J Bioenerg Biomembr (2009) 41:95–98
DOI 10.1007/s10863-009-9219-5

Mitochondrial matters of the heart: a plethora of regulatory modes to maintain function for a long lifetime

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Published online: 10 June 2009

Abstract The human/animal heart, comprised of cells called "myocytes" is an incredible organ that to remain beating must be fueled constantly via the hydrolysis of adenosine tri-phosphate (ATP). Deriving most of its ATP from mitochondrial oxidative phosphorylation (ox phos), and a smaller amount from "glycolysis", i.e., glucose conversion to pyruvate or lactate, the heart helps in the delivery of oxygen (via hemoglobin) to every organ/tissue in our body. Then, the empty (deoxy) hemoglobin returns to load more oxygen and the journey to tissues is repeated 24 h a day, year after year, until "death do us part". To support this essential "pumping" process the heart must work constantly, i.e., 70–80 years (life expectancy in the U. S.). This is a remarkable feat when compared with one of our most costly people-made technologies, i.e., automobiles (cars). In the past century, it was rare to see the family car survive more than 10–15 years unless it had been subjected to motor replacement surgery. Most were laid to rest at a much earlier age. Now, in this new millennium should a brilliant car manufacturer succeed in constructing a car engine as efficient as the human heart, each family member requiring a car would need only one per life time. With this in mind, one of the major future "matters of the heart" is to keep it pumping, not only for the current 70–80 year life span but much longer. To do this depends on, among other matters, the two processes noted above, i.e., oxidative phosphorylation and glycolysis. The former is strictly a mitochondrial process that works only in the presence of oxygen whereas glycolysis, dependent on mitochondrial bound hexokinase 2 (MB-HK-2), works either in the presence or absence of oxygen. In addition, the MB-HK 2 is anti-apoptotic and helps with other factors to retard cell death. Current estimates reveal that the human heart of an individual living 70–80 years will have undergone 2.5–3.0 billion beats, a feat that is energetically feasible only due to the heart cells' (cardiomyocytes) large population of mitochondria with bound HK-2.

Keywords Heart · Cardiomyocyte · Mitochondria · Oxidative phosphorylation · Hexokinase-2 (HK-2) · Apoptotic · Anti-apoptotic

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Introduction

This is the introductory article in a Minireview series entitled "Mitochondrial Matters of the Heart". Other invited lead authors who have kindly contributed to this series together with some of their colleagues are in alphabetical order by last name as follows: Grigory Belogrudov, Joan Heller Brown, Jenny Van Eyk, Keith Garlid, Andrew Halestrap, Charles Hoppel, Eduardo Marban, Irene Mavelli, Martin Modriansky, Brian O'Rourke, Richard Southworth, and Coert Zuurbier. The author of this introductory minireview is most grateful for all their contributions which he hopes the interested reader will find time to enjoy and obtain a more balanced assessment of where work related to mitochondrial matters of the heart currently stands.

Significantly, this mini-review series is very timely as current reports continue to conclude that heart disease, together with cancer, remain the leading causes of death both in the United States and throughout the world.

According to one very detailed report published earlier this year in "Circulation" (Lloyd-Jones et al. 2009), the following predictions were made: "In 2009, an estimated 785,000 Americans will have a new coronary attack, and about 470,000 will have a recurrent attack. It is estimated that an additional 195,000 silent first myocardial infarctions occur each year. About every 25 s, an American will have a coronary event, and about every minute someone will die of one". Although these data/predictions relate to the United States, many other countries will likely experience similar unfortunate "matters of the heart".

Mitochondrial players during normal heart function

Based on molecular details that we know in this year (2009) about heart mitochondria (Fig. 1a), the author can state generally that there are three major mitochondrial players involved in normal heart function. These are the electron transport chain (ETC) (Vonk and Schafer 2009), the ATP synthasome (ATP synthase/Adenine nucleotide carrier/Phosphate carrier complex) (Ko et al. 2003; Chen et al. 2004a) and hexokinase 2 bound to/near VDAC (Nakashima et al. 1986; Anflous-Pharaya et al. 2007). The relationships among

