). (v) Monocytes/macrophages and neutrophils express PRRs [39]; additionally, neutrophils shuttle to lymph node microorganisms and bacterial antigens [40–42], regulate macrophage/DC functions [43], deliver bacterial antigens to these cells, helping in the cross-presentation of bacterial antigens to T cells [44, 45], and present antigens to T cells directly [46], indicating that neutrophils cooperate with macrophages in the orchestration of adaptive immune responses [17, 47, 48]. (vi) Macrophages are the main scavenger phagocyte, efficiently removing erythrocytes, apoptosing, and dead cells and cell debris [21], but when the scavenging capacity of macrophages is overwhelmed, neutrophils may function as a backup system [49]. (vii) Conversion of neutrophils into macrophages or DCs has been reported. Postmitotic human neutrophils cultivated under defined conditions generated cells with morphologic, cytochemical, and phenotypic features of macrophages [50]. Neutrophils cultured in the presence of M-CSF differentiate into F4/80-positive macrophages [33]. Immediate precursors of end-stage [51] or mature [52] neutrophils can acquire characteristics of DCs under defined cultural conditions. (viii) Finally, mobilization of neutrophils and monocytes to infectious/inflammatory sites follows similar kinetics (see below).

Additionally, the progressive modifications characteristic of macrophage and neutrophil maturation [25] lead to the specialization of each phagocyte, providing them with distinct individual properties that complement the similarities associated with their common origin.

Although varying among mammals, the antimicrobial capacity of neutrophils is higher compared with that of macrophages [2, 53–55]. The former are equipped with a huge assortment of microbicidal mechanisms and use multiple antimicrobial molecules stored in enormous amounts in granules sequentially formed during granulopoiesis [54, 56]. Production of ROS is most prominent in neutrophils as compared with macrophages [31]. Following phagocytosis, neutrophils use the "cross-talk" between oxidants and granule proteins to attack ingested microbes in a collaborative way [18]. Several antimicrobial proteins that are an important part of the neutrophil arsenal are lacking or scarce in the tissue macrophage [57–60]. This is the case of defensins and cathelicidins, the major families of mammalian antimicrobial peptides of neutrophils [61], and lactoferrin. The bactericidal/permeability-increasing protein is also a specific component of neutrophils [62]. MPO is an important enzyme involved in oxidative antimicrobial mechanisms of neutrophils oxidizing chloride ions to the strong hypochlorous acid, which is the most bactericidal oxidant known to be produced by phagocytes [29]. MPO is present in circulating mammal monocytes but is lost as these mature into macrophages [63], which correlates with decay in antimicrobial activity [64].

The pattern of distribution of neutrophils and macrophages correlates with their different antimicrobial capacities (and associated cytotoxicity) and different lifespans. The abundant and powerful antimicrobial neutrophil granule molecules and oxidants are not selective against microorganisms but rather, unspecific biocidal molecules with high cytotoxicity and potential tissue-damaging activity [19, 65]. This makes the activated neutrophil a dangerous cell that must be tightly controlled. Neutrophils are thus rare in the tissues and body cavities; they are present as quiescent cells in blood and bone marrow as reserve pools, ready to be activated and put to work only where, when, and while required [66]. This "surgical" actuation is possible, as neutrophils are present in large numbers in the reserve pools, are recruited quickly, and are short-lived [67]. In contrast, the lesser microbicidal and thus, less cytotoxic resident macrophage is long-lived [68] and has species-variable [69], self-renewal capacity [70]. Therefore, it is a cell well suited to reside in all body compartments [71] as the first

phagocyte that invading pathogens encounter, irrespective of their route of entry [10]. Strategically positioned, tissue resident macrophages thus function as sentinels that recognize, phagocytose, and signal invading pathogens rapidly.

These distinctive features explain that macrophages and neutrophils are not able to replace each other as crucial elements of antimicrobial innate immunity, as indicated by the pathology associated with some human and murine phagocyte deficiencies [28]. The conjugation of overlapping and complementary characteristics of the two professional phagocytes allows for a cooperative participation as effectors and modulators in innate immunity, as will be reviewed later.

NEUTROPHILS AND MONOCYTES CLUSTER WITH MACROPHAGES AND DCS AT INFECTIOUS FOCI

The number of resident phagocytes in resting tissues is small, but following microbial invasion, neutrophils [19, 66] and monocytes [7, 8] are recruited quickly to infectious foci. Usually neutrophils are the first phagocytes to arrive at those foci [19]. Neutrophils change their phenotype under infectious/inflammatory situations (**Table 1**), becoming activated by microbial products [72] and by attracting molecules [19, 67]. This activation leads to the expression of powerful antimicrobial activities [72] and to the controlled release of granule components [78] and is crucial for the effective innate immunity. Recruited monocytes give rise locally to inflammatory macrophages [7, 8] and to a subset of DCs [10], both participating in innate antimicrobial defenses.

