

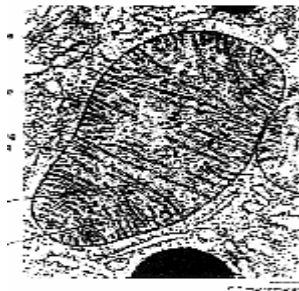
METABOLISM OF BARTH SYNDROME

Metabolism is the sum of all chemical processes that take place in our body. Some of these processes deal with the need of the body for energy to drive its vital needs. This can be understood as a way in which cells burn food to produce energy in a smart way without actually raising the temperature of the body. This is similar to a car's engine burning gasoline to produce the energy or torque that turns the drive train that spins the car's wheels (the energy we need to move and think). The major building blocks are carbohydrates, amino acids, and fats (lipids). Every step of metabolism can be defined as converting substance A into substance B. Every conversion step requires a specific protein, called an enzyme, to make the reaction happen in a precise way and without the need for elevating body temperature.

Enzymes are proteins with a specific purpose to promote particular chemical processes in the body, such as needed for growth, energy etc. Other proteins are part of the structure of our body comparable to building blocks. All proteins made by our body are made of amino-acids. These are the building blocks of the proteins. All proteins are made from such amino-acids. The order in which these amino-acids are arranged in the protein determines their function. This order is "encoded" by genes, which contain the blueprint for each protein. Mutations in a gene can cause a disturbed order of amino-acids in the protein, and the result is a malformed or inactive protein. Some mutations totally eliminate the protein. The degree of the mutation determines the degree to which the protein is functional (mild abnormality), or loses all of its function. In the case of Barth syndrome the mutated gene is the *Tafazzin* or *TAZ* gene. The protein is tafazzin or TAZ protein. We believe that the task of tafazzin is to modify cardiolipin which is a complete phospholipid, or fat, that is essential for normal energy production. Summarizing: a gene named *TAZ* encodes a protein called tafazzin that probably functions as an enzyme to help make mature cardiolipin.

Cardiolipin is made first with one kind of fatty acids attached to it which are mostly saturated, then the original fatty acids are removed and other fatty acids are attached, which are mostly unsaturated. For cardiolipin to work properly, it must have unsaturated fatty acids attached. The *TAZ* gene encodes a protein with an amino acid sequence called acyltransferases. Acyl- means fatty acid or fat. Transferase does mean to transfer this fatty acid from one thing or molecule to another. Acyltransferases are enzymes that remodel phospholipids. In Barth syndrome, cells cannot add the unsaturated fatty acids to the premature form of cardiolipin. Therefore, in Barth syndrome, the level of cardiolipin is reduced, and monolysocardiolipin (an intermediary product) accumulates. We believe that tafazzin is the enzyme involved in converting the premature cardiolipin to the mature form does not work properly. It should be understood that tafazzin is the name of the protein while acyltransferase means the function of the enzyme. As far as we know at this moment tafazzin is an acyltransferase. Acyltransferase literally means: an enzyme that transfers lipid tails (acyl groups). There are many different acyltransferases in our body, but only the acyltransferase involved in the synthesis of cardiolipin concerns us here. It is identical with tafazzin.

Cardiolipin is found only in particular regions of all living cells called mitochondria. Mitochondria are closed compartments, which are well insulated or separated from the rest of the cell by having an outer and an inner membrane. Their basic function is to produce energy in a form that can be carried to other parts of the cell to drive all kinds of enzymatic reactions. The energy produced by the mitochondria is stored in the form of a chemical called adenosine triphosphate, or ATP. When the breakdown products of the food that we eat enter the mitochondria for processing, they're passed along a well-orchestrated assembly line made up of hundreds of proteins, each with a specific role to play in the energy production process. Raw materials enter the beginning of the assembly line, and ATP energy molecules come out the other side. As a result, mitochondria are essential to the proper functioning of muscle cells, including those of heart and skeletal muscle. Mitochondria consist of a smooth outer membrane and a twisted inner membrane that is arranged in multiple folds. Many individuals with Barth syndrome have structural abnormalities of mitochondria, including mitochondria with unusually shaped inner membranes that contain collections of abnormally stored materials.



Electron microscopic photograph of a normal mitochondrion. Note the parallel array of so called "cristae" where energy producing complexes are attached.



Electron microscopic photograph of mitochondria in the heart of a child with Barth syndrome. Notice the abnormal course of cristae.

Metabolic Fact Sheet

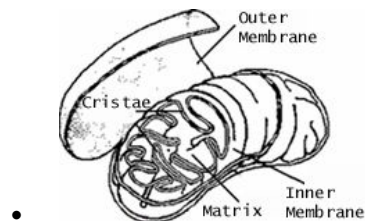
The Barth Syndrome Foundation www.barthsyndrome.org

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Glossary of Terms

- **Acidosis:** Elevated amounts of organic acids in the blood, which accumulate when food is not properly metabolized.
- **ADP:** Adenosine diphosphate; the low energy product produced when ATP releases energy to the cell.
- **ATP:** Adenosine triphosphate; cellular energy is stored in the third phosphate bond. ATP is formed from ADP and phosphate in the process known as oxidative phosphorylation.
- **Beta-oxidation:** A series of metabolic reactions necessary for burning fatty acids (fats).
- **Carbohydrates:** An organic compound derived from carbon, hydrogen, and oxygen that is an important source of food and energy for humans and animals. Sugar, starch, and cellulose are carbohydrates
- **Cardiolipin:** An important component of the mitochondrial membrane typically present in metabolically active cells of the heart and skeletal muscle. It has also been observed in certain bacterial membranes. It serves as an insulator and stabilizes the activity of protein complexes important to the electron transport chain.
- **Carnitine** (beta-hydroxy-gamma-N-trimethylamino-butyrate): Responsible for the transport of long chain fatty acids into mitochondria. Carnitine is made from muscle protein
- **Complex I:** NADH-Coenzyme Q oxidoreductase (part of the Electron Transport Chain).
- **Complex II:** Succinate dehydrogenase (part of the Electron Transport Chain).
- **Complex III:** Coenzyme Q-cytochrome c oxidoreductase (part of the Electron Transport Chain).
- **Complex IV:** Cytochrome c oxidase (COX) (part of the Electron Transport Chain).
- **Complex X V:** ATP synthase (part of the Electron Transport Chain).
- **Creatine:** Allows the muscle to use ATP.
- **Enzyme:** A protein that speeds up a chemical reaction or causes a chemical change in another substance. Enzymes do their work without being changed or used up in the process.
- **Lactate or Lactic Acid:** A chemical that is formed when sugars are broken down for energy without the presence of adequate oxygen. Lactic acid cannot be used by the body and will accumulate in blood and urine. Lactic acid causes the muscle pain when one runs too fast for too long. In people with mitochondrial disorders, lactic acid forms when the oxidative capacity (ability to burn foods using oxidative phosphorylation) of the person is impaired.
- **Lipids:** Any of a group of organic compounds consisting of fats, oils, and related substances that, along with proteins and carbohydrates, are the structural components of living cells.
- **Mitochondria:** A part of the cell (organelle) that is responsible for energy production. The organelle consists of two sets of membranes, a smooth continuous outer coat and an inner membrane arranged in tubules or in folds that form plate-like double membranes (cristae); the principal energy source of the cell, containing the cytochrome enzymes of terminal electron transport and the enzymes of the citric acid cycle, fatty acid oxidation, and oxidative phosphorylation. Responsible for converting nutrients into energy as well as many other specialized tasks.



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