Up-regulation of Nuclear and Mitochondrial Genes in the Skeletal Muscle of Mice Lacking the Heart/Muscle Isoform of the Adenine Nucleotide Translocator*

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Mice deficient in the heart/muscle specific isoform of the adenine nucleotide translocator (ANT1) exhibit many of the hallmarks of human oxidative phosphorylation (OXPHOS) disease, including a dramatic proliferation of skeletal muscle mitochondria. Because many of the genes necessary for mitochondrial biosynthesis, OXPHOS function, and response to OXPHOS disease might be expected to be up-regulated in the Ant1−/− mouse, we used differential display reverse transcription-polymerase chain reaction techniques in an effort to identify these genes. 17 genes were identified as up-regulated in Ant1-deficient mice, and they fall into four categories: 1) nuclear and mitochondrial genes encoding OXPHOS components, 2) mitochondrial tRNA and rRNA genes, 3) genes involved in intermediary metabolism, and 4) an eclectic group of other genes. Among the latter genes, we identified the gene encoding anti-apoptotic Mcl-1, the Skd3 gene, and the WS-3 gene, which were previously unknown to be related to mitochondrial function. These results indicate that identification of genes up-regulated in the skeletal muscle of the Ant1-deficient mouse provides a novel method for identifying mammalian genes required for mitochondrial biogenesis.

The mitochondria generate most of the cells’ energy via the process oxidative phosphorylation (OXPHOS).1 OXPHOS is catalyzed by five multi-subunit enzyme complexes (complexes I-V) located within the inner mitochondrial membrane. The protein subunits necessary for oxidative phosphorylation are encoded by both the nuclear and mitochondrial genome. The mitochondrial genome encodes 13 polypeptides (the subunits of complexes I-V) located within the inner mitochondrial membrane. Of these, the nuclear genome encodes all of the remaining proteins for oxidative phosphorylation (OXPHOS). These include the remaining subunits of the protein complexes I, II, III, and IV, and two subunits of complex V (ATPases 6 and 8) along with 22 tRNAs and 2 rRNA subunits necessary for translation of these polypeptides. Transcription of the mtDNA initiates at two sites, yielding polycistronic messages in which regions coding for protein are interspersed by regions coding for tRNA (1). The mature mRNAs, rRNAs, and tRNAs are released by cleavage. The nuclear genome encodes all of the remaining genes for mitochondrial biogenesis. These include the remaining subunits for OXPHOS; all of the proteins for mitochondrial regulation, transcription, and translation; and all proteins for mitochondrial intermediary metabolism (2).

Mutations in both the mitochondrial DNA and the nuclear DNA have been shown to cause OXPHOS disease. OXPHOS diseases have a highly variable clinical spectrum, showing the progressive deficits in tissues most reliant on cellular energy, with central nervous system, skeletal muscle, and heart frequently being affected. Mitochondrial myopathies are characterized pathologically by degeneration of the contractile elements and the proliferation of subsarcolemmal mitochondria, resulting in ragged red muscle fibers as revealed by the modified Gomori-trichrome stain. The proliferation of mitochondria appears to be a common compensatory response to energy deficiency in muscle, whether caused by OXPHOS disease or endurance training in athletes (3). The induction of the proliferation of mitochondria is a complex task, requiring coordinate regulation of hundreds of genes dispersed between the nuclear and mitochondrial genomes. The coordinate up-regulation of nuclear and mtDNA OXPHOS gene transcripts has been documented in the skeletal muscle of patients with three mitochondrial DNA mutation diseases: Kearns-Sayre syndrome; myoclonic epilepsy associated with ragged red fibers; and myopathy encephalopathic, lactic acidosis, and stroke-like episodes (4, 24).

