Study of the mechanism of reactions catalyzed by complexes of cytochrome c with cardiolipin

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When studying objects of the living world, we often encounter phenomena that are well described by algorithms from the category of nanomachines. Models of this class have existed for more than 50 years and effectively help mankind in understanding many phenomena and solving practical problems. Thus, in many cases, simplified models of nanomachines allow a fairly good understanding of complex multi-component biological processes. For instance, the complex of cytochrome C with the phospholipid cardiolipin, interpreted as a nanomachine, quite well describes one of the key nodes in triggering apoptosis – interaction of cytochrome C with the inner membrane of mitochondria, activating its peroxidase activity and further release into the cytoplasm.

Cytochrome C is a heme-containing protein that promotes electron transfer between mitochondrial respiratory complexes 3 and 4, and participates in triggering apoptosis. As shown [1], cytochrome C forms a complex with the membrane phospholipid cardiolipin, which activates its peroxidase activity and initiates lipid peroxidation in the mitochondrial membranes. This breaks the membrane barrier properties, releasing cytochrome C into the cytoplasm, where it binds to the protein Apaf-1, forming apoptosomes and triggering apoptosis. The general scheme of its peroxidase action is presented in Fig. 1.

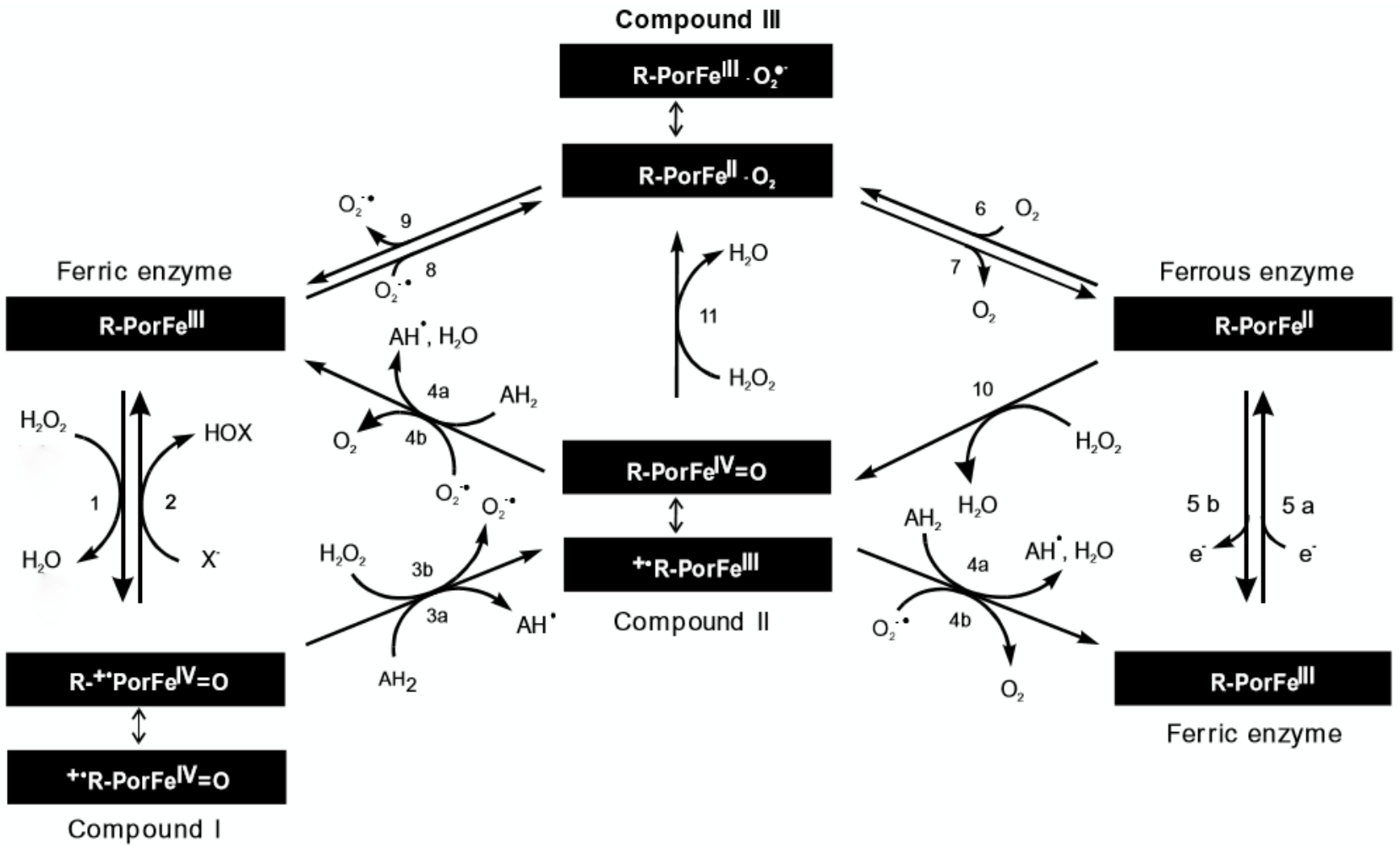

Fig. 1. General Reaction Scheme of Mammalian Peroxidases

Regarded as a nanomachine, the Cytochrome C / cardiolipin complex is especially valuable as a trigger, switching between normal cell functioning and apoptosis depending on its peroxidase activity. Generally speaking, the latter should be measured by the rate of free radical generation, but due to their extremely high reactivity, it cannot be done directly. Thus, it is estimated by the intensity of oxychemiluminescence, accompanying further reactions of the generated free radicals, and has to be done in dynamics – which demands the use of the so-called kinetic chemiluminescence .

Having the above experimental data available, in this work, we describe the mathematical model, creating an automated solution to the direct and inverse problems to study the mechanism of cytochrome C participation in apoptosis.

Importantly, in this work we consider only the control process, which is carried out by changing the protein/lipid structural ratio and membrane viscosity.

The reaction rates were expressed as the product of the concentration of the reactants and the corresponding rate constant (see Fig. 1). The rate constants were selected manually. The initially formed system of differential equations for reaction rates was solved by the Euler method.

Further, specific optimization was proposed for solving the inverse problem. Several algorithms, each of which could serve as the basis for optimizing the selection process both for the rate constants and for the concentrations of the given substances, were progressively compared with the experiment, with the best one finally selected.

A program for the automatic determination of the rate constants of chemical reactions was created and debugged, corresponding to the formulation of the inverse problem.
Unsatisfactory solutions were screened, and the best model selected.
The rate constants of the reactions proceeding in the system for measuring the activity of the luminescence intensity were determined.