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Expanding roles of neutrophils in aging hosts

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Neutrophils' role in the clearance of pathogens is well documented, but there is increasing appreciation that neutrophils can participate in the resolution of infection and inflammation. An obvious implication is that alteration of neutrophil functions with old age could significant impact both susceptibility of the host to infection and inflammatory conditions. Advances in recent years suggest additional chinks in the neutrophil antimicrobial arsenals in aged hosts, which render neutrophils less capable of killing pathogens. Moreover there is evidence that changes in neutrophil cross-talk with other immune cells also contribute to poor resolution of inflammation. These advances provide new insight on how these phagocytic cells could contribute to age-related diseases.

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Introduction

Neutrophils were once viewed as phagocytic cells packed with antimicrobial substances programmed solely to kill pathogens. After elimination of the microbes from the infection site, they are removed to bring the infection to a resolution. Exciting advances in recent years have altered this simplistic view of neutrophils [1–4]. Added to the phagocytes' arsenals are neutrophil extracellular DNA traps (NETs) which immobilize bacteria. Neutrophil subsets with either pro-inflammatory or anti-inflammatory properties have been characterized. Additionally, an abundance of data suggests that neutrophils are active players in the orchestration of host defense and resolution of inflammation. These novel findings have provided a more dynamic framework to reevaluate the role of neutrophils in age-related diseases.

In this review, we summarize recent developments in the neutrophil and aging field (Figure 1), and discuss their significance in the context of the new neutrophil biology and age-related diseases (Table 1). Because of space limitation, the reader is referred to many excellent reviews on the impact of aging on neutrophils [5–13].

