Differential Expression of Mitochondrial DNA Replication Factors in Mammalian Tissues*

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Mitochondrial biogenesis and mitochondrial DNA (mtDNA) replication are regulated during development and in response to physiological stresses, but the regulatory events that control the abundance of mtDNA in cells of higher eukaryotes have not been defined at a molecular level. In this study, we observed that expression of the catalytic subunit of DNA polymerase γ (POLγCAT) mRNA varies little among different tissues and is not increased by continuous neural activation of skeletal muscle, a potent stimulus to mitochondrial biogenesis. Increased copy number for the POLγ locus in a human cell line bearing a partial duplication of chromosome 15 increased the abundance of POLγCAT mRNA without up-regulation of mtDNA. In contrast, expression of mitochondrial single-stranded DNA-binding (mtSSB) mRNA is regulated coordinately with variations in the abundance of mtDNA among tissues of mammalian organisms and is up-regulated in association with the enhanced mitochondrial biogenesis that characterizes early postnatal development of the heart and the adaptive response of skeletal myofibers to motor nerve stimulation. In addition, we noted that expression of mtSSB is concentrated within perinuclear mitochondria that constitute active sites of mtDNA replication. We conclude that constitutive expression of the gene encoding the catalytic subunit of mitochondrial DNA polymerase is sufficient to support physiological variations in mtDNA replication among specialized cell types, whereas expression of the mtSSB gene is controlled by molecular mechanisms acting to regulate mtDNA replication or stability in mammalian cells.

Cells of vertebrate organisms differ markedly in their ability to utilize oxidative phosphorylation to meet cellular energy requirements, reflecting major variations in the cellular content of mitochondria and of respiratory proteins. This variation is most striking among specialized subtypes of striated myocytes (1). Mitochondria may occupy 50% or more of cell volume in cardiac myocytes of some species while type IIb skeletal myofibers have sparse mitochondria (approximately 1% of cell volume). Other subtypes of skeletal myofibers (type I or IIa) occupy intermediate positions on this spectrum. Mitochondria-rich muscle subtypes are resistant to fatigue, whereas glycolytic myofibers with few mitochondria are adapted for short bursts of high power output and fatigue rapidly with sustained activity. Cells adapted for high rates of respiration exhibit increased expression of both nuclear and mitochondrial genes encoding enzymes of oxidative phosphorylation, and enhanced mitochondrial gene expression is accompanied by amplification of the mitochondrial genome relative to nuclear DNA in mitochondria-rich muscle subtypes (2, 3). These specialized characteristics of myocytes with respect to respiratory capacity and mtDNA are established by developmental cues but can be modified in adults by changing physiological demands or disease processes (2–4).

In an effort to gain greater understanding of the molecular mechanisms by which developmental and physiological regulation of mitochondrial DNA (mtDNA) content is achieved, we examined expression of nuclear genes encoding two proteins required for mtDNA replication. DNA polymerase γ (POLγ) catalyzes replication of mtDNA, and conserved genes encoding the catalytic subunit of POLγ have recently been cloned from several eukaryotic species, including humans (5, 6). Disruption of the POLγ gene in yeast (7) demonstrates that the enzyme has no essential functions outside of mitochondria but is absolutely required for mtDNA replication. A mitochondrial single-stranded DNA binding protein (mtSSB) also is necessary for mtDNA replication in yeast (8), and mtSSBs have been identified in several vertebrate species (9). As assessed in cell-free reactions, mtSSB augments both fidelity and processivity of POLγ (10, 11).

In this study, we examined expression of the POLγCAT and mtSSB genes in different tissues or specialized subtypes of striated myocytes with markedly different contents of mtDNA. In addition, we characterized changes in expression of these genes in striated muscles responding to continuous motor nerve stimulation, a potent stimulus to mtDNA replication. The results show that expression of POLγCAT mRNA is constitutive while expression of mtSSB is strictly regulated and correlates directly with mtDNA content. Regulated expression of mtSSB also was observed in conjunction with the up-regulation of mtDNA that occurs within the myocardium during the first few weeks of post-natal life. Overexpression of POLγCAT evoked by an increase in gene dosage failed to affect the content of mtDNA. In addition, we noted that the mtSSB protein is distributed nonuniformly within murine myogenic cells in culture and is preferentially localized to perinuclear mitochondria that constitute active sites of mtDNA replication (12). These

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† The abbreviations used are: mtDNA, mitochondrial DNA; POLγ, DNA polymerase γ; POLγCAT, catalytic subunit of DNA polymerase γ; mtSSB, mitochondrial single-stranded DNA-binding; PCR, polymerase chain reaction; kb, kilobases; TA, tibialis anterior; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GST, glutathione S-transferase; PBS, phosphate-buffered saline.