This pattern of mobilization of the two professional phagocytes occurs early in the inflammatory response induced by infection with extracellular [79] or intracellular [80] pathogens. Mobilization of inflammatory neutrophils and monocytes is coordinated by complex networks of cytokines and chemokines that are produced in the context of the inflammatory process triggered by infection [81, 82] (**Table 2**). This inflammatory response and the associated cytokine and chemokine release are induced by microbial molecules that interact with complement [97] and with local cells. These include site-specific resident cells, mainly resident macrophages [83, 84, 98, 99], and DCs [100, 101]. To detect the occurrence of infection with the consequent recruitment of inflammatory neutrophils and monocytes, resident macrophages and DCs use invariant PRRs [39] that recognize conserved pathogen-associated molecular patterns present on extracellular and intracellular pathogens [102]. As PRRs are also expressed by neutrophils [103], these participate in the triggering of innate immune responses [17, 47]. Upon detecting the presence of invading pathogens, tissue macrophages (**Fig. 1**, upper panel, A) and DCs secrete CXCL8 (IL-8), CXCL1/2/3 (growth-related oncogene; MIP-2 in the mouse), CCL2 (MCP-1; JE in the mouse), and CCL3/4 (MIP-1) [10, 83, 98], which attract neutrophils and monocytes that become activated [19, 67].

Recruited, activated neutrophils exhibit relevant immunomodulatory abilities, which result in the release of proinflammatory cytokines and chemokines, an important activity that amplifies the initial chemotactic role of resident macrophages and DCs. Among the cytokines secreted by activated neutrophils are the proinflammatory IL-1β and TNF-α [5, 36], which stimulate the production by several cells of chemokines that primarily attract neutrophils [104] or monocytes [93]. The cytokine IL-17 is typically described as relevant in chronic inflammation and autoimmune diseases [105], but it is also an efficient first line of defense during the innate immune response associated to infection [106–109]. IL-17 acts on neutrophils by indirect expansion of their numbers through regulation of G-CSF and by recruitment through regulation of chemokine expression by several cell types [110]. Among these chemokines are the important neutrophil-attracting CXCL1, CXCL2, and CXCL8. IL-17 is produced mainly by $\gamma\delta$ T cells, CD4+ TH17 lymphocytes, and NKT cells [109–111], but it is also produced by neutrophils [112, 113]. Thus, neutrophils are here using another way to increase and sustain their presence at infectious/inflammatory sites, as they do with the direct secretion of neutrophil-attracting chemokines. This is important, as inflammatory neutrophils, having a short lifespan [67], have to be recruited continuously as long as they are needed. As in the case of several proinflammatory chemokines, in infectious/inflammatory situations during innate im-

TABLE 1. Main Phenotypic Changes in Inflammatory Neutrophils

	Resting neutrophils	Inflammatory neutrophils	References
Localization	Bone marrow and blood	Inflammatory sites	[66]
Lifespan	6–12 h	24–48 h	[67]
Increase in Ca2+ mobilization	–	+	[72]
Antimicrobial activity	–	+	[73, 74]
Cytotoxicity	–	+	[74]
Release of granule molecules	–	+	[67, 75]
Secretion of proinflammatory cytokines	–	+	[34, 35, 67]
Secretion of chemokines for neutrophils and monocytes	–	+	[34, 35] (see Table 2)
Induction of monocyte and macrophage activation	–	+	[76, 77]

Resting neutrophils recruited from reserve pools to infectious/inflammatory sites acquire the new phenotype of activated, inflammatory neutrophils.

TABLE 2. Main Neutrophil, Monocyte, and Macrophage Chemokines and Their Receptors in Inflammatory Settings [a]

Chemokines				Receptors		
	Produced by				Expressed on	
Name	Macrophages Ref.	Neutrophils Ref.	Monocytes Ref.	Name	Neutrophils Ref.	Monocytes Ref.
CXCL1/2/3	[83, 84]	[34, 35]	[85]	CXCR2, CXCR1	[35]	[86, 87]
CXCL8	[83]	[34]	[88]	CXCR2, CXCR1	[35]	[86, 87]
CCL2	[89]	[34, 35]	[90]	CCR2	[91, 92]	[86, 87]
CCL3/4	[83, 93]	[34, 35]	[94]	CCR1/4	[91, 95]	[86]

[a] All of the indicated references report results obtained in vivo. Although CXC chemokines mainly attract neutrophils, and CC chemokines mainly attract monocytes [96], a CXC chemokine may recruit monocytes, and a CC chemokine may recruit neutrophils, as receptors for CXC and CC chemokines may be concomitantly expressed in neutrophils or monocytes as shown in this table. Moreover, CXC and CC chemokines may be secreted by monocytes, macrophages, and neutrophils. This, as discussed in the main text, reflects a facet of the commonalities between neutrophils and monocytes/macrophages and makes questionable the use of genetically modified animals lacking CXC or CC receptors or deficient in production of CXC or CC chemokines to assess the specific roles of each phagocyte.

munity, IL-17 not only recruits and activates neutrophils but also inflammatory monocytes/macrophages that are attracted directly [107, 114, 115] or as a consequence of the induction of secretion of CCL2 [110].

