ATP-Synthasis

INTERESTING ARTICLE. CONCLUSION A BIT WEAK.

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ATP- Synthesis

1. Introduction

The nucleoside triphosphate Adenosine- triphosphate (ATP) has a main role in the energy pathway in cells. ATP synthesis is a basic requirement in living cells. ATP can be produced by substrate-level phosphorylation (6.1. table) or by a much higher energy process, called oxidative phosphorylation. It involves four complexes utilized as proton pumps (6.2. table). The required electrons are obtained by delivery via electron donors (NADH, FADH2). The energy of the electron transfer is stored in the proton-gradient. The resulting proton motive force leads to the ATP-synthesis catalysed by the complex F_0F_1-ATP synthase (6.3. graphic)

2. Medical aspects

Defects of ATP synthase, disorders of ATP synthesis and ATP depletion are important in genetic research. It is recognized as a frequent cause of human disease.[1] The current inadequacy of treatment in patients with mitochondrial disorders highlights the need to develop strategies to heal it.

3. Reduced ATP synthesis – disorders

Defects in the enzyme ATP synthase – as a key component in mitochondrial energy conversation - cause mitochondrial diseases. Deficiency can be described, as primary (mutations) or secondary (increased production of free oxygen radicals, decreased intermediary metabolism, metabolic acidosis). The subunits of F_0F_1- ATPase are encoded by the nuclear and mitochondrial genome. Disorders can have their origin here, or in the levels of transcription, translation and folding of the enzyme. Two mitochondrially encoded subunits of F_0F_1- ATPase (∝, A6L) mutations and one nuclear mutation (ATP12) has been identified.[2] Clinical manifestation is neuropathy, ataxie and rethinis prigmentosa (NRAP syndrome) etc. Several point mutations in the ATP6 gene can be distinguished. For example a mutation at position nt8993 results in a replacement of leucine by arginine and leads to heteroplasmy and NRAP syndrome. ATP6 mutations can cause disturbance of the intraenzyme coupling of protons.[3] A secondary deficiency is reactive oxygen species. They lead to an unproductive electron transfer between complex I and III (table 2) and decrease the respiratory chain. This includes processes, which lead to a reduced content of ATP.[4] Those patients show an uniform phenotype with hypertrophic cardiomyopathy, and elevated levels of acid in urine. Aging of post- mitotic tissue is associated with a continuous decrease of mitochondrial capacity to produce ATP. This, and enhanced oxidative stress triggers senescent disfunction of lived post – mitotic cells, as e.g. neurons and cardiac myocytes.[5]

4. Therapeutic approaches to ATP synthase deficiencies.

Therapeutic approaches are limited. Difficulties arise because of multiple mtDNA copies per cell, heteroplasmy and complexity of manipulating the mitochondrial genome in living cells. One treatment is the allotropic expression of mtDNA- encoded polypeptides. A protein is therefore synthesized in the cytosol from an alternative nuclear vision and fused to a mitochondrial targeting sequence (MTS). Replication of mutant mtDNA (heteroplasmy) can be inhibited through a sequence- specific binding of peptid nucleic acids (PNAs) using a zinc finger metylase. This allows a sequence- specific modification of mtDNA.[6] Low- level laser therapy (LLLT) or photobiomodulation can be used in physical medicine to increase the ATP amount, if the reduced ATP is not caused by mutations. Low- power laser light (λ = 632- 1064nm) induces a photochemical reaction in complex IV of oxidative phosphorylation chain.[7]

5. Conclusion

Efficient therapy is missing. Genetic research has a big impact on medical treatment.

6. Annex

6.1. Table. ATP synthesis – other reactions[8]

Process	Direct Product	Final ATP
Glycolysis	2 NADH (cytosolic) 1 ATP	3 or 5* 2
Pyruvate oxidation (2 per glucose)	2 NADH (mitochondrial matrix)	5
Acetyl- Co A oxidation in citric acid cycle (2 per glucose)	6 NADH (mitochondrial matrix) 2 FADH2 2 ATP or 2 GTP	15 3 2
Total yield per glucose		30 or 32

6.2. Table. Complexes of oxidative phosphorylation[9]

H_N: matrix side H_P: membrane interspace e^-: electrons
1. NADH – ubiquinone oxidoreductase a) exergonic transfer: H_N hydrid- ion (from NADH), proton → H_P - Ubichinone b) endergonic transfer: H_N (4 protons) → H_P $NADH + 5H_N^+ + Q \rightarrow NAD + QH_2 + 4H_P^+$ c) function: proton – pump
2. Succinate to ubichinone a) e^- transfer: Succinate → FAD b) e^- transfer: trough 3 Fe- S centres to ubichinone
3. Ubichinone to cytochrome c a) e- transfer: ubichinol (QH_2) → cytochrome c b) transport: H_N 4 protons → H_P $QH_2 + 2\ Ctyc_1\ (oxidized) + 2H_N^+ \rightarrow Q + 2\ Ctyc_1\ (reduced) + 4H_P^+$ c) function: proton- pump
4. Cytochrome c to O_2 a) e^- transfer: cytochrome → O_2 b) reduction: O_2 $O_2 + 4\ Ctyc_1\ (reduced) + 8\ H_N^+ \rightarrow 2H_2O + 4\ Ctc_1\ (oxidized) + 4\ H_P^+$
Proton motive force $ADP + P_i + nH_P^+ \rightarrow ATP + H_2O + nH_n^+$

6.3. Graphic ATP- Synthase[10]

Links

- Adenosine triphosphate
- Respiratory chain and oxidative phosphorylation

7. References

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8 Nelson, Cox, Lehninger Biochemie, Springer Berlin- Heidelberg, 4th edition, Heidelberg 2011, p. 968.

9 Nelson, Cox, Lehninger Biochemie, Springer Berlin- Heidelberg, 4th edition, Heidelberg 2011, p. 944-64.

10 https://classconnection.s3.amazonaws.com/713/flashcards/971713/jpg/atp_synthase-145F4DA86DD36E066F9_jpg, (30/11/2015).