was detected in the cytosol preceding its detection in membranes [40]. Activation of the neutrophil oxidase system appeared to be dependent upon phosphorylation of the cytosolic 47 kDa protein [41], and incomplete phosphorylation was found to lead to failure of the subunit to translocate to the membrane for interaction with other membrane components of the oxidase. In intact neutrophils it was conclusively demonstrated that both p47phox and p67phox translocate to the membrane during activation of the respiratory burst [42]. This translocation was also normal in the variant X-linked form of CGD in which cytochrome-b_{558} is present but does not transfer electrons, demonstrating that the absence of translocation in other forms of CGD is not a secondary effect of the failure to generate $O2^{-\cdot}$ [43]. Ding and colleagues [44] were unable to detect any alterations in the protein kinases in CGD neutrophils that could explain these defects in phosphorylation of p47phox. The GTP-binding protein Rac2 was also found to migrate from the cytosol to the membrane cytoskeleton with p67phox and p47phox, indicating that Rac2 behaves like a dedicated component of the respiratory burst oxidase [45]. A schematic of NADPH oxidase activation is shown in Figure 1.

The primary biochemical defect in CGD that leads to impaired microbicidal activity was thought to be failure of phagocytes to generate sufficient quantities of reactive oxygen species (ROS), which are responsible for the so-called respiratory or oxidative burst. These compounds are derived from initial production of the extremely unstable and weakly bactericidal $O2^{-\cdot}$, which subsequently is dismutated into H_2O_2., In the presence of myloperoxidase which is delivered by primary granules into the phagosomes, H_2O_2 gives rise to more potent oxidants such as oxyhalides (most frequently hypochlorous acid), the hydroxyl radical ($OH^{-\cdot}$), or singlet oxygen ($O^{\cdot-}$) [46]. The high concentrations of ROS generated within the phagosome were thought to kill directly because of their oxidizing capacity.

The fact that phagocytes kill microbes through toxic oxygen radicals and their metabolites provided much of the biological basis for theories relating the toxicity of oxygen radicals to the pathogenesis of CGD. However, recent evidence [47] indicates that microbes might be killed by proteases, activated by the oxidase through the generation of a hypertonic, K^+-rich and alkaline environment in the

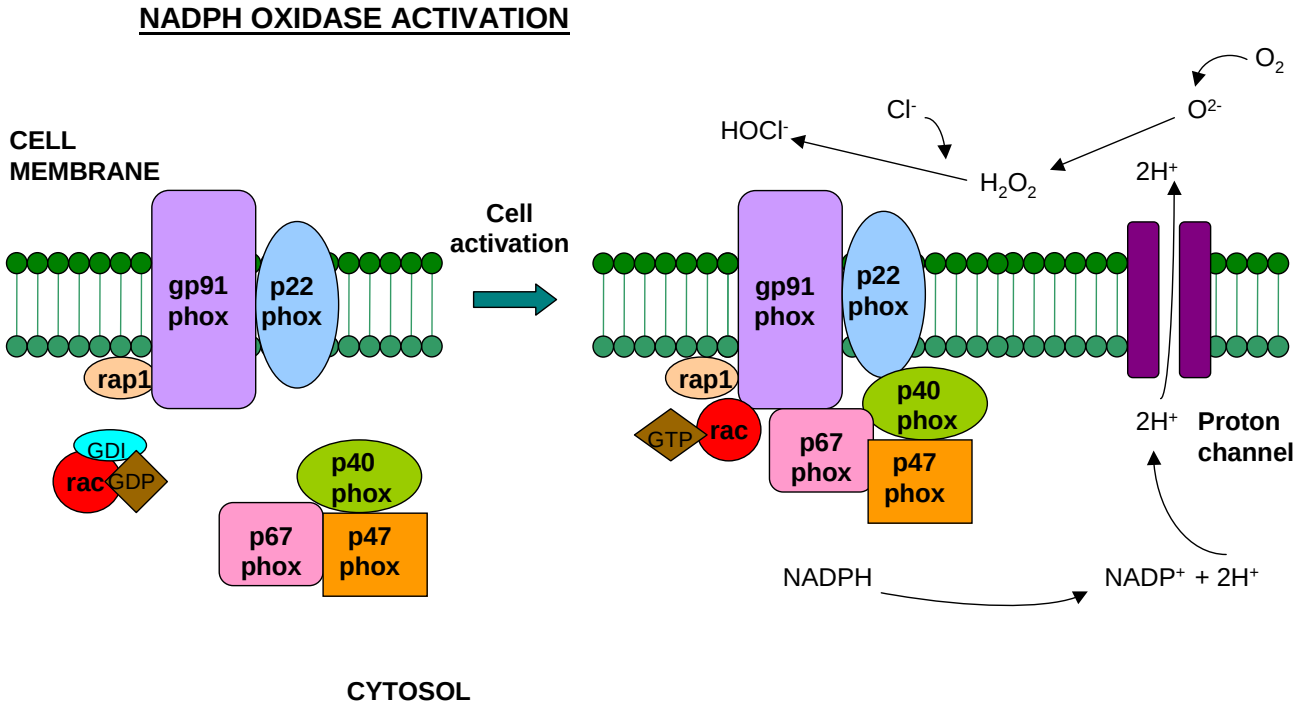

Figure 1

Schematic representation of the NADPH oxidase enzyme. The integral membrane of the phagocyte consists of two subunits: p22phox and gp91phox which respectively produce the smaller and larger chain of the cytochrome-b_{558}. Two cytosolic subunits: p67phox and p47phox; a p40phox accessory protein and a Rac-GTP binding protein then translocate to the cell membrane upon cell activation to form the NADPH oxidase complex which generates a respiratory burst. Superoxide can react to form hydrogen peroxide and hypochlorus acid, which together participate in bacterial killing.