Besides proinflammatory cytokines, activated neutrophils secrete CXC chemokines, primarily attracting neutrophils (including CXCL8 and CXCL1/2/3), and CC chemokines, primarily attracting monocytes (such as CCL2 and CCL3/4; Fig. 1, upper panel) [34, 35]. In the cross-talk with other cells, inflammatory neutrophils also use released granule molecules for relevant direct and indirect immunomodulatory activities [116, 117]. These include direct chemotaxis for neutrophils and monocytes [118] (that amplify the activity of neutrophil-secreted chemokines) and activation of monocytes and macrophages with enhancement of their phagocytic and antimicrobial abilities [119–121].

These networks of proinflammatory cytokines and chemokines originate the clustering at infectious/inflammatory foci of neutrophils, monocytes, macrophages, and DCs.

NEUTROPHILS AND MACROPHAGES CLUSTERED AT INFECTIOUS FOCI COOPERATE AS CENTRAL PLAYERS OF INNATE IMMUNITY

Macrophage-neutrophil cooperation at the immunomodulatory level

The previous overview about the macrophage and neutrophil involvement in the modulation of immune responses to infection shows that the two professional phagocytes cooperate in the orchestration of the innate immunity as well as in the translation between this initial response and adaptive immunity. Regarding innate immunity, the cooperation between macrophages and neutrophil is based on the common expression of PRRs by both phagocytes [103]; the common secretion of proinflammatory cytokines and chemokines (Table 2); and the common expression of some cytokine and chemokine receptors (Table 2). This interconnectivity between professional phagocytes creates several feedback loops that amplify and sustain their clustering and activation. The cooperation macrophage-neutrophil in the orchestration of the adaptive immune response is based on the common capacity to shuttle antigens to lymph nodes [40], to regulate DC functions [43, 122], and to present antigens directly to these cells [46].

Macrophage-neutrophil cooperation as an effector mechanism

One logical approach to assess the roles of neutrophils in physiological and pathological situations is to use animal models lacking this phagocyte. As viable genetic mutants selectively deficient in neutrophils are not available, and there are no drugs for selective pharmacological induction of neutropenia, antibody-mediated depletion of these phagocytes has been used widely. The mAb RB6-8C5 has been used in many studies, but it is a problematic reagent. RB6-8C5 targets the antigens Ly6G and Ly6C [123] expressed on neutrophils [124]. However, Ly6C (but not Ly6G) is also expressed on monocytes [8]. Thus, RB6-8C5 depletes neutrophils and monocytes when injected at a high dose [38] but depletes neutrophils selectively when administered in a single low dose (100 μg or less) [75, 125, 126]. This is the result of neutrophils being the major target of RB6-8C5, as this mAb targets Ly6G mainly, which is expressed almost uniquely on neutrophils [123]. Moreover, administration of RB6-8C5 should be done before the microbial challenge, as RB6-8C5 treatment may induce pathological side-effects if administered after microbial challenge [127], which may complicate the interpretation of the effects of induced neutropenia.

Another approach to assess the specific roles of each professional phagocyte would be through the use of genetically modified animals engineered to prevent the recruitment of each phagocytic line selectively. However, the commonalities already discussed between neutrophils and monocytes/macrophages regarding expression of some chemokine receptors complicate the assessment of the roles of each phagocyte line using mice genetically lacking chemokine receptors.

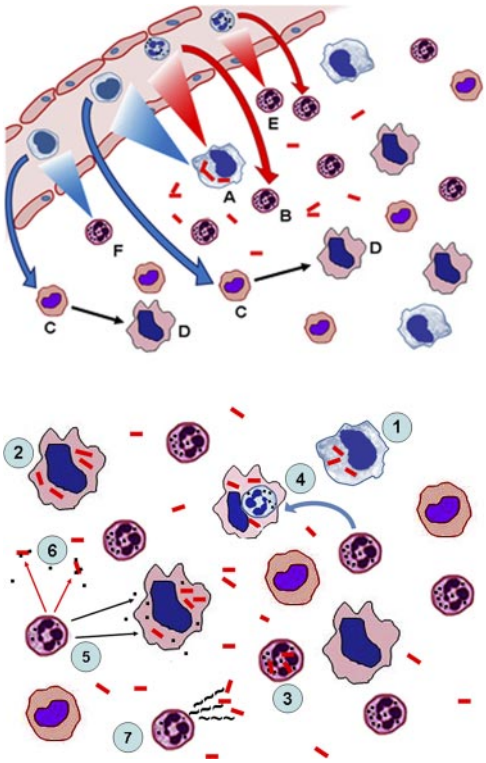

Figure 1. Schematic representation of the clustering and interactions of neutrophils, monocytes, and macrophages at inflammatory sites of infection by extracellular or intracellular pathogens. (Upper panel) Resident macrophages that detect the presence of invading pathogens (red rods) phagocytose them (A) and secrete chemokines, primarily recruiting neutrophils (such as CXCL8 and CXCL1/2/3; large red gradient) and monocytes (such as CCL2 and CCL3/4; large blue gradient; see Table 2). Recruited neutrophils become activated (B; see Table 1). Activated neutrophils complement the macrophage recruiting of inflammatory phagocytes by attracting additional inflammatory neutrophils (E) and monocytes (F) through the secretion of CXCL8 and CXCL1/2/3 (small red gradient) and CCL2 and CCL3/4 (small blue gradient), respectively (see Table 2). Recruited monocytes (C) give rise to inflammatory macrophages (D). (Lower panel) Infectious focus with resident macrophages clustered with recruited inflammatory neutrophils, monocytes, and macrophages (same cell styles as in upper panel). Effector mechanisms activated by phagocytes against invading pathogens (red rods) include: phagocytosis by resident (1) and inflammatory macrophages (2) and by recruited neutrophils (3); infected macrophages ingest neutrophils (4) and released neutrophil granule proteins (5) to enhance their antimicrobial capacity; activated neutrophils release granules and antimicrobial granule proteins that directly kill pathogens free in the extracellular space (6); neutrophil extracellular traps kill pathogens free in the extracellular space (7).