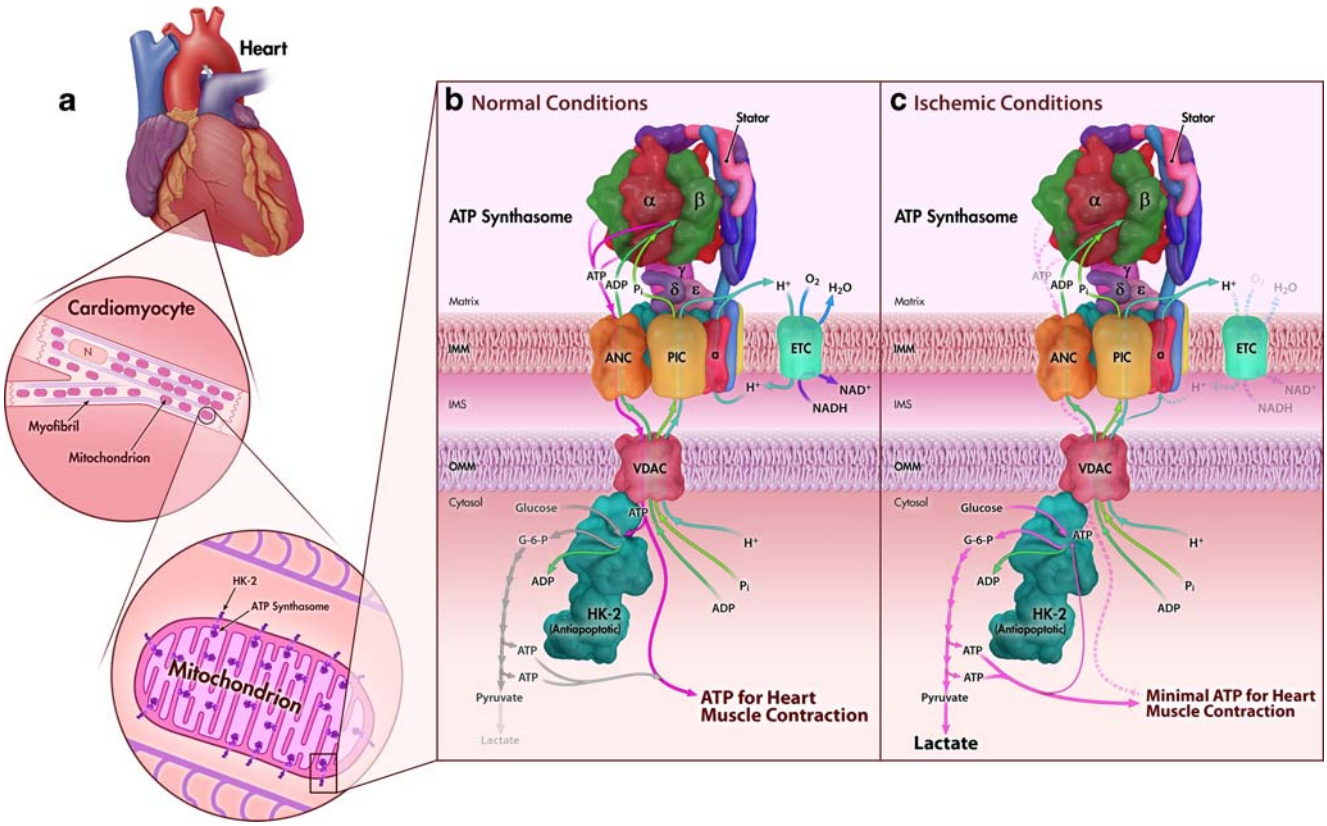

Fig. 1 a. **Heart Features, i.e., cardiomyocytes, myofibrils, mitochondria, ATP synthasomes**. Shown here is an illustration of the human heart (*top*), a single heart cell (cardiomyocyte) (*center*) lined with structures called myofibils containing many mitochondria, and finally a single "expanded" mitochondrion (*bottom*) that comprises one of several thousand mitochondria within the myofibrils. The "**ATP synthasomes**" that make the ATP from ADP and P_i line the inner mitochondrial membrane and face toward the matrix. Recall the **ATP synthasome** is comprised of the **ATP synthase** complex F_0F_1 together with a transport system (**ANC**) for adenine nucleotides (ADP&ATP), and a transport system (**PIC**) for inorganic phosphate (P_i). The overall ATP synthase/ANC/PIC complexes (ATP synthasomes) line the inner membrane cristae (invaginations of the inner membrane), face inward toward the matrix, and are the site of ATP synthesis from ADP and P_i. **b**. **Normal Heart Conditions (ample oxygen)**. ***Top***. Here is shown that the **electron transport chain** (**ETC**) oxidizes an end product (NADH) of metabolism using molecular oxygen and in so doing forms an electrochemical proton (H^+ gradient) across the mitochondrial inner membrane that drives ATP synthesis. The ATP is transported out of the mitochondria on the adenine nucleotide carrier (ANC) where it then travels through a protein in the outer mitochondrial membrane called **VDAC** (voltage dependent anion channel), after which the **ATP is used to drive contraction of the heart muscle.c. Ischemic Conditions.** ***Note, here oxygen is low, the ETC does not work well, little ATP is made, and the risk for heart failure is great.*** Under such condition hexokinase 2 (HK-2) is bound to or very near the outer membrane protein VDAC (voltage dependent anion channel). Significantly, at this site HK-2 is believed to be both anti-apoptotic, and in the presence of blood glucose and residual ATP, to make some glucose-6-phosphate (G-6-P). This would "kick off" glycolysis resulting in some net ATP formation. Because HK-2 bound to VDAC under these conditions is anti-apoptotic and because some net ATP formation is preserved, albeit small, this may represent a final effort of the heart to save its myocytes from apoptosis resulting in cell death. [Acknowledgement to David Blum and Dr. Young H. Ko for the figure.]