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data indicate that expression of nuclear genes encoding proteins essential for mtDNA replication is differentially, rather than coordinately, regulated in response to signaling pathways that control mitochondrial biogenesis in mammalian cells.

**EXPERIMENTAL PROCEDURES**

**Cloning of cDNA and Genomic Sequences Encoding mtSSB and POLγCAT**—Using primer sets based on the published sequences of the rat and human mtSSB cDNAs, partial cDNAs encoding rabbit and mouse mtSSB proteins were cloned using reverse transcriptase-PCR. 20 μg of total heart RNA were reversed transcribed using Superscript II (Boehringer Mannheim) as recommended. The PCR primers for cloning rabbit mtSSB cDNA were: 1) 5'-CTGCGCAACAGAARATGGTGG-3' and 2) 5'-ACRTTRTTYTRTCCATRTAYTC-3'. The PCR primers for cloning mouse mtSSB cDNA were: 1) 5'-AGGCCCTT-GCGGTCAAGAGA-3' and 2) 5'-TAGACTGTACATCATTTGAAAGG-3'. Amplification products were cloned and sequenced. The mouse and rabbit partial cDNAs (~200 nucleotides) exhibited 94% and 85% nucleotide sequence identity, respectively, with the published rat mtSSB sequence (9).

Experiments designed to establish a detailed physical map of chromosome 15q26.1, including direct selection of partial cDNA clones encoded by this region, yielded three expressed sequence-tagged clones with near perfect homology to the <i>S. cerevisiae</i> mtSSB gene (7). Subsequent screening of HeLa and human brain cDNA libraries yielded numerous clones with homology to yeast Pol, the largest being 2.8 kb. Repeated rounds of 5'-rapid amplification of cDNA ends were used to complete cloning of the PolγCAT cDNA. The composite sequence proved identical to that of the human PolγCAT cDNA which was independently isolated and reported by Ropp and Copeland (5). A partial rabbit PolγCAT cDNA was cloned to provide a species-specific probe for analysis of PolγCAT mRNA in rabbit tissues. Comparison of mouse and human PolγCAT cDNA sequences revealed a region of high conservation at the nucleotide level from position 3257 to 3733 within the human cDNA sequence. Primers matching the mouse sequence were used to amplify a 476-base pair product from rabbit mRNA which was cloned and sequenced. This region harbors 92% identity to the human nucleotide sequence.

**Animals and Tissues**—Eighteen New Zealand White rabbits were purchased from Myrtle's Rabbity (Thompson Station, TN). The common peroneal nerve was stimulated continuously at 6–10 Hz as described previously (13). Animals were sacrificed after 1, 3, 7, 14, or 21 days of stimulation (n = 3 at each time point), and tibialis anterior (TA) muscles were harvested and stimulated hindlimbs were frozen in liquid nitrogen and stored at −70 °C. From control animals, the TA, soleus, gastrocnemius, plantaris, and extensor digitorum longus were removed and stored in a similar manner. Pregnant mice (strain ICR) were purchased from Harlan Sprague Dawley, Inc. Litter sizes ranged from 8–12 pups. Littermates were sacrificed on day 1, day 5, day 10, day 15, and day 20 post-partum, and as adults (n = 4–6 at each time point). Tissues described in the hearts were removed, frozen in liquid nitrogen, and stored at −70 °C. All animal protocols were reviewed and approved by the Institutional Animal Care and Research Advisory Committee and were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

**Analysis of Muscle RNA and DNA**—Muscle and skin were harvested from stimulated and unstimulated hindlimbs of mice and Northern and Southern DNA samples were prepared and used by standard procedures. DNA samples were restricted with HindIII (rabbit DNA) or EcoRI (mouse DNA) to permit unambiguous identification of mtDNA. mRNA samples prepared from specific human tissues were obtained from a commercial source (CLONTECH). Species-specific radiolabeled probes were prepared by PCR or by extension of random hexamer oligonucleotides using mtSSB cDNA, PolγCAT cDNA, glyceroldehyde-3-phosphate dehydrogenase (GAPDH), 28 S ribosomal RNA, mtDNA, or a chromosome 15 marker, D15S10, as the template.