An animal model of mitochondrial myopathy and cardiomyopathy has recently been created by genetically inactivating mouse Ant1 (6). AN1 exchanges mitochondrial matrix ATP for cytosolic ADP across the mitochondrial inner membrane. Knock-out mice deficient in AN1 exhibit many of the hallmarks of human OXPHOS disease, including a defect in coupled respiration, lactic acidosis, exercise intolerance, and a dramatic proliferation of skeletal muscle mitochondria. The dramatic increase in mitochondrial number and volume in the muscle of Ant1-deficient mice suggests that there might be a coordinate up-regulation of genes required for energy production. In an effort to identify the up-regulated genes, we have analyzed Ant1-deficient mouse muscle RNA using differential display RT-PCR technology (7). This has resulted in the identification of 17 genes up-regulated in mutant mouse muscle. Among these are genes known to be involved in OXPHOS, as well as genes previously unknown to be involved in mitochondrial function.

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‡ The abbreviations used are: OXPHOS, oxidative phosphorylation; PCR, polymerase chain reaction; RT-PCR, reverse transcription-PCR; DD, differential display; nt, nucleotide(s); WS, Werner syndrome; RACE, rapid amplification of cDNA ends.

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The resulting $^{33}$P-labeled RT-PCR was amplified using the differential display RNAimage Kits 1–4 (GenHunter Corporation, Nashville, TN). The resulting bands were cut from the gel, eluted, and subjected to differential display PCR using various arbitrary primers (exemplified in Fig. 1). Using 96 primer pairs that displayed approximately 5,000 cDNA PCR products, 84 PCR products were initially extracted, reverse transcribed, and subjected to differential display PCR in the presence of $[^{32}]$P(CTP). Reactions were run on 6% denaturing polyacrylamide gels, with the reactions from $+/−$ mice run in the inner two lanes, and those from $+/+$ mice run in the outer two lanes. Bands identified as putatively differentially expressed are marked by arrowheads.

**TABLE I**  
Identity of up-regulated differential display products

| DD Band | Origin | Identity | Function |
|---------|--------|----------|----------|
| DD2 mtDNA ND4 | NADH dehydrogenase subunit |
| DD4 Nuclear CI-B18 | Ubiquinone oxidoreductase subunit |
| DD7 Nuclear CoxVb | Cytochrome c oxidase subunit |
| DD21 Nuclear MGP | Glycogen phosphorylase |
| DD24 Nuclear Sdh1 | Unknown |
| DD25 Nuclear WS-3 | Unknown |
| DD26 Nuclear Mcl1 | Anti-apoptotic |
| DD40 mtDNA ND6 | NADH dehydrogenase subunit |
| DD44 Nuclear CI-B8 | Ubiquinone oxidoreductase subunit |
| DD46 mtDNA COI | Cytochrome c oxidase subunit |
| DD57 mtDNA 16 S RNA | Mitochondrial protein synthesis |
| DD60 Nuclear CoxVa | Cytochrome c oxidase subunit |
| DD62 mtDNA ND2 | NADH dehydrogenase subunit |
| DD63 mtDNA tRNA | Polycistronic transcript |
| DD65 mtDNA ND1 | NADH dehydrogenase subunit |
| DD67 Nuclear Mor2 | Malate dehydrogenase |
| DD69 mtDNA ND5 | NADH dehydrogenase subunit |

**EXPERIMENTAL PROCEDURES**

**Differential Display**—Total RNA was isolated from gastrocnemius muscle of two wild type and two $Ant1^{+/−}$ mice using TRIZOL Reagent (Life Technologies, Inc.). DNA contamination was removed with the MessageClean kit, and the mRNA was reverse-transcribed and amplified using the differential display RNAimage Kits 1–4 (GenHunter Corporation, Nashville, TN). The resulting $^{32}$P-labeled RT-PCR products were run on 6% LongRanger polyacrylamide gels. Putative differentially regulated bands were cut from the gel, eluted, and reamplified.

Differential display (DD) products were identified by the direct sequencing of reamplified products (8) using the ABI PRISM Dye Terminator Cycle Sequencing Ready Reaction kit (Perkin-Elmer Corp.) and the ABI 377 DNA sequencer. The resulting sequence information was compared with GenBank® and EST data bases at the National Center for Biomedical Information via the BLAST computer program.