these three major players are shown also in Fig. 1b and c. The ETC is a key mega-player (Vonk and Schafer 2009) comprised of three mainstream "sub-players" (not shown). These are Complex I (NADH dehydrogenase), Complex III (cytochrome bc_1), Complex IV (cytochrome oxidase), and one side-stream sub-player Complex 2 (succinic dehydrogenase). Although each of these sub-players (except Complex II) is quite complex in terms of its subunit structure, the major role of each is quite simple, i.e., to transport electrons from biological substrates (resulting from metabolizing our food intake) to molecular oxygen. This in turn, via what is called a "chemiosmotic mechanism" (Mitchell and Moyle 1967), generates an electrochemical gradient of protons across the mitochondrial inner membrane (protons outside and hydroxyl ions inside). Then, during the working of the heart as ADP and P_i rise as a function of ATP usage to drive heart contraction, the mitochondria take up the ADP and P_i and, at the expense of the available electrochemical gradient of protons ATP is made. (If the heart contains a pool of creatine phosphate, it may also react with newly formed ADP that results from contraction and re-synthesize it to ATP via the enzyme creatine kinase.)

Aside from the above, the long term maintenance of most ATP for heart muscle contractions that continue for a lifetime must ultimately be derived via mitochondrial oxidative phosphorylation from ADP and P_i using the ATP synthasomes (Ko et al. 2003; Chen et al. 2004a).

Mitochondrial players during pathological (ischemic) conditions

As shown near the bottom of Fig. 1b, some ATP for heart muscle contraction is derived also from aerobic glycolysis, commencing with the conversion of glucose to glucose-6-phosphate via the enzyme hexokinase-2 (HK-2) bound at or near VDAC. In certain cell types, i.e., malignant cells, HK-2 is also known to inhibit apoptosis (Gottlob et al. 2001; Pastorino et al. 2002). Therefore, HK-2 may be playing a dual role in cardiomyocytes when attached near/at VDAC. First, HK-2 may "ward off" initiation of the cell death program, particularly during a time of crisis (i.e., ischemia), or if such a crisis is unavoidable, it may "kick in" glycolysis to supply sufficient ATP to maintain cardiomyocyte viability.

Brief summary of those agents or processes now known or believed to impact on the regulation of the heart and/or other mammalian mitochondrial ATP synthase/ATPase complexes

Identification of agents that are in some way involved in the regulation (activation or inhibition) of the heart mitochondrial ATP synthase/ATPase Complex continues to grow. Table 1 list 15 different known or proposed regulators. Many of these have been known or suggested for many years and include, Mg^{++} and Ca^{++} (metal ion activators of F_1 catalytic activity, ATP synthesis/ATP hydrolysis), ADP (product inhibitor of F_1 ATPase activity), IF_1, a natural peptide inhibitor of F_1 ATPase activity (Pullman and Monroy 1963), CaBI, natural peptide inhibitor of F_1 ATPase activity (Yamada and Huzel 1985), Factor B (small protein) (Joshi and Sanadi 1979; Lee et al. 2008; 9), calmodulin (Pedersen and Hullihen 1984), and the anions bicarbonate (Pedersen 1976) and sulfite (Das and Liungdahl 2003). However, only recently have a number of new regulatory modes been added to the list, (Arrell et al. 2006). For the most part these have arisen from signaling pathways that remain to be elucidated, and result in covalent modifications of the mitochondrial ATP synthase. These modifications include in addition to phosphorylation (Arrell et al. 2006), also nitrosylation (Sawicki and Jugdutt 2007), glutathionylation (Towsend et al. 2006) and tri-methylation

Table 1 Regulators or proposed regulators of mammalian mitochondrial ATP synthase (F_0F_1)

Regulator	Effect
Mg^{++}	Required for ATP hydrolysis/synthesis
Ca^{++}	Can replace Mg^{++} but less effective
ADP	Product inhibitor of ATP hydrolysis by F_1
IF_1	Peptide inhibitor of ATP hydrolysis by F_1
CaBI	Ca^{+2}—dependent peptide inhibitor of ATP hydrolysis by F_1
Factor B	Small protein Binds to F_0 part of ATP synthase; Prevents H^+ leaks & ATP hydrolysis
Calmodulin	Binds IF_1 preventing its inhibition of ATPase activity
Bicarbonate/Sulfite	Anion activators of ATPase activity of F_1
Covalent Modifications: (Phosphorylation, nitrosylation, acylation, glutathionylation, methylation, glcNAcylation)	Mostly unknown

(Chen et al. 2004b). In other work (Hu et al. 2008), the major complexes of the electron transport chain of heart mitochondria have been subject to "sugar" modification involving O-glcNAcylation. The latter has clear implications for the effects of type 2 diabetes on compromising normal heart function and has yet to be examined for its effect on ATP synthetic function.

Acknowledgments The author is supported in part by NIH grants 5P01HL081427, 5R01CA10951, and 2R01CA080118 all of which are related to the roles that mitochondria play in disease. The author is most grateful to Dr. Young H. Ko of Cancer Cure Med LLC for her expert help in both critically reading this manuscript and helping conceptualize and design Fig. 1, and to David Blum, Professional Artist and pre-doctoral student Department of Biological Chemistry for also helping to both conceptualize and design Fig. 1 and for performing the art work.

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