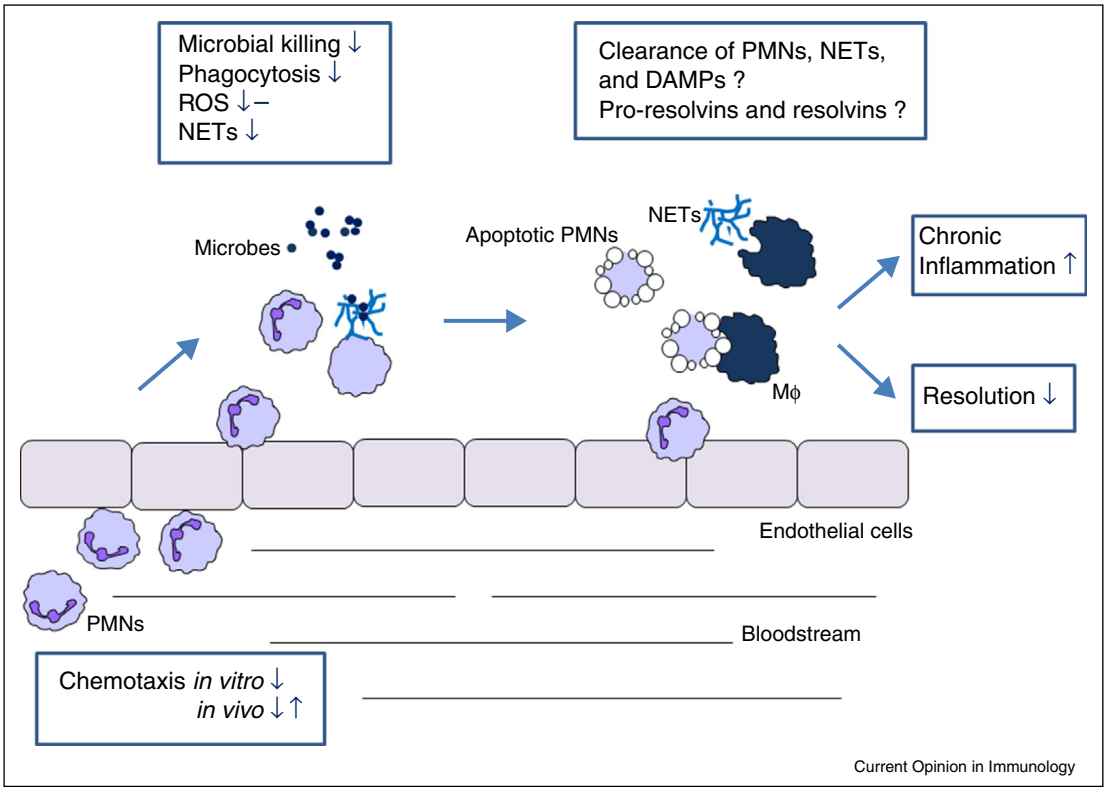
Recruitment to the site of inflammation

It is well documented that aged individuals are more susceptible to infection. This is unlikely the effect of aging on myelopoiesis since the numbers of circulating neutrophils at baseline and during acute inflammation are not reduced in elderly hosts (reviewed in [13]). Instead, defects in neutrophil recruitment or microbial killing are probably responsible for age-related susceptibility to infection. Neutrophil recruitment is an elaborate process in which circulating neutrophils are attracted to the site of inflammation by following chemokine trails laid out by microbes or host cells [2]. Surface chemokine receptors allow neutrophils to survey chemokine gradients along the vascular endothelium, and subsequent engagement of integrins and CD15 on neutrophils with P-selectin glycoprotein ligand-1 (PSGL-1), and P-selectins, L-selectins and E-selectins, and ICAMs on endothelial cells leads to neutrophil attachment and transmigration.

Though defects in neutrophil chemotaxis are well documented in aging hosts, several new studies have provided important insight on how recruitment is compromised with aging. The most interesting report is a study by Sapey and colleagues describing decreased accuracy of neutrophil migration to various inflammatory stimuli without loss of chemokinesis [14••]. The authors showed that constitutive activation of phosphoinositide 3-kinase (PI3K) was responsible for the inaccurate migration and inhibition of PI3Kγ or δ restored accuracy of the directional chemotaxis. In a model of pseudomonas lung infection, inaccurate neutrophil migration was offered as an explanation for the high number of neutrophils stranded in the lung parenchyma of aged mice [15]. By comparison, neutrophils from young mice were primarily recruited to the alveolar space to more effectively combat the infection.

Though neutrophil chemotactic deficits are well described *in vitro* in aged hosts (reviewed in [13]), several reports in the past years have underlined the complexity of neutrophil recruitment *in vivo*. Three infection studies performed using *Staphylococcus aureus* or *P. aeruginosa* reported reduced neutrophil numbers at the infection site [15,16•,17•]. Impaired neutrophil recruitment could not be explained by local chemokine release as chemokines were found to be more elevated in aged mice in two of the studies [15,16•]. Additionally, elevated chemokine

Figure 1



PMN functions and senescence. Arrows indicate changes with aging.

receptor (CXCR2) expression on circulating neutrophils did not improve recruitment of the neutrophils in one study [16•]. The findings led the authors to suggest that intrinsic defect in CXCR2 signaling likely accounted for the recruitment defect. In contrast to the infectious stimuli, LPS injection or thermal injury induced higher neutrophil accumulation in aged mice compared to young mice [18,19•,20]. Increased expressions of ICAM-1 on lung endothelial cells or E-selectins and P-selectins in the kidneys correlated with neutrophil accumulation and

Table 1

Changes of neutrophil-related functionsin aged hosts

	Changes	Comments
Neutrophil number	↔	[12,13]
Neutrophil chemotaxis		
In vitro	↓	[13,14••]
In vivo	↓, –, or ↑	[15,16•,17•,18,19•,20,36•]
Neutrophil antimicrobial functions		
Phagocytosis	↓	[13]
ROS	↓ or ↔	[13]
Elastase	Variable	Stimulus dependent [32]
NETs	↓	[17•]
Clearance of dead neutrophils	Unknown	↓ clearance of apoptotickeratinocytes and T cells with aging [38•]
Clearance of DAMPs or NETs	Unknown	
Pro-resolvins, resolvins, or protectins	Unknown	↓ urinary LXA4 with aging [49]
Cytokines		
Pro-inflammatory	↓ or ↔	Stimulus dependent [17•,22•,32]
Anti-inflammatory	↑	[32]
Existence of neutrophil types/subsets		
Pro-inflammatory/promoting tissue injury	[14••,36•,50••]	Pro-inflammatory MDSCs ↑with aging [57••]
Anti-inflammatory/protective against tissue injury	[19•]	

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