In conclusion, the closeness highlighted previously between the two lines of professional phagocytes complicates the efficacy of methods to deplete each of them selectively.

Macrophages extend the survival of recruited neutrophils at infectious foci. The short lifespan of resting neutrophils (6–12 h) is prolonged (to 24–48 h) after their recruitment to infectious/inflammatory sites [67]. This extension of neutrophil survival is associated with the delayed entering in senescent apoptosis [128] and is accompanied by prolongation of the functional lifespan of these phagocytes [129, 130]. Thus, prolonged survival of recruited, activated neutrophils contributes to the enhancement of the defense against infection [130]. However, as will be discussed later, if not properly regulated, this survival extension contributes to tissue damage-associated pathology [131].

Factors that prolong survival of neutrophils recruited to infectious/inflammatory sites include, besides some microbial products, IL-1β, TNF-α, G-CSF, and GM-CSF [128, 132–134]. Macrophages participate in the secretion of those factors [13, 129, 135]. Therefore, macrophage-induced extension of neutrophil survival at infectious foci represents another modality of macrophage-neutrophil cooperation.

Macrophage-neutrophil cooperation in protective immunity against bacterial intracellular pathogens. Macrophages are the preferred host cells for bacterial intracellular pathogens [136], and intramacrophage residence and multiplication are crucial phases in the life cycle of those pathogens [137]. When protective immunity ensues, macrophages turn into effectors of pathogen clearance [80], so that macrophages are classically considered the main professional phagocyte involved in the control of this type of infection [138]. However, several results point to the cooperation of neutrophils in the elimination of bacterial intracellular pathogens. The clustering at the infectious foci of macrophages and neutrophils was described, for example, in mycobacteriosis [139–143], in systemic [10] and oral [144] listeriosis, in salmonellosis [145], and in legionellosis [146].

Depletion of neutrophils under conditions considered above to induce adequate and selective neutropenia suggested neutrophil participation in the early innate defense mechanisms against infection by bacterial intracellular pathogens such as *Listeria monocytogenes* [147, 148], *Legionella pneumophila* [149], *Francisella tularensis* [150], *Burkholderia pseudomallei* [151], *Chlamydia trachomatis* [152], *Salmonella enterica* serovars Typhimurium [147], and Dublin [153].

Several studies using the mAb RB6-8C5 to assess the participation of neutrophils in mycobacterial infections found an early exacerbation of the infection (reviewed in ref. [154]). However, those studies used prolonged RB6-8C5 administration of high doses, thus not conforming to the conditions discussed above for the induction of adequate experimental neutropenia. Protocols following the adequate conditions are likely to be insufficient to induce the lasting neutropenia necessary in the case of the slow-growing pathogenic mycobacteria. Therefore, this approach may not be adequate to evaluate the participation of neutrophils in the protective innate immunity against mycobacteria. However, there are other data suggesting a role of neutrophils in that immunity. An inverse relationship between peripheral blood neutrophil counts and risk of *Mycobacterium tuberculosis* infection was demonstrated in a large cohort of tuberculosis contacts [155]. Moreover, that work found that whole blood samples from healthy human donors have antimicrobial activity against *Mycobacterium bovis* bacillus Calmette-Guerin and *M. tuberculosis*, an activity that is neutrophil-associated, as it was decreased significantly by selec-

tive neutrophil depletion of the blood samples with anti-CD15 antibodies. Other data favoring the view that neutrophils participate in the innate defense against mycobacterial infections will be discussed below.

The cooperation of neutrophils in the innate immunity against bacterial intracellular pathogens may involve immunomodulatory [151, 154, 156] and/or effector activities, which can use different mechanisms (Fig. 1, lower panel) as discussed next.

Neutrophils enhance macrophage antimicrobial abilities. As the macrophage is the primary effector of antimicrobial activity against those pathogens, an efficient strategy in the participation of neutrophils as effectors against those agents would be through supplying the macrophage with potent antimicrobial neutrophil granule molecules lacking in the macrophage. This would reinforce the limited antimicrobial capacity of macrophages.

