NAD(P)H Oxidase in Non-Phagocytic Cells

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Introduction

The importance of reactive oxygen intermediates (ROI) is evident from the vast literature describing the involvement of free radicals in the pathogenesis of various disorders including neurological (Alzheimer's disease, Parkinson's disease), viral human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), and degenerative (atherosclerosis, cancer, cataract) diseases.

The generation of ROI is an activity normally associated with phagocytes. As part of the body's host defense system these cells are able, when stimulated by various agents including bacterial toxins, to generate large amounts of superoxide in the respiratory burst in order to kill invading microorganisms. Over the past ten years it has become increasingly apparent that non-phagocytic cells also share the capacity to generate oxygen radicals. Such activity has been detected in a wide variety of different cells including endothelial cells, vascular smooth muscle cells, mesangial cells, fibroblasts, oocytes, spermatozoa, Leydig cells, various tumor cells, thyroid cells, B-lymphocytes, adipocytes, platelets, chondrocytes and osteoblasts. Since the capacity to generate ROI is widespread, the risk-benefit relation for these potentially hazardous molecules becomes a matter of interest. Whereas the controlled generation of these highly reactive molecules may serve an important second messenger role in many different cell types, their uncontrolled production may contribute to the etiology of pathological conditions through the initiation and propagation of peroxidative damage. Therefore the identification of sources of ROI in non-phagocytic cells is of considerable interest.

Recently, evidence has accumulated that nicotinamide adenine dinucleotide (phosphate) [NAD(P)H] oxidases might also be present in non-phagocytic cells. However, the molecular identity and function of these systems are only beginning to be elucidated. This article will summarize current knowledge about the presence of NAD(P)H oxidases in non-phagocytic cells.

NADPH Oxidase in Phagocytes

NADPH oxidase is a highly regulated membrane-bound enzyme complex which was initially found in phagocytes. As the key enzyme for the respiratory burst, it catalyzes $O_2^-$ production according to the following reaction [1]:

\[ 2O_2 + \text{NADPH} \rightarrow 2O_2^- + \text{NADP}^+ + H^+ \] (1)

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Although $O_2^-$ is a free radical, it is unreactive towards many organic molecules and not an oxidant at neutral pH [2]. It is highly solute in water and is not expected to be transported through membranes or to penetrate into hydrophobic regions of cells and peroxide lipids. However, it readily, either spontaneously or catalyzed by superoxide dismutase (SOD), dismutes to hydrogen peroxide ($H_2O_2$), an oxidant, germicide and cytotoxic agent. This ROI is stable and carries no charge, allowing it to cross membranes and to travel freely to its targets. It readily participates in one-electron processes with metal ions such as the Fenton reaction, thereby generating highly reactive hydroxyl radicals. Other toxic weapons generated in phagocytes from $O_2^-$ include oxidized halogens and singlet oxygen [3].

In resting cells NADPH oxidase is dormant and the protein components are segregated into cytoplasmic and plasma membrane compartments [1]. The enzyme can be activated by receptor-dependent stimuli such as complement fragment C5α, the chemotactic tripeptide N-formyl-methionyl-leucyl-phenylalanine (fMLP) and immune complexes, for example via the G-protein activated phospholipase C pathway, finally stimulating protein kinase C and phospholipase D. Receptor-independent stimuli include long-chain unsaturated fatty acids and phorbol-myristate-acetate (PMA) [4, 5].

On stimulation, the cytosolic proteins p47, p67 and p40 form a complex and translocate to the plasma membrane, where they associate with a membrane-bound flavocytochrome composed of two subunits, p22 and gp91 (Fig. 1) [4]. The low molecular weight guanosine tri-phosphate (GTP)-binding protein, rac, changes from an inactive guanosine diphosphate (GDP)-bound to an active GTP-bound form and translocates separately to the plasma membrane, where it probably modulates the function of one or more NADPH oxidase proteins [6]. The role of additional factors such as p40, which also translocates to the membrane, and the membrane bound rap1A, known as tumor suppressor gene, in the activation process are not

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**Fig. 1.** Assembly of the NADPH oxidase components in phagocytes. Under resting conditions membrane-bound components are separated from cytosolic factors. On activation, the cytosolic components assemble and translocate to the membrane where they associate with cytochrome b558. Independently, rac also translocates to the membrane.