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MINI-REVIEWS

Introduction: Respiratory Burst Oxidase and Its Regulation

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The role of oxidative metabolism in microbial killing by neutrophilic polymorphonuclear leukocytes (PMN) is now well-established. Following ingestion of microbes by phagocytosis, there is a massive increase in nonmitochondrial oxygen consumption, referred to as the "respiratory burst." Initially, oxygen is reduced to superoxide which is released into the phagocytic vesicle. The superoxide then reacts either enzymatically or nonenzymatically to generate secondary oxygen-derived products such as hydrogen peroxide, HOCl, and probably hydroxyl radical. Together these and other neutrophil products provide an inhospitable and, in most cases, lethal milieu for the ingested microbe. The importance of the respiratory burst to host defense is illustrated by the inherited condition chronic granulomatous disease, wherein the respiratory burst fails to occur, and the host suffers chronic and debilitating infections. At the other extreme, under some pathological conditions, surrounding host tissue is exposed to the neutrophil's noxious brew, resulting in the tissue damage associated with inflammatory diseases. The normal neutrophil must therefore strike a cautious balance between destruction of microbes versus preservation of host tissue.

Fundamental knowledge regarding the enzymatic machinery responsible for the respiratory burst and the mechanisms of its activation is central to the understanding of both normal and abnormal neutrophil physiology and associated pathological conditions. The key enzyme in initiating the oxidative metabolism is the "superoxide-generating respiratory burst oxidase" (or "NADPH-oxidiase"). These latter terms convey the misimpression that the oxidase is a plain and ordinary enzyme that can be readily plucked out of the cell and studied. However, just as in the 1960s and 70s there occurred a

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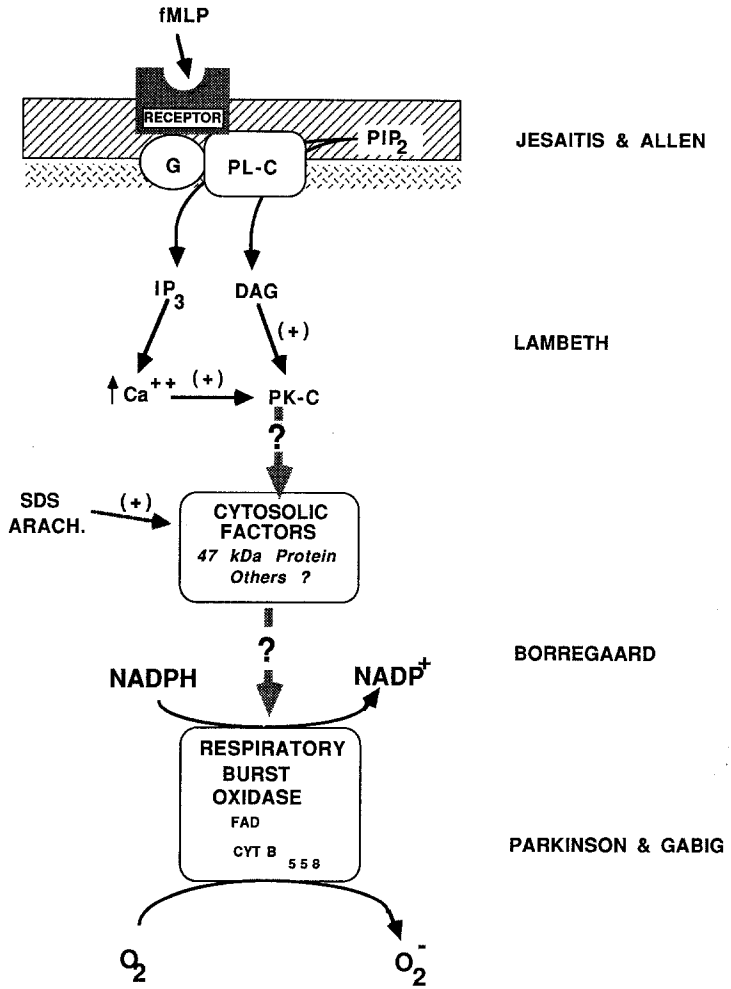

Fig. 1. Hypothetical sequence for activation of the respiratory burst by an extracellular stimulus. See text and subsequent reviews for explanation.

gradual appreciation of the enormous complexity of mitochondrial respiration, the 80s have seen the growing realization that the respiratory burst oxidase and its associated regulatory machinery is far more complicated than anyone ever expected. Although final answers are not yet in, a great deal has been learned within the last several years, and it seems an opportune time to summarize what has become an increasingly difficult and unmanageable literature.

The review series is organized (see Fig. 1) around a (hypothetical) progression which may occur from the time an extracellular signal (e.g., a

microbe, or a soluble inflammatory mediator) encounters the plasma membrane of a neutrophil to the time the respiratory burst is initiated. Jesaitis and Allen summarize current knowledge regarding the interaction of fMLP (a chemotactic peptide and important model compound for investigating the triggering of the respiratory burst) with its receptor, and subsequent receptor dynamics, including cytoskeletal interactions and possible structural organization of the neutrophil plasma membrane which may affect the function of both the receptor and the oxidase. Lambeth reviews data regarding triggering of cellular lipases by activating stimuli, in particular as may relate to the generation of key second messengers including those which activate protein kinase C; the evidence, pro and con, for the participation of protein kinase C is also scrutinized. A recently described cell-free system in which the oxidase is activated by anionic amphiphiles in the presence of "cytosolic factors" is alluded to in several reviews, and will be the topic of a future review article in this journal. One of the cytosolic components is phosphorylated upon activation of intact cells, and may provide a link with protein kinase C. Presumably, these cytosolic components participate in some way, either as activators or as components of the respiratory burst oxidase. One possibility is that the complete oxidase is assembled at the plasma membrane from components which were previously located elsewhere. Borregaard's article deals with the location and possible translocation of oxidase components upon activation. The final article by Parkinson and Gabig deals with the current state of knowledge regarding two of the coenzyme-containing protein components which are now thought to catalyze the electron transfer from NADPH to oxygen to generate superoxide: an FAD-containing protein and a heme-containing protein.

All the authors have done an extraordinary job in summarizing this complex and often contradictory area, and the reviews will undoubtedly serve as valuable resources for both the neophyte and the initiated. The fact that there remain some internal contradictions and unresolved controversies only serves to emphasize that there remains much to be done.