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Short Communication

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Compartmentalization of Mitochondrial Processes

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Abstract

Compartmentalization is the division of eukaryotic cells into compartments (compartments), covered with a membrane of lipid bilayer, in which certain biochemical processes are localized. Most organelles in a eukaryotic cell are compartments - mitochondria, chloroplasts, peroxisomes, lysosomes, endoplasmic reticulum, cell nucleus and Golgi apparatus. Within a number of compartments (including mitochondria), there are also subcompartments that differ in form and function. Inside compartments surrounded by a lipid bilayer, different pH values can exist and different enzymatic systems can function. The principle of compartmentalization allows a cell to perform different metabolic processes simultaneously. The mitochondrial matrix is a compartment bounded by the inner mitochondrial membrane. The word "matrix" comes from the fact that this environment is much more viscous compared to the more watery cytoplasm.

Keywords: Regulation, Mitochondrial Respiration, Compartmentalization

Very often, when describing metabolic cycles, we present them purely schematically, that is, we limit ourselves to only listing the precursors, intermediate products and final products of metabolism. Meanwhile, we now know well that multienzyme systems have the ability to self-regulate, which is the result of a specific organization of the sequence of reactions, specific properties of individual enzymes of the system, feedback mechanisms and compartmentalization [1].

Compartmentalization is the division of eukaryotic cells into compartments (compartments), covered with a membrane of lipid bilayer, in which certain biochemical processes are localized. Most organelles in a eukaryotic cell are compartments - mitochondria, chloroplasts, peroxisomes, lysosomes, endoplasmic reticulum, cell nucleus and Golgi apparatus. Within a number of compartments (including mitochondria), there are also subcompartments that differ in form and function. Inside compartments surrounded by a lipid bilayer, different pH values can exist and different enzymatic systems can function. The principle of compartmentalization allows a cell to perform different metabolic processes simultaneously. The mitochondrial matrix is a compartment bounded by the inner mitochondrial membrane. The word "matrix" comes from the fact that this environment is much more viscous compared to the more watery cytoplasm. The matrix contains many substances, including enzymes, mitochondrial DNA (circular), ribosomes, small organic molecules, nucleotide coenzymes and inorganic ions. Matrix enzymes facilitate the reactions of biochemical processes that synthesize ATP, such as the tricarboxylic acid cycle, oxidative phosphorylation, pyruvate oxidation, and fatty acid beta-oxidation. The composition and structure of the matrix environment contribute to the optimal occurrence of reactions of the anabolic and catabolic pathways. The electron transport chain and enzymes in the matrix play a large role in the tricarboxylic acid cycle and oxidative phosphorylation. In the tricarboxylic acid cycle, electrons are transferred to NADH and FADH2 molecules, which are subsequently transferred to the respiratory chain, where ATP is formed during oxidative phosphorylation reactions [1-3].

It is known that the inner membrane of mitochondria is impermeable to many specific substrates, intermediates, electron donors and acceptors. Therefore, on the one hand, these barriers may separate some extramitochondrial substrates from mitochondrial enzymes capable of oxidizing or reducing these substrates; on the other hand, they prevent the “leakage” of necessary cofactors and intermediate products from the intramitochondrial space [1,4].

The most illustrative example of specific impermeability is the impermeability of the mitochondrial membrane to pyridine nucleotides. In 1951, Lehninger discovered that isolated rat liver

mitochondria do not oxidize external, or added, NADH2, but have the ability to actively oxidize internal NADH2, which is formed during the reduction of intramitochondrial NAD by enzymes such as beta-hydroxybutyrate and malate dehydrogenase. It is now generally accepted that impermeability to extramitochondrial NAD is a property of almost all mitochondria. As will be shown below, it is this property that underlies important mechanisms for the regulation and integration of the relationship between mitochondria and the extramitochondrial cytoplasm. However, if isolated rat liver mitochondria are first exposed to a hypotonic environment, which increases the permeability of the mitochondrial membrane, then they acquire the ability to actively oxidize exogenous NADH2 [4,5].

