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Serial Review: Redox Signaling in Immune Function and Cellular Responses in Lung Injury and Diseases
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# Reactive oxygen and nitrogen species as signaling molecules regulating neutrophil function ☆

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**Abstract**

As a cornerstone of the innate immune response, neutrophils are the archetypical phagocytic cell; they actively seek out, ingest, and destroy pathogenic microorganisms. To achieve this essential role in host defense, neutrophils deploy a potent antimicrobial arsenal that includes oxidants, proteinases, and antimicrobial peptides. Importantly, oxidants produced by neutrophils, referred to in this article as reactive oxygen (ROS) and reactive nitrogen (RNS) species, have a dual function. On one hand they function as potent antimicrobial agents by virtue of their ability to kill microbial pathogens directly. On the other hand, they participate as signaling molecules that regulate diverse physiological signaling pathways in neutrophils. In the latter role, ROS and RNS serve as modulators of protein and lipid kinases and phosphatases, membrane receptors, ion channels, and transcription factors, including NF-κB. The latter regulates expression of key cytokines and chemokines that further modulate the inflammatory response. During the inflammatory response, ROS and RNS modulate phagocytosis, secretion, gene expression, and apoptosis. Under pathological circumstances such as acute lung injury and sepsis, excess production of ROS may influence vicinal cells such as endothelium or epithelium, contributing to inflammatory tissue injury. A better understanding of these pathways will help identify novel targets for amelioration of the untoward effects of inflammation.
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*Keywords:* Neutrophil; Signal transduction; Tyrosine phosphatase; Tyrosine kinase; Nuclear factor κB; Free radicals

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The primary function of neutrophilic polymorphonuclear leukocytes (neutrophils) in the innate immune response—to contain and kill invading microbial pathogens—is achieved through a series of rapid and coordinated responses culminating in phagocytosis and killing of the pathogens [1]. Neutrophils boast a potent antimicrobial arsenal that includes oxidants, proteinases, and antimicrobial peptides. Neutrophils also produce prodigious quantities of reactive oxygen (ROS) and nitrogen (RNS) species such as $O_2^{\bullet -}$ and $NO^{\bullet}$ through the activity of oxidant-generating systems such as the phagocyte NADPH oxidase [2] and nitric oxide synthase (NOS) [3,4] respectively. During ingestion (phagocytosis) of invading pathogens, antimicrobial compounds contained in granules and ROS generated at the phagosome membrane are released directly into the phagosome. This process compartmentalizes both the pathogen and the cytotoxic products and facilitates intracellular killing [5]. Additionally, neutrophils can release granule proteins and chromatin that form neutrophil extracellular traps (NETs), which degrade virulence factors and bind and kill bacteria in a contained microenvironment [6]. Despite these safeguards, under pathological circumstances, potent cytotoxic compounds may be released into the extracellular space and damage host tissues [1,5,7]. Given this potential for tissue injury, it is evident that regulatory mechanisms must exist to limit leukocyte activation and extracellular release of cytotoxic products.

Conventionally, ROS and RNS have been considered to function primarily in host defense as antimicrobial factors. However, strong evidence supports a role for ROS and RNS in the regulation of pivotal cellular signaling events involved in homeostasis, cell proliferation and differentiation, and inflammatory and immune responses [8–11]. In this regard, ROS and RNS fulfill important prerequisites for intracellular messenger molecules: they are small, diffusible, and ubiquitous molecules that can be rapidly synthesized and destroyed, thus conferring spatial and temporal specificity to signaling events [12,13]. However, because of their toxicity, there is a narrow concentration range in which they can function effectively as second messengers. The purpose of this article is to review the evidence that ROS and RNS participate as physiological signaling molecules in the regulation of intracellular signaling pathways in leukocytes and the implications of this for regulation of the inflammatory response. Although the intent of this discussion is to focus primarily on neutrophils, we will also discuss other leukocyte types, including macrophages and lymphocytes, where appropriate to illustrate the effects of ROS and RNS on conserved signaling pathways fundamental to immune and inflammatory responses.

## Sources of reactive oxygen species

### *NADPH oxidase*

Neutrophils possess a membrane-bound multicomponent enzyme complex termed the NADPH oxidase that, when activated, generates large quantities of ROS [14,15]. This system is responsible for the neutrophil “respiratory burst” (increased respiration of phagocytosis). This term describes the phenomenon wherein, during ingestion of microorganisms, phagocytic cells demonstrate a striking increase in oxygen consumption [16]. Interestingly, a family of NADPH oxidases (NOXs) is also expressed in nonphagocytic cells [15]. NOXs produce ROS in a regulated manner and at lower levels than in phagocytes [15].

The phagocyte NADPH oxidase is dormant in resting cells and can be rapidly activated by a variety of soluble mediators (e.g., chemoattractant peptides and chemokines) and particulate stimuli (e.g., bacteria and immune complexes) that interact with cell-surface receptors. The phagocyte oxidase exhibits a marked preference for NADPH (a product of the hexose monophosphate shunt) as the electron donor and converts molecular oxygen to its one-electron reduced product, superoxide ($O_2^{\bullet -}$), the major end product:

$$NADPH + H^+ + 2O_2 \rightarrow NADP^+ + 2H^+ + 2O_2^{\bullet -}$$

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