**Northern and Reverse Northern Analysis**—Northern hybridization analysis was performed using glyoxal and Me$_2$SO to denature 10-$μg$ of total RNA, followed by electrophoresis and transfer to Hybond N membrane (Amersham Pharmacia Biotech). To verify the differential expression of the genes identified by differential display, DD products were cloned into the TA vector (Invitrogen, Carlsbad, CA), and the resulting cDNAs were used as probes for Northern and reverse Northern hybridization. First, Northern blot strips that contained only skeletal muscle RNA were probed with the corresponding cloned and reamplified DD product. If this Northern blot showed up-regulation of the gene of interest, then RNA samples from the tissues containing various ratios of $Ant1^{+/+}/Ant2^{−/−}$ mRNAs (skeletal muscle, heart, and brain) were blotted and probed with the corresponding cloned and reamplified DD product. Probes for evaluation of mitochondrial DNA transcripts were created by amplification of nt 3351–7570 and nt 8861–14549 of the mtDNA of mouse genomic DNA using mitochondrial DNA specific primers. The Rediprime DNA labeling system (Amersham Pharmacia Biotech) was used to label probes with $[^{32}]$P(CTP). The intensity of bands was quantitated using a PhosphorImager (Molecular Dynamics, Sunnyvale, CA).

For reverse Northern blots, DD PCR products were immobilized on membrane and hybridized to probe synthesized by reverse transcription of RNA from either wild type or $Ant1^{−/−}$ mice. One μg of each DD PCR product was applied to duplicate Hybond N membranes via a dot blot apparatus (Millipore). Probes were made by reverse transcription of 20 μg of total RNA derived from gastrocnemius muscle of either wild type or $Ant1^{−/−}$ mice using the ReversePrime kit (GenHunter Corporation).

**Rapid Amplification of cDNA Ends (RACE)**—The 5′ ends of cDNAs identified by differential display were isolated using the RACE technique. Template for amplification was mouse skeletal muscle Marathon-Ready cDNA (CLONTECH, Palo Alto, CA). Gene-specific primers designed from the differential display product sequence were combined with linker-specific primers of the cDNA and the Advantage cDNA polymerase mix (CLONTECH), and the 5′ end of the gene was amplified. The products were sequenced directly using the ABI PRISM Dye Terminator Cycle Sequencing Ready Reaction kit (Perkin-Elmer) and analyzed using an ABI 377 DNA sequencer. The products were also cloned into the TA vector (Invitrogen).

**RESULTS**

DD RT-PCR techniques (7) were used to identify genes up-regulated in $Ant1^{−/−}$ mice. Total RNA from the gastrocnemius muscle of a 3-month-old littermate $Ant1^{+/+}$ and $−/−$ mice was extracted, reverse transcribed, and subjected to differential display PCR using various arbitrary primers (exemplified in Fig. 1). Using 96 primer pairs that displayed approximately 7,500 cDNA PCR products, 84 PCR products were initially identified as differentially expressed. These DD products were...
then reamplified, sequenced, and cloned into a plasmid vector. Seventeen genes were verified as up-regulated in the Ant1 knock-out mouse, and they fell into four categories: 1) nuclear and mitochondrial genes encoding OXPHOS components, 2) mitochondrial tRNA and rRNA genes, 3) other genes involved in intermediary metabolism, and 4) an eclectic group of other genes.

OXPHOS Genes Up-regulated in Mice Deficient for Ant1—The sequences of ten of the DD products (Table I) revealed genes encoding subunits of the electron transport chain. Six of these are mitochondrially encoded and include the complex I subunit genes ND1, -2, -4, -5, -6, and the complex IV subunit gene COI (Fig. 2). Northern analysis revealed that all six of these mRNAs, and three others tested (ND4L, COII, and COIII) were up-regulated in the skeletal muscle of the ANT1-deficient mice (Fig. 3). All mitochondrial mRNAs tested were up-regulated between 2.5–3.5-fold. Similar increases are seen for patients with mitochondrial myopathies (4).