Intact mitochondria are impermeable not only to NADH2 and NAD, but also to oxidized forms of these coenzymes, at least under some conditions. This conclusion is confirmed not only by direct experiments with labeled pyridine nucleotides, but also by the data that some mitochondrial dehydrogenases associated with pyridine nucleotides are inaccessible to external nucleotides. For example, the reduction of exogenous NAD by exogenous substrates in the presence of intact mitochondria containing large amounts of substrate-specific dehydrogenases (beta-hydroxybutyrate, malate, and glutamate dehydrogenases) can be very slow compared to substrate oxidation by the respiratory chain involving endogenous NAD. If mitochondria are placed in a hypotonic environment, the rate of recovery of exogenous NAD increases sharply [5].

Some NAD-related dehydrogenases, such as glutamate dehydrogenase, are present in the mitochondrial matrix in a relatively soluble form; the mild effect of a hypotonic environment on mitochondria completely unmasks the activity of such enzymes; alpha-hydroxybutyrate dehydrogenase, on the contrary, is more deeply "hidden" in mitochondria; therefore, more vigorous processing of mitochondria is required for the full activity of this enzyme in relation to exogenous NAD [1,2].

Agents that cause mitochondrial swelling, such as phosphate, thyroxine and Ca++, increase the permeability of the mitochondrial membrane and cause the "leakage" of intramitochondrial pyridine nucleotides into the environment. Kaufman and Kaplan showed that only in the oxidized form NAD easily leaves the mitochondria, while the reduced form remains fixed on the mitochondrial structures. After the "leakage" of pyridine nucleotides, mitochondria regain the ability to bind them in the presence of ATP; the mechanism of this process remains completely unclear [2,5,6].

The mitochondrial membrane is also relatively impermeable to Krebs cycle substrates. For example, Peters and co-workers observed that in isolated kidney mitochondria, citrate generated from common precursors in Krebs cycle reactions was oxidized faster than added exogenous citrate. Indeed, isolated mitochondria have been shown to contain very high concentrations of citrate [5-7].

Probably the most convincing evidence of the relative impermeability of the mitochondrial membrane to Krebs cycle substrates was obtained in the experiments of Van den Bergh and Slater on the flight muscle of the housefly (this tissue is known to have a high rate of respiration). The mitochondria of this muscle very intensively oxidize pyruvate + malate (probably in the Krebs cycle), and this process is characterized by effective phosphorylation and a high coefficient of respiratory control. However, intermediate products of the Krebs cycle, such as succinate, α-ketoglutarate and isocitrate, are very weakly oxidized by intact flight muscle mitochondria when added to the incubation medium instead of pyruvate and malate. Ultrasound treatment of flight muscle mitochondria leads to a sharp increase in the intensity of oxidation of these substrates, apparently due to an increase in membrane permeability. Since the mitochondria of this tissue are characterized by perhaps the highest intensity of oxygen absorption of all mitochondrial preparations studied so far, it is obvious that the maintenance of a high intramitochondrial concentration of intermediate products of the Krebs cycle due to the impermeability of the membrane can be considered a manifestation of their functional adaptation [6,7].

Mitochondria are also relatively impermeable to adenine nucleotides and phosphate. As is known, the rate of "renewal" of the terminal phosphate of endogenous ATP differs sharply from the rate of renewal of exogenous ATP. Sikiewitz and Potter proposed that internal ATP does not leave the mitochondria, but transfers its terminal phosphate group to external ADP with the participation of membrane-bound phosphate transporters, probably phosphotransferases such as adenylate kinase. It is this "compartmentalization" of ATP within the mitochondrion that Chance and Hess refer to when interpreting some of the problems associated with the integration of glycolysis and respiration [5–7].

There is now increasing evidence that intramitochondrial substances (for example, intramitochondrial NAD) are in turn also divided into two (or more) "funds". Chappel's suggestion of such "funds" was mentioned above. It confirms old data about the existence of isolated NAD "pools" available for reduction with succinate or O-p-hydroxybutyrate. Structural isolation of mitochondrial substrates or NAD can be provided not only by an impermeable membrane (so to speak, at the macro level), but also due to the connection with the active site of specific mitochondrial enzymes, for example alpha-hydroxybutyrate dehydrogenase [8].