**Production of a Polyclonal Antibody against the Rat mtSSB Protein**—A 409-base pair fragment of the rat mtSSB cDNA, corresponding to the full-length mature protein, was obtained through PCR using a rat mtSSB full-length cDNA as the template. NoI and EcoRI restriction sites were engineered into the 5' and 3' ends of the cDNA, respectively, and the fragment was subcloned into the expression vector, pGEX-CS (14). Induction of transformants with 0.1 mM isopropyl-1-thio-β-D-galactopyranoside-generated recombinant rat mtSSB fused to glutathione S-transferase (GST). The purification procedure included affinity chromatography using glutathione-agarose beads (Sigma), followed by incubation with tobacco etch virus protease (Life Technologies, Inc.) to release mtSSB from the resin-bound GST moiety. The supernatant was concentrated with a Centriprep unit (Amicon), and mtSSB was purified to apparent homogeneity by preparative electrophoresis on a 15% sodium dodecyl sulfate-polyacrylamide gel using the Prep-Cell (Bio-Rad). Purified antigen (100 μg) was mixed with an equal volume of Titer-Max adjuvant (Ridgway & Co.) and injected both intramuscularly and subcutaneously into a New Zealand White rabbit. Blood and serum samples were acquired by standard methods. The antisera was purified further by precipitation in 33% ammonium sulfate.

**Cell Culture and Histochemistry**—Murine C2C12 myogenic cells were propagated as described previously (15) and plated onto gelatin-coated coverslips and further cultured by the manufacturer's recommendations. The PCR primers for cloning rabbit mtSSB cDNA were: 1) 5'-AGGCCCTT-GCGGTCAAGAGA-3' and 2) 5'-TAGACTGTACATCATTTGAAAGG-3'. Amplification products were cloned and sequenced. The mouse and rabbit partial cDNAs (~200 nucleotides) exhibited 94% and 85% nucleotide sequence identity, respectively, with the published rat mtSSB sequence (9).

**RESULTS**

Expression of POLγCAT mRNA in Different Mammalian Tissues—Mammalian tissues differ markedly with respect to the abundance of mtDNA (2) and to expression of certain nuclear genes encoding mitochondrial proteins (4, 17). Northern analysis indicated that expression of POLγCAT mRNA in a variety of human tissues bears no apparent relationship to mitochondrial mass or mtDNA content. After normalization to an internal standard (GAPDH mRNA), expression of POLγCAT mRNA in heart differed by no more than 2-fold from levels observed in any other human tissue (pancreas, kidney, liver, lung, brain, colon, prostate, thymus, and spleen; data not shown). The expression of POLγCAT mRNA in mitochondria-rich cardiac tissue by comparison to lung is illustrated in Fig. 1A where the quantitative analysis revealed expression in the lung to be approximately 2-fold greater than that found in the heart. In rabbit TA muscles subjected to chronic stimulation via the motor nerve, a potent stimulus to mitochondrial biogenesis and mtDNA replication (3), there was no detectable induction of expression of POLγmRNA (Fig. 1B). The magnitude of the increase in mtDNA in this set of animals (3.5-fold at 10–21 days) was comparable with that observed previously in our laboratory (3, 13).