A mechanism of macrophage-neutrophil cooperation based on the transfer to infected macrophages of neutrophil antimicrobial molecules was proposed initially in a murine model of experimental mycobacteriosis [139]. That study showed that in mycobacteria-infected sites, where macrophages and neutrophils cluster, including peritoneal cavity, foot-pad s.c. tissue, liver, and lung, macrophages ingested neutrophils, and lactoferrin was found within macrophages and predominantly in those infected with mycobacteria [139] (Fig. 1, lower panel, 4). Additionally, that study showed that the transfer of neutrophil granule molecules to cultured macrophages infected with *Mycobacterium avium* or *Mycobacterium microti* enhanced the antimycobacterial capacity of macrophages against those pathogens. This observation led to the novel concept that neutrophils participate in the macrophage-mediated control of mycobacterial infections by supplying potent antimicrobial molecules lacking in macrophages [139]. This mechanism of macrophage-neutrophil cooperation was suggested later for infections by *M. tuberculosis* [157] and *L. pneumophila* [158]. Moreover, a role in that mechanism of neutrophil HNP-1 and MPO in infections by *M. tuberculosis* and *M. avium* was suggested [157, 159–161].

Several data support that cooperative mechanism and suggest that it operates in other infections by bacterial intramacrophage pathogens besides mycobacteria. On the one hand, neutrophil granule molecules are known to be microbicidal in vitro against several intracellular pathogens [155, 157, 159, 161–164]. On the other hand, those molecules were found to be taken avidly by macrophages in vitro and to enhance the antimicrobial activity against several intramacrophage pathogens [158, 161, 165–170]. Additionally, neutrophil molecules are detected in vivo within macrophages at infectious sites resulting from intramacrophage bacterial pathogens [139, 171].

Recent results using human macrophages and neutrophils [163] confirmed and extended those initial observations by showing that phagocytosis of apoptotic neutrophils by macrophages infected with *M. tuberculosis* resulted in the transfer of the antimicrobial peptide HNP-1 to the compartments in which mycobacteria reside within macrophages; this transfer was accompanied by a dose-dependent reduction in the viability of intramacrophage *M. tuberculosis*. Uptake of purified granules alone also decreased growth of intracellular mycobacteria.

The above data indicate that at infectious/inflammatory sites, macrophages may acquire neutrophil antimicrobial molecules through phagocytosis of neutrophils (Fig. 1, lower panel, 4) or intake of neutrophil granules (Fig. 1, lower panel, 5). Macrophages are the main scavenger of senescent, apoptotic neutrophils [172], which provides one mechanism of acquisition of neutrophil molecules. Macrophages with phagocytosed neutrophils are constantly seen at infectious foci, and its occurrence is maintained as long as the neutrophil influx persists [171]. This phagocytosis is associated to an active anti-inflammatory response in macrophages (reviewed in ref. [65]). Phagocytosis of *M. tuberculosis* by neutrophils in vitro induces rapid apoptosis of these phagocytes [173], and phagocytosis by macrophages of mycobacterium-infected apoptosing neutrophils, instead of inducing an anti-inflammatory response, activates macrophages [173, 174]. Therefore, phagocytosis by macrophages of *M. tuberculosis*-infected apoptotic neutrophils may represent an important host defense mechanism leading to the enhancement of the antimicrobial activity of macrophages.

The above data indicate that phagocytosis of apoptosing neutrophils by macrophages is not a mechanism solely involved in the removal of senescent neutrophils but additionally, may be used to procure the acquisition of additional antimicrobial molecules to help fight intramacrophage pathogens. It is expectable, therefore, that macrophages would phagocytose not only apoptosing neutrophils as a scavenging process but also viable neutrophils as a cooperative antimicrobial mechanism. This implies that nonapoptosing neutrophils would be able to express surface "eat-me" signals that promote their uptake by macrophages. One major eat-me signal on the surface of apoptosing cells is externalized PS [128], and it has been reported that PS exposure on neutrophils leading to phagocytic recognition and removal by macrophages can occur independently of apoptosis following neutrophil activation [175–178].

Neutrophil granules and antimicrobial granule proteins are known to be released in a controlled manner at infectious sites as a result of degranulation associated to activation [78]. The activation discussed previously of macrophages and enhancement of their phagocytic activity by released neutrophil granule proteins at infectious/inflammatory sites [165, 179] represent other modalities of neutrophil-macrophage cooperation, boosting the antimicrobial innate immune response.

The above data suggest that when bacterial intracellular pathogens invade macrophages, these phagocytes call neutrophils to help and use the highly potent and abundant antimicrobial molecules of this phagocyte to enhance their limited antimicrobial capacity. This is a safe way of macrophages using powerful microbicidal molecules without the risk of permanently carrying them.

Direct effector activity of neutrophils toward intracellular pathogens. Intracellular pathogens can be exposed to the direct effector activity of the neutrophil when they are outside of their host cell. This extracellular location occurs when the pathogens transit from one host cell to the next; additionally,

some of them may have a phase of extracellular residence and multiplication in the host [1].

Direct neutrophil effector antibacterial activity against free intracellular pathogens may operate through phagocytosis (Fig. 1, lower panel, 3), release of granule antimicrobial molecules (Fig. 1, lower panel, 6), or use of extracellular traps [180] (Fig. 1, lower panel, 7). Bacterial intracellular pathogens can be seen within neutrophils in vivo, as reported in infections by *Mycobacteria* [40, 139, 181], *Salmonella* [182, 183], *L. monocytogenes* [184, 185], and *L. pneumophila* [146, 186]. Several studies show that many, but not all [148, 181, 183, 187], intracellular pathogens can survive within neutrophils (reviewed in ref. [188]), suggesting that a direct effector activity of these phagocytes would not be a widespread host defense mechanism in infections by those pathogens, in contrast to infections by bacterial extracellular pathogens [79].

