

NOX2-Derived ROS: Not Just For Microbial Killing Anymore

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Neutrophils are the first cells to migrate out of the blood to the infection site during bacterial or fungal invasion [1]. After phagocytosis of the pathogen, the neutrophils produce and use different toxic agents to kill and eliminate the pathogen. Among these agents, reactive oxygen species (ROS) such as superoxide anion ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), hydroxyl radical (OH^{\cdot}) and hypochlorous acid (HOCl) are pro-oxidants that react quickly with the various biological molecules (lipids, proteins and DNA) of the pathogens or the host [2-4]. The enzyme responsible for ROS production is called the phagocyte NADPH oxidase (NOX2). It is composed of two trans-membrane proteins (p22phox and gp91phox) that form the flavocytochrome b_{558} , and four soluble cytosolic proteins (p47phox, p67phox, and p40phox and a small G-protein, Rac2 in neutrophils or Rac1 in other cells) [2-4]. In resting cells, the membrane and cytosolic components of NOX2 are segregated, but assemble at the membrane upon activation. For several decades, the role of NOX2-derived ROS was thought to be restricted to its toxic and killing properties to eliminate pathogens during the immune response. In fact, this function is well illustrated by chronic granulomatous disease (CGD), a genetic defect in which one of the NOX2 subunits is missing, resulting in absence of ROS production, and of killing/elimination of pathogens [2,3]. The generation of NOX2 knockout mice confirmed the requirement of NOX2-derived ROS for bacterial killing [5,6]. Although the bactericidal effect of NOX2-derived ROS is well established in vitro and in vivo in neutrophils, other effects of NOX2-derived ROS are also very important in innate and adaptive immunity. Indeed, NOX2 is also expressed in other immune cells, such as eosinophils, monocytes, macrophages, dendritic cells, and B and T lymphocytes, where they exert other functions [7,8]. In addition, some ROS such as H_2O_2 can diffuse outside the cells to act as a "paracrine-redox signaling agent", thus altering the functions of neighboring cells and potentially modulating the immune response [9,10]. ROS, and particularly the diffusible H_2O_2 , can oxidize cellular macromolecules (proteins, lipids, DNA), leading to tissue injury or to the alteration of cellular functions such as an imbalance of intracellular signaling pathways, production of cytokines, and activation and release of proteases [11,12].

Although NOX2 is also required for pathogen killing by monocytes and macrophages, it can regulate phagosomal protein degradation for antigen presentation, especially in macrophages, through oxidative inactivation of cysteines in cathepsin [13]. NOX2 also participates to cell signaling and protein synthesis in monocytes and macrophages [12]. Dendritic cells, which are professional antigen-presenting cells and key players in adaptive immunity, have developed a mild phagocytic pH environment to prevent complete degradation of peptides, thus allowing antigen presentation [14]. In these cells, NOX2 activity is much lower than in neutrophils, monocytes and macrophages, but regulates phagosomal proteolysis through pH alkalization. Indeed, dismutation of $O_2^{\cdot-}$ into H_2O_2 consumes protons present in the phagosome, thus preventing intraphagosomal acidification and lowering protease activity for a better antigen processing. Thus, the principal role of NOX2 in dendritic cells is to control antigen cross-presentation. In circulating T and B cells, the expression of NOX2 has not been well established; however, it is well known that EBV-transformed B lymphocytes express all NOX2 subunits and produce ROS [8]. It was also reported that T cells express NOX2, which acts as a regulator of signaling pathways and cytokine production in these cells [7]. However phagocytes-derived ROS can dampen T-cell-dependent inflammation through alteration of the T-cell membrane oxidation status and of Th17/Treg cell development [10].

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In conclusion, NOX2-derived ROS were first considered as destroying/killing agents in professional phagocytes, and this function is well established. However, more subtle functions of NOX2-derived ROS, either in neutrophils or other cells, are emerging. These effects are either due to NOX2 expressed by the cell or to a diffusible ROS such as hydrogen peroxide acting as a signaling agent. Further studies will be needed to better understand these novel functions in immunity.

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