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MINIREVIEW

Adenine Nucleotide Translocator in Heart

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The adenine nucleotide translocator (ANT) spans the inner mitochondrial membrane and facilitates exchange of cytosolic ADP for ATP within the mitochondrial matrix. ANT represents the most prominent single protein component of the inner mitochondrial membrane (1). However, its role in cardiac disease processes and physiology has only recently been a major focus of attention. ANT participates in the regulation of myocardial respiration, in the pathogenesis of cardiomyopathy, and in the mechanisms of programmed cell death. These salient features provide the basis for this review.

REGULATION OF MYOCARDIAL RESPIRATION DURING MATURATION

Cytosolic ADP exchange for mitochondrial ATP operates in coordination with oxidative phosphorylation (2,3). The exchange through ANT occurs in tandem with proton translocation via mitochondrial ATPase (F1-F0 ATPase), which uses free energy generated by the membrane electrochemical potential to phosphorylate ADP (4,5). Linkage of mitochondrial oxidative phosphorylation to cytosolic energy utilizing processes in heart requires rapid and unlimited exchange by ANT. Work performed *in vitro* (isolated mitochondria) has generally implied that mitochondrial oxidative phosphorylation responds to increases in cytosolic ADP in a hyperbolic relation emulating Michaelis–Menten mechanisms (3,6), which are consistent with respiratory control through ANT. However, various studies employing control flux theory in normal adult ventricular mitochondria have generally indicated that minimal relative control strength can be attributed to ANT *in vitro* (7–10). Similarly, studies in mature myocardium *in vivo,* which use ^{31}phosphorous magnetic resonance spectroscopy, have demonstrated that substantial increases in cardiac respiratory rate are accompanied by little or no change in ADP concentration (11,12). Thus, signal transduction in mature healthy myocardium does not approximate kinetics proposed from isolated mitochondrial studies, and is thus not regulated by ANT.

However, the role of ANT in respiratory regulation changes if this protein is limited in either quantity or functionality within the mitochondrial membrane (13,14). ANT accumulates within the mitochondrial membrane during maturation (7,14). Thus, the relatively ANT-deficient newborn heart mitochondria from various species demonstrate different respiratory control patterns than those observed in adult counterpart mitochondria. Support for these contentions occurs from a variety of experiments. Wells *et al.* demonstrated that decoupling of oxidative phosphorylation through DNP produces increases in state III respiratory rates in fetal and newborn mitochondria, while no comparable changes occurred in adult mitochondria (15). This maturational difference implies that fetal and newborn mitochondrial respiration can be limited or regulated at the phosphorylation level, which consists

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of two principal membrane components: ANT and the F0-F1-ATPase. Schonfeld (7) isolated rat heart mitochondria at different developmental states and titrated these preparations with the specific ANT inhibitor, carboxyatractyloside, during state III respiration. Flux control coefficients estimated from the titration curves indicate that ANT exerts substantial control over respiration in the newborn rat heart mitochondria at state III, which declines progressively to near zero as maturation is achieved. Similar control patterns were demonstrated by the F1-F0-ATPase (7). The changes in control through the translocator corresponded to ANT activity as well as protein content. These data obtained *in vitro* conform to kinetic models drawn from ^{31}P magnetic resonance studies performed *in vivo* (11,16,17). Specifically, steady-state ADP levels increase in newborn lamb heart *in vivo* as oxygen consumption increases. ADP does not vary during comparable myocardial respiratory change in the mature lamb. The relationship between oxidative phosphorylation rate and ADP appears to follow a simple Michaelis–Menten kinetic model, which presumes that respiratory regulation occurs through ANT (11,16,17). Apparent maturational alterations in respiratory mode are accompanied by increases in mitochondrial ANT accumulation (16).

Although, the newborn heart differs from that of adults in respect to kinetics of respiratory control, oxygen consumption rates achieved *in vivo* approximate those obtained in the mature counterparts (11,16,17). These differences imply that deficiencies in ANT exchange do not limit myocardial respiratory rate, but do alter the regulatory mode. However, pathological models, which are ANT deficient, also demonstrate an inability to substantially increase oxygen consumption (discussed later) (18–20).

REGULATION OF ANT EXPRESSION

Three distinct nuclear encoded ANT isoforms (ANT1, ANT2, ANT3) have been identified, which each correspond to similar isoforms in other mammalian species (21,22). These isoforms demonstrate tissue specificity, and their expression is sensitive to the particular cell's physiological conditions. Transcript levels respond to cellular demands by varying the rate of isoform mRNA synthesis and/or stability (23). Cardiac muscle expresses all three isoforms, although ANT1 gene expression predominates (21,22). Location of this gene has been assigned to chromosome 4. Chung *et al.* have demonstrated that transcriptional regulation of ANT1 in myogenic mouse cells occurs through a muscle-specific positive promoter element (OXBOX), as well as a tissue ubiquitous (REBOX) region, which overlaps OXBOX (24). Binding of REBOX factors was found to be sensitive to NADH and thyroid hormones, T4 and T3, suggesting that ANT1 regulation can be modulated by these environmental factors. Furthermore, the muscle-specific promoter element appears to be shared by the ATP synthase β subunit, and occurs upstream of the putative transcription start sites for each gene. Sharing of this unit indicates that these genes, in part responsible for oxidative phosphorylation, are coordinately expressed. Accordingly, steady-state mRNA expression of both these genes increases during transition from fetal to mature stage in hearts of at least two species, ovine and rabbit (14,16).