The remaining four up-regulated OXPHOS transcripts are derived from the nuclear DNA and encode components of complexes I and IV. The complex IV subunit genes encode two subunits of cytochrome c oxidase, COXVa (9) and COXVb (10). The complex I subunits are homologues of the bovine genes encoding CI-B8 and the 18-kDa Fe-S protein (11). Because these genes had not been cloned from mouse, RACE was used to isolate, clone, and sequence the mouse CI-B8 and CI-18k genes (GenBank™ accession numbers AF124786 and AF124785, respectively). Northern blots of all four of these subunits has confirmed that they are up-regulated in the ANT1-deficient skeletal muscle (Fig. 4 and data not shown).

mtDNA Transcripts Involved in Mitochondrial Protein Synthesis—Two of the DD RT-PCR products were identified by sequence analysis to correspond to mtDNA genes encoding structural RNAs, the mitochondrial 16 S rRNA (DD57) and a cluster of three tRNAs encompassed in nucleotides 4821–5171 (DD65). The differential display product DD65 contains the 3’ end of ND1, in addition to the three contiguous tRNA genes. The association in one RNA of these continuous genes suggests that this is a processing intermediate of the polycistrionic H-strand transcript.

Intermediary Metabolism Genes—Sequence analysis of two...
differential display products revealed that they encode the intermediary metabolism proteins malate dehydrogenase and glycogen phosphorylase. The sequence of DD67 is identical to the 3' region of the mouse gene for the mitochondrial isofrom of malate dehydrogenase (12). Malate dehydrogenase catalyzes the final reaction of the citric acid cycle, the regeneration of oxaloacetate. The sequence of DD21 reveals that it is the mouse homologue of the gene for the rat muscle isozyme of glycogen phosphorylase (13). Glycogen phosphorylase catalyzes the breakdown of glycogen to yield glucose-1-phosphate. The mouse homologue of the glycogen phosphorylase gene was isolated by RACE (GenBank™ accession number AF124787). The RNA levels of both malate dehydrogenase and glycogen phosphorylase genes were shown to be up-regulated in Ant1 knockout mice (Fig. 5).

Other Genes Up-regulated in the Ant1 Knockout Mouse—

Skd3. Northern blots probed with DD product DD24 revealed that this message is up-regulated in both heart and skeletal muscle of the Ant1−/− mice (Fig. 6A). The DNA sequence of DD24 is identical to the previously cloned gene Skd3. Skd3 was isolated from a mouse cDNA library based on its ability to recognize this deficiency, and sends an as yet unidentified signal to the nucleus to increase transcription of mitochondrial genes. Accordingly, most of the genes shown to be up-regulated in Ant1−/− mice should encode products directly involved in the synthesis of ATP, including components of the mitochondrial energy generating apparatus, such as the electron transport chain and the citric acid cycle, machinery for mitochondrial biogenesis, including the mitochondrial rRNAs and tRNAs, and functionally related proteins such as glycogen phosphorylase and malate dehydrogenase.

Previous studies have shown that human glycogen phosphorylase mRNA is up-regulated in mitochondrial myopathy patients and that the gene contains a 5' REBOX binding site. The 8-base pair REBOX sequence motif was identified as a specific protein binding site in Ant1 and ATP synthetase β subunit promoters by electrophoretic mobility shift assays (20). This binding is sensitive to NADH and thyroxine, suggesting that it may modulate OXPHOS gene expression in response to environmental and hormonal changes (20).

Several of the genes shown to be up-regulated are not likely to be directly involved in ATP synthesis. Up-regulation of Mcl-1, a Bcl-2 homologue, is more likely a response to oxidative stress in the cell. Mcl1 has been shown to be up-regulated in response to reactive oxygen species (21), which have shown to be at higher levels in Ant1−/− mice. The finding that Mcl1 is up-regulated in this animal model for mitochondrial myopathy suggests that apoptosis plays a role in the pathogenesis of mitochondrial mutations in human patients.