Neutrophils transfer intracellular pathogens to macrophages. Neutrophils that ingested intracellular pathogens can be phagocytosed by macrophages coexisting at the same infectious site. This ingestion will transfer to macrophages the pathogens initially within neutrophils [139, 143, 171, 184, 189]. An outcome of that transfer that represents another example of cooperation between macrophages and neutrophils in the innate defense against infection is the elimination within the macrophage of the transferred pathogen with the participation of the antimicrobial mechanisms of the macrophage and of the ingested neutrophil.

Macrophage-neutrophil cooperation against bacterial extracellular pathogens. As in the case of intracellular pathogens, the recruitment of neutrophils and monocytes to sites of infection by bacterial extracellular agents [79, 190, 191] is largely a result of neutrophil- and monocyte-attracting chemokines secreted by resident macrophages following the recognition of the invading pathogens [192–194]. Human macrophages infected in vitro with *Streptococcus pyogenes* secrete the chemokine CXCL8, primarily attracting neutrophils, and the chemokines CCL2 and CCL3, primarily attracting monocytes [195].

Although neutrophils are the main effectors in innate immunity against bacterial extracellular pathogens [79] through phagocytosis [79] (Fig. 1, lower panel, 3), release of granule antimicrobial molecules [78] (Fig. 1, lower panel, 6), or use of extracellular traps [196] (Fig. 1, lower panel, 7), the participation of monocytes/macrophages in cooperation with neutrophils has been shown to be relevant for the early control of those pathogens [194, 197]. Macrophage depletion in mice increased susceptibility to *S. pyogenes* [190] and *Staphylococcus aureus* [198]. One modality of this cooperation depends on the macrophage direct effector activity through phagocytosis and killing of the extracellular parasite [190] (Fig. 1, lower panel, 1 and 2). The observation that the antimicrobial activity of cultured macrophages against ingested *Escherichia coli* [199] or *Pseudomonas aeruginosa* [167] is enhanced following the acquisition by the infected macrophages of neutrophil MPO suggests that the mechanism of macrophage-neutrophil cooperation, based on the transfer of neutrophil antimicrobial molecules to infected macrophages, may operate in infections by bacterial extracellular pathogens as well.

Macrophage-neutrophil cooperation against eukaryotic pathogens. Some results suggest the occurrence of a cooperative participation of macrophages and neutrophils also in infections by protozoans such as *Trypanosoma cruzi* [165], *Leishmania major* [77, 200], and *Cryptosporidium parvum* [201] and fungi such as *Aspergillus fumigatus* [202], *Histoplasma capsulatum* [166], and *Candida albicans* [168, 203].

The antimicrobial activity of macrophages infected in vitro with *T. cruzi* [165], *C. albicans* [168, 169], or *H. capsulatum* [166] is enhanced by the acquisition of neutrophil lactoferrin, MPO, or HNP-1, respectively. This suggests that the mechanism of macrophage-neutrophil cooperation based on the transfer to infected macrophages of neutrophil antimicrobial molecules may also operate in those infections.

Macrophages and neutrophils cluster in the inflammatory exudate produced early after i.p. infection with *Toxoplasma gondii*; the macrophage is the major host cell for the parasite in this exudate [204]. Both phagocytes have been implicated in the innate defense against the parasite (reviewed in ref. [205]). However, this implication is based on controversial data, as the studies with mice made neutropenic with RB6-8C5 used protocols of administration of that mAb that do not conform to the conditions discussed already to achieve an adequate neutrophil depletion. However, although not definitive, the observations that in mice genetically deficient in CXCR2 [206] or IL-17R [207], infected with virulent *T. gondii*, the defective early neutrophil recruitment is associated with higher susceptibility, suggest that neutrophils participate with macrophages in the innate defense against that pathogen.

MACROPHAGE-NEUTROPHIL COOPERATION IN THE RESOLUTION OF INFECTIOUS INFLAMMATION

Upon effective control of the infection, the presence of potentially dangerous neutrophils at infectious/inflammatory foci can be terminated quickly, as these phagocytes are short-lived cells, which when senescent, enter apoptosis and are removed by macrophages before lysis and associated tissue damage [65, 172]. Indeed, although the survival of neutrophils is prolonged after recruitment to infectious sites, they ultimately undergo apoptosis and are removed mainly by scavenger macrophages [128].

Usually, phagocytosis of apoptosing neutrophils by macrophages leads to resolution of inflammation with restitution of tissue homeostasis soon after neutrophils have accomplished their task [172]. Appropriately, this phagocytosis is associated to an active anti-inflammatory response in macrophages by induction of TGF-β and IL-10 production (reviewed in ref. [65]). When the scavenging capacity of macrophages is overwhelmed, neutrophils may function as a backup system [49]; monocytes also phagocytose apoptosing neutrophils [208]. Senescent monocytes and macrophages also enter apoptosis and are removed by scavengers, mainly

macrophages [68, 209]. Therefore, besides their effector and modulator activities, the members of the phagocyte system accumulate the function of scavengers of the senescent cells of the system, thus contributing to its safer operation. These results indicate another modality of macrophage-neutrophil cooperation.