The signals, which alter expression of these genes during cardiac maturation, require further clarification. Dummler *et al.* demonstrated T3 upregulation of the tissue ubiquitous isoform, ANT2, in rats (25). Sheep thyroidectomized immediately after birth demonstrate marked decreases in steady-state expression for all three ANT isoforms, but show no deficit in βF1-ATPase expression (13). This implies that thyroid hormone specifically regulates ANT through mechanisms that do not involve the shared promoter sites.

ANT protein content coordinates with steady-state mRNA levels in heart during development (13,16). Furthermore, thyroidectomy-induced decreases in transcript levels for all three isoforms are accompanied by comparable decreases in mitochondrial ANT accumulation (13). Although ANT content is diminished, adenine nucleotide transport at individual exchanger sites is not reduced, indicating that thyroid deficiency does not alter conformation of this protein within the mitochondrial membrane. However, myocardial respiratory control in thyroidectomized sheep heart conforms to the ADP mode of regulation seen in newborn lambs. Thus, thyroid hormone appears to regulate maturation of myocardial respiratory control in part through nuclear-mediated increases in ANT protein content.

ANT1 DEFICIENT MOUSE

Abnormal mitochondrial ANT content or isoform distribution produces oxidative phosphorylation deficiencies in heart (26). The ANT1 deficient mouse provides an extreme example of this phenomenon.

Cardiac mitochondria from homozygous ANT1 deficient mouse express some ANT2. Nevertheless, these mitochondria achieve lower rates of state III or ADP-stimulated respiration than normal littermates (26). However, sophisticated assessment of respiratory control such as control flux experiments in isolated cardiac mitochondria or [^{31}P]NMR kinetic studies in intact heart from these mice have not yet been performed.

Heart mitochondria from ANT1 deficient mice also produce markedly increased amounts of reactive oxygen species hydrogen peroxide (27). Esposito *et al.* have postulated that deficits in ANT1 protein content reduce matrix ADP and limit proton translocation through F1-F0-ATPase, which accompanies ADP phosphorylation. Inability to maintain proton flux back across the inner mitochondrial membrane would preserve or even increase the electrochemical membrane gradient and thereby limit electron transfer through the respiratory chain. Electrons would then accumulate and be available for production of reactive oxygen species $O_2^{\cdot}$ from O_2, and yield the heart more vulnerable to damage during reoxygenation.

Finally, hearts from ANT1 deficient mice develop progressive myocardial hypertrophy and left ventricular wall thickening. These findings imply that this mitochondrial protein deficit contributes to myocardial remodeling seen in hypertrophic diseases (26).

DILATED CARDIOMYOPATHY AND VIRAL MYOCARDITIS

Abnormalities in quantity or function of ANT appear to contribute to the pathophysiology of cardiomyopathy and congestive heart failure (28,29). However, data discrepancies exist between various forms of CHF as well as species with regard to ANT expression and function (28–30). Most investigators concur that ANT mRNA expression closely coordinates with protein content regardless of mechanism involved in the alteration. Dorner *et al.* found that ANT protein content obtained from explanted heart tissue or endomyocardial biopsy from patients with dilated cardiomyopathy was higher than that found in explanted hearts from patients with ischemic or valvular heart disease (28). They also found that a relative isoform shift toward ANT1 expression occurred in dilated cardiomyopathy, when compared to ischemic or valvular heart disease. The authors' comparisons with a control group are difficult to interpret, since the method of sampling from 12 hearts without cardiac disease was not clearly defined. As data from our laboratory shows that ANT1 mRNA levels are rapidly downregulated in hearts exposed to ischemia (31,32), one might suppose that these levels were decreased in those human control hearts. Nevertheless, a clear difference exists in isoform expression and ANT content between dilated cardiomyopathy and ischemic heart. This difference might stem from enteroviral infections (33), which are the major cause for dilated cardiomyopathy and have been shown to modify ANT mRNA isoform expression (34). Coxsackie B3 infection in mice stimulates generation of ANT protein autoantibodies, which inhibit ADP/ADP exchange on incubation with isolated mitochondria *in vitro* (28). Hearts from these mice exhibit reductions in cytosolic phosphorylation potential, which are consistent with ANT dysfunction (35). Thus, enteroviral infection and generation of autoantibodies to ANT appear to play a role in the pathogenesis of dilated cardiomyopathy.