A striking example of the interaction of different compartments (mitochondrion and cytoplasm is the presence of "shuttle mechanisms." Thus, in the extramitochondrial cytoplasm, NAD is constantly restored by extramitochondrial dehydrogenases, for example, glyceraldehyde-3-phosphate dehydrogenase in the glycolytic cycle. Although the mitochondrial membrane is impermeable to NADH2 itself, electrons from external NADH2 can react with the respiratory chain of mitochondria due to the existence of the so-called "shuttle systems." The most well-studied shuttle system is the α-glycerophosphate-dihydroxyacetone phosphate system, which was first described in the laboratories of Bucher

and Sacktor. The extramitochondrial cytoplasm of many cells, for example, the flight muscle of insects, contains a large amount of the amount of soluble a-glycerophosphate dehydrogenase associated with NAD. In the presence of dioxyacetone phosphate, this enzyme catalyzes the reoxidation of NADH2 formed at the oxidative stage of the glycolytic cycle. The equilibrium of the second reaction is sharply shifted to the right due to the relatively positive redox potential of the a-glycerophosphate - dioxyacetone phosphate system. The reducing equivalents of external NAD-H2 are thus converted into reducing equivalents of the reaction product α-glycerophosphate. As it turned out, mitochondria also contain α-glycerophosphate dehydrogenase, which, unlike the extramitochondrial enzyme, is not associated with NAD, but probably with flavin and interacts directly with cytochrome b of the respiratory chain [3,8].

External α-glycerophosphate, unlike NADH2, freely penetrates mitochondria and is quickly oxidized; the dihydroxyacetone phosphate formed in this case leaves the mitochondria and acquires the ability to accept electrons from the next molecule of extramitochondrial NAD H2. When electrons are transferred from intramitochondrial α-glycerophosphate dehydrogenase to oxygen, two phosphorylation reactions occur. Thus, the α-glycerophosphate–dihydroxyacetone phosphate system acts as a shuttle during the oxidation of exogenous NADH2 by the mitochondrial respiratory chain associated with energy accumulation [3].

The main function of mitochondria is the synthesis of ATP, the universal form of chemical energy in any living cell. As in prokaryotes, this molecule can be formed in two ways: as a result of substrate phosphorylation in the liquid phase (for example, during glycolysis) or in the process of membrane phosphorylation associated with the use of energy from a transmembrane electrochemical gradient of protons (hydrogen ions). At the same time, the uniqueness of mitochondria as energy-producing organelles of a eukaryotic cell is determined by the second pathway of ATP generation, called "chemiosmotic coupling." Essentially, this is a sequential conversion of the chemical energy of reducing equivalents of NADH into an electrochemical proton gradient ΔμH+ on both sides of the inner mitochondrial membrane, which activates the membrane-bound ATP synthase and ends with the formation of a high-energy bond in the ATP molecule [5,9].

In general, the entire process of energy production in mitochondria, due to the compartmentalization of processes, can be divided into four main stages, the first two of which occur in the matrix, and the last two on the mitochondrial cristae:

1. Conversion of pyruvate and fatty acids received from the cytoplasm into the mitochondria into acetyl-CoA;
2. Oxidation of acetyl-CoA in the Krebs cycle, leading to the formation of NADH and two CO2 molecules;
3. Transfer of electrons from NADH to oxygen through the respiratory chain with the formation of H2O;
4. Resynthesis of ATP as a result of the activity of the membrane ATP synthase complex.

While still in the cytoplasm, in a series of 10 separate enzymatic reactions of glycolysis, a six-carbon molecule of glucose is partially oxidized to two three-carbon molecules of pyruvate to form two molecules of ATP. Pyruvate is then transported from the cytosol through the outer and inner membranes into the matrix, where it is initially decarboxylated and converted to acetyl-CoA. This process is catalyzed by a large pyruvate dehydrogenase complex, comparable in size to a ribosome, and consisting of three enzymes, five coenzymes and two regulatory proteins. Similarly, fatty acids obtained from the breakdown of insoluble triglycerides in the cytoplasm are transferred to the mitochondrial matrix in the form of acyl-CoA derivatives and undergo beta-oxidation to form acetyl-CoA, a substrate of the Krebs cycle [10].

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