MACROPHAGE-NEUTROPHIL COOPERATION IN INFECTION-ASSOCIATED TISSUE DAMAGE

Infection-associated cell and tissue damage involves a synergistic interaction among many microbial- and host-derived proinflammatory agonists [210–212]. Within the context of this review, the phagocyte-associated tissue damaging will be highlighted. Protective immunity is only beneficial if well contained. Phagocyte accumulation at infectious/inflammatory foci may contribute to pathology through the relevant proinflammatory and tissue-damaging effects of these cytotoxic phagocytes (reviewed in refs. [65, 213]).

As discussed elsewhere [210, 214, 215], leukocyte-inflicted tissue damage involves a network of marked complexity, requiring the cross-talk among different cell types, mediators, cytotoxic agents, and their respective inhibitors. The participation of professional phagocytes in infection-associated tissue injury may involve the direct, deleterious effects of excessive activity of phagocytic cytotoxic molecules released during uncontrolled neutrophil degranulation [78] or as a consequence of nonprevented neutrophil lysis (reviewed in ref. [65]). Phagocyte-associated tissue injury is mediated by the microbicidal molecules that participate in antimicrobial defense, including ROS, RNS, peroxynitrite, and cationic proteins [210, 216]. Proinflammatory cytokines (such as IL-1β, TNF-α, and IL-17) and chemokines are involved in excessive inflammatory tissue damage associated to infection. A likely indirect mechanism may also participate, whereby phagocyte granule antimicrobial proteins, in addition to their killing effects as a result of permeabilization of microbial membranes, also activate nascent autolytic wall enzymes; this activation will lead to bacteriolysis with release of the highly phlogistic, LPS, lipoteichoic acid, and peptidoglycan envelope components [212]. Regarding the direct damaging activity of phagocytes, it is relevant that neutrophils are particularly potentially cytotoxic as a result of their powerful oxidative, enzymatic, and peptidic antimicrobial mechanisms [19, 65] and that the prolonged neutrophil survival at infectious sites may contribute to tissue injury. Additionally, the more limited antimicrobial/phlogistic activities of macrophages may participate in the infection/inflammation-associated tissue damage [210]. This indicates that besides the cooperation in protective, beneficial defense mechanisms, macrophage-neutrophil cooperation also participates in the infection/inflammation-associated pathogenesis. In other words, macrophage-neutrophil cooperation might have two opposing faces.

MACROPHAGES AND NEUTROPHILS ARE TARGETED BY MICROBIAL PATHOGENICITY MECHANISMS

So far, this review has been centered on the host innate immune phagocytic mechanisms that control microbial infections efficiently. However, the other possible outcome of the host/parasite interaction results in the defeat of the host immunity by the pathogenicity factors of the infectious agent.

As the pathogenic success of extracellular pathogens is largely dependent on resistance to the effector mechanisms of phagocytes, mainly neutrophils [79, 138], the major virulence factors of those pathogens include means to prevent phagocytosis. In accordance with the concept highlighted in this review are the observations showing that the same molecule is able to attack neutrophils and macrophages in several bacterial pathogens; this is the case of toxins from the highly virulent *P. aeruginosa* [217], *Photobacterium damselae* subspecies *piscicida* [218], *Yersinia pestis* [219], and *S. aureus* [191], among others.

Intracellular bacterial pathogens are dependent on living macrophage host cells and many of their functions [220], and they have evolved mechanisms to evade macrophage antimicrobial mechanisms [137]. In accordance with the participation of neutrophils in the innate host defense against intracellular bacterial pathogens, one relevant virulence factor of these pathogens is to attack neutrophils [213, 221, 222]. Significant examples are *Brucella abortus* [223], *B. pseudomallei* [224], *Burkholderia cepacia* [217], *F. tularensis* [225], *C. trachomatis* [213], *Chlamydia pneumoniae* [217], *M. tuberculosis* [213], *Mycobacterium ulcerans* [226], *L. monocytogenes* [217], *Legionella micdadei*, *L. pneumophila* [227], and *Haemophilus somnus* [217].

MACROPHAGES AND NEUTROPHILS FUNCTION AS PARTNERS IN A MYELOID PHAGOCYTE SYSTEM

Following the Ludwig Aschoff concept, cellular systems have been created based on the sharing of a set of features, mainly origin and function. Based on this criterion, the mononuclear phagocyte system [4] was created as a system of dedicated phagocytic cells, grouping macrophages and their precursors but excluding neutrophils. This exclusion was based on the argument that "Although polymorphonuclear phagocytes are mononuclear too, they belong to another cell line because of their different origin and divergent kinetic and functional behavior." [4].

