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Forum Editorial

Biomedical Aspects of Plasma Membrane Redox

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THIS FORUM is devoted to a topic that has, until recently, attracted so little attention among biochemists that many still think of it as involving just one enzyme. The NADPH oxidase that mediates the respiratory burst of activated neutrophils was discovered in 1933 and has been characterized in great detail; its synthesis of superoxide in the phagocytic vacuole, using electrons transferred from cytosolic NADPH, is the paradigm of a plasma membrane (PM) redox activity with biomedical significance. Indeed, the study of the respiratory burst was enormously aided by the existence of chronic granulomatous disease, which is an inherited syndrome caused by defects in the oxidase system.

The neutrophil oxidase is not the only biomedically relevant PM redox activity, however. Trans-PM electron transport has been identified in every cell type investigated, and in many cases the electron flux that this activity can support is comparable to that of the respiratory burst. The electron donor for this activity is sometimes obligatorily NADH, sometimes obligatorily NADPH, and sometimes either. Additionally, surface oxidase activity (that is, redox activity bound to the cell surface but for which the electron donor, as well as the acceptor, is extracellular) has been identified on many cell types. It is these non-neutrophil systems that are the major topic of this forum.

These activities were identified many years ago. Why, then, are they so little known? The primary reason, in my view, is that unlike the NADPH oxidase of neutrophils they have not been unambiguously linked to any specific disease. In fact, the situation is much more extreme than that: it is no exaggeration to state that we are still uncertain what these multifarious and ubiquitous systems are for. This has not only hindered the spread of knowledge about these systems: it has also, inevitably, hindered progress in characterizing them at the molecular level. The electron acceptors (and, in the case of surface oxidases, the electron donors) used to examine these enzymes *in vitro* are mostly not present in the extracellular environment *in vivo*; they are used in spite of this, largely because the physiological substrates are as yet unknown.

The reader may at this point be wondering how I can describe the forum as focusing on the biomedical aspects of PM redox, if no medical condition is actually established to be caused by dysfunction of the enzymes that the following articles discuss. The answer is this: the emerging consensus regarding the role of these enzymes is that they are critical elements of systemic homeostasis, with the result that defects in them may have very pleiotropic consequences that are not obviously linked to any specific phenotype. My own interest in PM redox, which will not be featured in this forum, concerns the part it may play in that most pleiotropic of pathologies, aging. I have proposed that cells that have lost the ability to respire aerobically, due to accumulation of mitochondrial DNA mutations, may toxify the ex-

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tracellular medium by dysregulation of their PM redox systems.

The 11 contributions that follow are divided almost equally between reviews and original research articles, with six of the former. The review by Smith deserves special mention, because it concerns a topic not always thought of as part of the PM redox field, namely the transport of heme to tissues by hemopexin. This is a process with similarities to the more widely studied transferrin-mediated transport of iron; both involve transmembrane electron transport as necessary precursors of uptake. What is more surprising is that the uptake of heme is intimately linked to redox cycling of copper at the cell surface.

All five other reviews discuss aspects of the redox activities that form the mainstream of mammalian PM redox biology. Chueh surveys the role that PM electron transport plays in cancer, which may in due course prove to make it a highly effective target for chemotherapy. Goldenberg *et al.* discuss the interactions between trans-PM electron transport and ascorbate recycling: the well-known instability of the oxidized form, dehydroascorbate, and the consequent value of reducing it as rapidly as possible whenever it becomes oxidized, makes this a major candidate for the principal physiological role of PM electron transport. Baker and Lawen provide a wide-ranging analysis of its possible functions, including ascorbate stabilization; they also summarize the relatively recent evidence that PM redox activity may be involved in apoptosis. This topic is addressed in detail in the review by Villalba and Navas, who describe the possible role of reduced coenzyme Q in preventing the activation of PM sphingomyelinase that leads to induction of apoptosis; like extracellular ascorbate, PM coenzyme Q is maintained in the reduced state with the help of electrons from NAD(P)H in the cytosol. The remaining review, by Berridge and Tan, brings surface oxidases into the discussion, presenting reasons for doubting that they are identical to, or even components of, the trans-PM electron transport system.

The five research articles are similarly varied in their topics. May and Qu report that a drug already well known for its antidiabetic effects appears also to be a potent antioxidant in blood, specifically protecting erythrocytes (to which it binds). Arroyo *et al.* highlight the remarkable versatility of the trans-PM electron transport system, demonstrating that it incorporates NADH−, NADPH−, and NAD(P)H-dependent components at the cytosolic face, all of which can reduce PM coenzyme Q, and whose levels are adjusted in accordance with availability of the two donors. Fernandez-Ayala *et al.* return to the involvement of PM redox activity in apoptosis, presenting data in support of the antiapoptotic role of reduced PM coenzyme Q. Berridge and Tan show that the surface oxidase activity of many different cells types can be assayed with a tetrazolium salt, and that the enzyme responsible for this activity is shed into the culture medium; however, they also present evidence that it is not the terminal component of the trans-PM electron transport chain. They thereby distinguish it from another shed PM redox enzyme that is the main topic of the remaining article. Peter *et al.* discuss a surface oxidase which they have argued to be such a terminal component, and in this article they focus on one of its most remarkable properties—its periodicity.

This collection of articles provides both a detailed background and a wide variety of new results in a field with which many readers will be unfamiliar. I hope and expect that they will provide illumination of this unduly neglected topic; perhaps they will also make a few converts to it.

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