By analogy with the other genes found to be up-regulated, we propose that WS-3 and Skd3 are involved in mitochondrial biogenesis. BLAST searches performed with the predicted WS-3 protein reveal a similarity to the third enzyme in enterobacterial lipid A biosynthesis (17, 18). Because mitochondria are believed to have originated by endosymbiosis of bacteria, and several important mitochondrial proteins such as DNA polymerase γ (1) have greater similarity to bacterial proteins than eukaryotic proteins, it seems possible that this WS-3 plays a role in mitochondrial lipid synthesis. This hypothesis is strengthened by comparison with the model of the two families of fatty acid biosynthesis enzymes. In addition to the previously known eukaryotic (type I) cytosolic enzymes of fatty acid biosynthesis, bacterial homologues of these enzymes (type II) have been discovered in various eukaryotic species (22). Some of these enzymes have been localized to the mitochondrion, and deletion of the corresponding gene leads to defects in respiratory function. It is possible that prokaryotic type genes involved in lipid synthesis have also been retained from the endosymbiotic ancestor of the mitochondrion and that WS-3 is one of these genes. Because Ant1−/− mice have a dramatic proliferation of mitochondria, enzymes involved in mitochondrial lipid synthesis would be expected to be up-regulated in these mice.

DISCUSSION

In the absence of the adenine nucleotide translocator, ATP synthesized in the mitochondrion is not transported into the cytoplasm, and an energy deficient state is created. The cell recognizes this deficiency, and sends an as yet unidentified signal to the nucleus to increase transcription of mitochondrial genes.

**Mcl-1**—The sequence of the DD26 product is identical to the 3' end of the Mcl1 gene. Mcl-1, a member of Bcl-2 family of anti-apoptotic proteins, is located at least partially in the mitochondrion (19). Northern analysis verified that Mcl1 is up-regulated in the skeletal muscle of mice deficient in Ant1 (Fig. 5). In addition to being up-regulated in the ANT1 knock-out mouse, Mcl1 mRNA also appears to have an altered mobility on Northern blots.

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3 L. A. Esposito and D. C. Wallace, unpublished results.

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![Diagram](https://via.placeholder.com/150)
Skd3 encodes a predicted protein with a putative mitochondrial targeting signal, ankyrin-like repeats, and similarity to the Clp/HSP104 family of proteins. Interestingly, Saccharomyces cerevisiae Hsp78, another member of the Clp/HSP104 family, appears to cooperate with the mitochondrial matrix protein Hsp70 in maintenance of mitochondrial function (23). In addition, Hsp78 is responsible for compartment-specific thermotolerance in yeast (5). SKD3, unlike other members of the Clp/HSP104 family, contains four ankyrin-like repeats in its N-terminal domain. In erythrocytes, ankyrin is responsible for attachment of spectrin to integral membrane proteins, whereas in noneerythroid cells, ankyrin is thought to be involved in protein/protein or protein/cytoskeleton interactions. Because of these sequence motifs, we hypothesize that the SKD3 protein is localized to the mitochondria, where it may interact with an unknown protein and assist in the assembly of some multisubunit complex.

In this work, we have identified 17 genes up-regulated in the Ant1−/− mice by DD RT-PCR. Interestingly, 33 other differential display products isolated have been identified by sequence, but their relative expression cannot be assessed by filter hybridization techniques, because they are of very low abundance in muscle (data not shown). Six mRNAs, one tRNA, and one rRNA encoded by the mitochondrial genome were identified as differentially expressed by differential display. Because all mitochondrial mRNAs appear to be up-regulated, differential display methods identified half of all up-regulated transcripts from the mitochondrial genome. By extrapolation to the nuclear genome, the 17 mRNAs with levels high enough to be identified as up-regulated, and the 33 genes with low level expression identified by differential display, should represent a significant proportion of the genes up-regulated in Ant1−/− deficient mice. We conclude that differential expression methods provide an effective means to identify genes involved in mitochondrial biogenesis and function. Experiments using complementary differential expression methods, such as serial analysis of gene expression, are in progress.

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