ISCHEMIC CARDIOMYOPATHY

Myocardial ischemia acutely depresses steady-state mRNA expression for ANT1 and β-F1-ATPase (32,36), and rapidly diminishes ANT protein content in isolated perfused heart (37). These changes are associated with metabolic changes consistent with shifts in kinetic regulation of myocardial respiration. Recently, deficiencies in energy metabolism in porcine heart *in vivo* have been demonstrated during ventricular remodeling, which occurs after myocardial infarction (19,38,39). Hearts which progress to clinically and hemodynamic apparent congestive failure demonstrate deficits, which include diminished phosphorylation potential and limitations in the oxygen consumption response to inotropic stimulation. Although these deficits can be caused in part by changes in other mitochondrial proteins, the respiratory kinetics in these hearts imply that deficiencies in ANT are responsible. Accordingly, decreases in expression for ANT1 mRNA and total ANT content occur in hearts, which progress towards congestive failure, but not in those which demonstrate hemodynamic and metabolic compensation (29). The coordination, which occurs among these levels, energy metabolism, and cardiac function, implies that ANT plays a significant role in remodeling and contractile failure after infarction.

APOPTOSIS IN HEART

Recent evidence suggests that apoptosis or programmed cell death participates in the pathological processes of ischemic heart disease and cardiomyopathy (40). It is now apparent that most apoptotic processes involve mitochondrial dysfunction and an eventual loss of mitochondrial membrane potential and integrity, characterized by release of cytochrome *c* into the cytoplasm (41). The permeability transition pore complex (PTPC) regulates mitochondrial permeability and probably participates in control of apoptosis. The PTPC appears to be formed by ANT and the voltage dependent anion channel at contact sites respectively between the inner and outer mitochondrial membranes (42). Opening of the PTPC may promote leakage of protons and/or other ions, which lead to a loss of mitochondrial membrane potential. Several models for opening of the permeability transition pore have been proposed. These generally include participation of ANT, as well as the voltage dependent anion channel.

Cyclophilins are a family of cyclosporin-A-binding proteins, which catalyze rotation about prolyl peptide bonds, and can thus alter protein conformation (43). Protein import studies have established that cyclophilin D locates to the mitochondrial matrix in heart. Thus, this protein presumably binds to the permeability transition pore at ANT within the inside face of the mitochondrial inner membrane (43). Oxidative stress or thiol reagents enhance binding of the mitochondrial cyclophilin D to ANT in heart (44). This binding enhances Ca^{2+}-triggered ANT conformational changes, which promote PTPC opening in heart during reperfusion *in situ* (45).

Regulation of PTPC also occurs in part through binding of the Bax protein, a known proapoptotic modulator of the cell death cycle. Bax induces cell death in wild-type, but not in ANT deficient yeast (46). Furthermore, recombinant Bax and ANT form channels in artificial membranes. Opening of these channels is stimulated by the specific ANT inhibitor atractyloside, but inhibited by ATP (46,47). Thus, Bax and ANT cooperate within the PTPC to increase mitochondrial permeability and trigger cell death. The antiapoptotic protein, Bcl-2, neutralizes cooperation between Bax and ANT and prevents opening of PTPC (46–48). Some studies demonstrate specificity for ANT1 in participation of PTPC, as ANT2 expression in yeast does not permit induction of cell death (47), although this has not been confirmed in heart.

Vander Heiden and coauthors have recently proposed that though ANT participates in apoptosis, PTPC opening is not the primary mitochondrial defect in the initiation of programmed cell death (49). Data, obtained from studies examining apoptosis induced by growth factor withdrawal, indicate that an increase in mitochondrial membrane potential precedes loss of the outer membrane integrity and cytochrome *c* release (49). Mitochondria isolated from growth factor deprived cells demonstrate deficient ADP/ATP exchange. Hyperpolarization of the mitochondrial membrane during growth factor withdrawal, as well as deficits in ADP uptake, can be prevented by expression of the antiapoptotic protein, Bcl-X_L. Hence, these investigators suggest that deficient ADP uptake through ANT or the voltage dependent anion channel reduces matrix ADP dependent proton translocation through F0-F1-ATPase. The reduction in proton transport to the mitochondrial matrix yields hyperpolarization of the mitochondrial membrane, reduces the rate of oxidative phosphorylation, acidifies the intermembrane space, and promotes formation of reactive oxygen species. This sequence of events would lead to mitochondrial swelling, membrane rupture, and release of cytochrome *c* into the cytoplasm.

CONCLUSION

ANT facilitates ADP/ATP exchange across the mitochondrial membrane. This function provides this protein a central role as a regulator of several mitochondrial processes, which change according to developmental or pathological state. ANT also appears to participate in the cycle of programmed cell death, although the precise mechanisms and order of events still require clarification.

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