However, present knowledge about the biology of phagocytes does not justify the maintenance of neutrophils outside of a system of dedicated phagocytes. The concept of the mononuclear phagocyte system was proposed at a conference about mononuclear phagocytes held in 1969 [4]. At the time, details of myelogenesis were not known, and neutrophils were considered to belong to another cell line and to be a terminally differentiated phagocytic effector that releases preformed mediators and kills pathogens but is de-

void of transcriptional activities. However, the advances in the knowledge of neutrophil biology helped to change that traditional view, and neutrophils emerged progressively as immune cells with important roles in the regulation of immune responses. Moreover, and as highlighted here, neutrophils and macrophages have a common origin, share several essential capabilities, and cooperate in important immune activities. Finally, two functional criteria that were taken into consideration to select cells to be grouped in the mononuclear phagocyte system, namely pinocytosis and the ability to attach firmly to a glass surface, are now known to be exhibited by neutrophils as well [228, 229]. Thus, the view that neutrophils should be included with the members of the mononuclear phagocyte system (monocytes, macrophages, and DCs) in a broader myeloid phagocyte system is justified. Because of their crucial phagocytic and antimicrobial capabilities, neutrophils and macrophages are the effector arms of this revised system.

CONCLUDING REMARKS

The data here highlighted indicate that the common origin and the specialization during differentiation endow macrophages and neutrophils with overlapping and complementary abilities, which they use in a concerted innate immune attack strategy to fight infection. That strategy is based on several modalities of cooperation between the two professional phagocytes (summarized in **Table 3**).

When intracellular or extracellular pathogens invade mammal host tissues, resident macrophages detect the pathogen and recruit neutrophils from reserve pools to assist them in the antimicrobial effector mechanisms. Indeed, although the phagocytes with more important roles against intracellular and extracellular pathogens are macrophages and neutrophils, respectively, the two professional phagocytes operate in concert in both infectious situations: Neutrophils help macrophages to fight intracellular pathogens, and macrophages assist neutrophils in the defense against extracellular pathogens.

Starting from a common myeloid precursor in the bone marrow, which provides many overlapping characteristics, macrophages and neutrophils split during differentiation, specialize with the acquisition of distinctive features that complement the shared properties, and finally, join at the infectious foci for a cooperative antimicrobial defense: (i) Resident macrophages are long-lived cells strategically distributed in all body territories as sentinels of microbial invaders and conveniently, for a tissue-resident cell, are limited in cytotoxic mechanisms at the cost of some antimicrobial activity. (ii) Neutrophils are more microbicidal as a result of expression of high amounts of powerful and cytotoxic antimicrobial molecules; consequently, they are potentially dangerous phagocytes strategically stored as reserve pools during steady-state conditions as resting cells in bone marrow and blood, activated and used only in emergency situations, when, where, and while needed. (iii) At the beginning of the infectious process, tissue macrophages that detect invading pathogens recruit monocytes, which mature into inflammatory macrophages, and neutrophils. (iv) The immunomodulatory abilities of attracted neutrophils complement macrophages in the recruitment of additional phagocytes; these redundant recruitment circuits lead to the clustering of macrophages and high numbers of neutrophils at infectious sites. (v) In these sites, macrophages participate in the extension of neutrophil survival and macrophages and neutrophils interact and cooperate at infectious foci for an effective innate antimicrobial immunity through effector mechanisms as specialized partners of a myeloid phagocyte system; additionally, the two phagocytes cooperate in immunomodulatory activities, including in the orchestration of innate and adaptive immunities. (vi) Upon effective control of the infection, the presence of potentially dangerous neutrophils at infectious/inflammatory foci is terminated quickly through the removal of senescent/apoptotic neutrophils by macrophages before lysis and associated tissue damage.

The specialization behind the neutrophil and monocyte/macrophage lineage specification is the basis of an advanta-

TABLE 3. Aspects of the Cooperation between Macrophages and Neutrophils As Effectors and Modulators in Protective Antimicrobial Innate Immunity

	References
Macrophages and neutrophils participate in the orchestration of innate immunity:	
Neutrophils and macrophages express PRRs.	[103]
Macrophages and neutrophils secrete proinflammatory cytokines.	[34, 35]
Macrophages and neutrophils recruit neutrophils and monocytes to infectious sites.	(see Table 2)
Neutrophils activate macrophages, and macrophages activate neutrophils.	[67, 121]
Macrophages and neutrophils cooperate as effectors of antimicrobial innate immunity:	
Neutrophils and macrophages phagocytose and kill microbial pathogens.	[156, 190]
Neutrophils enhance the phagocytic ability of macrophages.	[179]
Neutrophils supplement macrophages with molecules that enhance macrophage antimicrobial capacities.	[139, 163]
Neutrophils transfer to macrophages intracellular pathogens.	[230, 231]
Macrophages and neutrophils cooperate in the resolution of infectious inflammation.	[49, 172, 208]
Macrophages and neutrophils participate in the translation of innate to adaptive immunity.	[17, 47, 156]

geous, cooperative innate immune attack strategy that allows the efficient and safe use in antimicrobial mechanisms of powerful and dangerous microbicidal molecules. To achieve this, the two mammalian professional phagocytes combine overlapping and complementary capabilities and work in concert as two specialized effectors and modulators of a myeloid phagocyte system.

ACKNOWLEDGMENTS

I am grateful to João Pedro Pereira, Margarida C. Neves, Jorge Pedrosa, and A. Gil Castro for helpful discussions, to Anabela Costa for editorial assistance, and to Bernardo Gama for the graphic work.

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KEY WORDS:
myelopoiesis · phagocytosis · chemotaxis · antimicrobial mechanisms · pathogenicity mechanisms