Expression of POLγCAT mRNA Is Influenced by Gene Dosage Without Changes in mtDNA—A Northern blot was performed

2 L. D. McDaniel and R. A. Schultz, unpublished observation.
with mRNA from normal control cell lines (SC-1, SMITO-1, and GM01604) and a line established from a patient expected to be triploid for the PolγCAT locus (SA15q-3). Expression of POLγ mRNA was elevated approximately 3-fold over that seen in the diploid control cell lines (Fig. 2A). Southern blots of DNA derived from control and SA15q-3 cell lines were probed with a fragment of the PolγCAT gene or with a sequence (D15S10) mapping to the proximal non-duplicated region of the chromosome. The results demonstrated a 9-kb HindIII PolγCAT band consistent with a 9,081-base pair size predicted from genomic sequencing of this region.2 Moreover, the results confirm that the PolγCAT locus is triploid in this cell line (Fig. 2B). Quantitation of the relative band intensities revealed an SA15q-3: control ratio for PolγCAT of 1.52 when normalized for the diploid marker D15S10. Southern blots probed with a fragment of human mtDNA encoding the cytochrome b gene demonstrated a 10-kb band, consistent with a size of 10,202 base pairs predicted from the human mtDNA sequence (18). A quantitative comparison of the relative intensities of the hybridization signals from SA15q-3 and control cells (Fig. 2B) was calculated at a ratio of 1.06, demonstrating that the increased expression of PolγCAT mRNA is not associated with a greater abundance of mtDNA in this cell line in which the PolγCAT locus is amplified.

Regulated Expression of mtSSB mRNA in Mammalian Tissues—Using rabbit mtSSB cDNA as the probe under conditions of high stringency, two transcripts with molecular weights of approximately 940 and 650 bases were detected in RNA extracted from rabbit muscles (Fig. 3A and B). The smaller of the two transcripts corresponds to the size of mtSSB mRNA described previously in rat and human cells (9) and to the single transcript observed in murine cells (Fig. 3C). Drosophila express two transcripts of 0.6 and 1.5 kb that hybridize to a mtSSB cDNA probe (19), and two isoforms of mtSSB have been described in Xenopus laevis (20), but this is the first demonstration of multiple mtSSB transcripts in a mammalian species. The relative abundance of the 650 base transcript correlated directly with the oxidative capacity, fractional volume of mitochondria, and mtDNA content (2) of individual striated muscles of this species (heart ≫ soleus ≫ plantaris ≫ gastrocnemius ≫ extensor digitorum longus = tibialis anterior (2)). The blot was stripped and reprobed with an end-labeled oligonucleotide complementary to 28S rRNA. B, changes in expression of mtSSB mRNA during the adaptive response to motor nerve stimulation of rabbit tibialis anterior skeletal muscles. C, changes in expression of mtSSB mRNA during post-natal development of the mouse heart.

The abundance of mtSSB mRNA, as compared with that of 28S rRNA, was up-regulated after only 1 day of chronic motor nerve stimulation of the rabbit tibialis anterior and increased further between 3 and 7 days of stimulation (Table I). Thus, significant changes in expression of mtSSB accompany activity-induced amplification of mitochondrial genomes in this model.

The mouse mtSSB cDNA probe detected only a single mRNA of 650 bases on Northern blots prepared with mouse cardiac RNA (Fig. 3C). The relative expression of this RNA species was
increased more than 3-fold within the first 10 days of post-natal life. Cardiac mtDNA concentrations increased more than 4-fold between day 5 and day 20 post-partum.

Subcellular Localization of mtSSB—In mammalian cells, replication of mtDNA takes place preferentially within a subset of mitochondria clustered within a perinuclear domain (12). We observed that mtSSB protein is not distributed uniformly within all mitochondria of murine C2C12 myogenic cells but is more abundant within perinuclear regions (Fig. 4). Mitochondria within cell processes more distant from the nucleus are devoid of mtSSB, at least at the level of detection of this immunofluorescent technique.

DISCUSSION

The principal observation of this study is that expression of nuclear genes encoding mitochondrial DNA replication factors in mammalian cells is regulated in a differential rather than a coordinated manner. Expression of mRNA encoding the catalytic subunit of POL\(_{\gamma}\) is constitutive among specialized tissues that differ markedly in their relative contents of mtDNA. Likewise, we could detect no appreciable up-regulation of POL\(_{\gamma}\) mRNA in skeletal muscles subjected to chronic motor nerve stimulation, a potent stimulus to mtDNA replication. Other investigators have noted constitutive expression of POL\(_{\gamma}\) mRNA and protein in human tumor cells depleted of mtDNA by exposure to ethidium bromide as compared with the parental cell line (22). Mammalian cells, therefore, appear to lack a feedback mechanism to respond to a deficiency of mtDNA by up-regulation of POL\(_{\gamma}\) gene expression.

In contrast, expression of mtSSB mRNA correlates directly with the abundance of mtDNA within specialized muscle subtypes. This relationship is consistent in three independent analyses: (a) the comparison of different striated muscles within adult animals, (b) the response of the rabbit tibialis anterior skeletal muscle to chronic motor nerve stimulation, and (c) post-natal development of the murine heart. We conclude that expression of the mtSSB gene, unlike the POL\(_{\gamma}\) gene, is regulated by developmental cues or physiological stimuli that promote changes in mitochondrial biogenesis. Preliminary immunoblot analyses\(^3\) indicate that mitochondria-rich striated muscles contain greater amounts of mtSSB protein, corresponding to the changes in mtSSB mRNA described in this paper. Moreover, we demonstrate here that mtSSB is preferentially localized to a perinuclear subset of mitochondria that are active sites for mtDNA replication (12).

How should these findings be interpreted with respect to the biochemical and molecular mechanisms that govern replication and maintenance of mtDNA in mammalian cells? Constitutive expression of the POL\(_{\gamma}\) gene in tissues with differing requirements for mtDNA replication suggests that, under physiological conditions, the enzymatic activity of POL\(_{\gamma}\) is not constrained by limited expression of this subunit. Indeed, in a previous study we observed an increased specific activity of POL\(_{\gamma}\) in mitochondria-rich muscle tissues (21) in comparison with glycolytic muscles that we now show to express a comparable abundance of POL\(_{\gamma}\) mRNA. We cannot exclude the possibility that the abundance of the catalytic subunit of POL\(_{\gamma}\) is regulated independently of changes in its mRNA through mechanisms that modify translational efficiency or stability of the protein. A more likely explanation, however, is that the availability of other mtDNA replication factors, and not POL\(_{\gamma}\), is rate-limiting to mtDNA replication. Our observation that the cellular content of mtDNA is not increased when the POL\(_{\gamma}\) gene is amplified and overexpressed supports this viewpoint.

The abundance of mtSSB could influence the cellular content of mtDNA in one of several ways. Since the activity of purified POL\(_{\gamma}\) is stimulated by mtSSB in vitro (10, 11), it is possible that expression of mtSSB likewise is rate-limiting to mtDNA replication in vivo. Alternatively, higher concentrations of mtSSB may increase the stability of mtDNA, particularly under conditions where partially replicated D-loop forms of the mitochondrial genome are abundant (21). The consistent correlation between expression of the mtSSB gene and the cellular content of mtDNA among different mammalian tissues supports the notion that increased intramitochondrial concentrations of mtSSB are required for, even if not the primary regu-

\(^3\) S. Swoap and R. S. Williams, unpublished results.

**Table I**

| Duration of stimulation | mtSSB mRNA | RNA yield | mtSSB mRNA |
|-------------------------|------------|-----------|------------|
|                         | AU/28 S rRNA | \(\mu g\) RNA/g | AU/mg |
| Control                 | 13 ± 3     | 247 ± 29  | 31 ± 7     |
| 1 days                  | 42 ± 10*   | 492 ± 39* | 208 ± 38*  |
| 3 days                  | 56 ± 13*   | 524 ± 103* | 296 ± 27*  |
| 7 days                  | 36 ± 2*    | 932 ± 47* | 333 ± 16*  |
| 14 days                 | 41 ± 10*   | 1384 ± 395* | 570 ± 208* |
| 21 days                 | 42 ± 2*    | 1789 ± 245* | 758 ± 71*  |

\[\text{S.E. (n = 3 at each time point). AU, arbitrary units based on densitometry of autoradiographs; asterisk, } p < 0.05 \text{ versus control.}\]

**Fig. 4. Subcellular distribution of mtSSB in cultured cells.** Confocal fluorescence microscopy for detection of mtSSB (green) and mitochondria (red) in murine C2C12 myogenic cells shows the selective localization of mtSSB in perinuclear mitochondria (yellow) within these cells and demonstrates the absence of mtSSB in peripherally located mitochondria (red, arrows) within cell processes.
latory determinant of, the greater abundance of mtDNA in cells faced with high physiological demands for mitochondrial respiration.

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