Expression of SFT (Stimulator of Fe Transport) Is Enhanced by Iron Chelation in HeLa Cells and by Hemochromatosis in Liver*

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SFT (stimulator of Fe transport) is a novel transport protein that has been found to facilitate uptake of iron presented to cells as either Fe(II) or Fe(III). When HeLa cells are exposed to the iron chelator desferrioxamine, levels of SFT mRNA increase in an actinomycin D-sensitive manner. In contrast, cells exposed to high levels of iron down-regulate SFT expression in a time-dependent and reversible fashion. Thus, homeostatic regulation of SFT expression not only ensures that sufficient levels of iron are maintained but also limits excessive assimilation to prevent potentially harmful effects of this toxic metal. The unexpected observation that SFT transcript levels are up-regulated in hemochromatosis patients therefore suggests that enhanced SFT expression contributes to the etiology of this iron overload disorder.

Transport of iron by microbes, plants, and animals is a tightly regulated process that is limited to prevent harmful effects due to overload of this toxic metal (for a comprehensive review of this field, please see Ref. 1). Iron is taken up by bacteria through direct ferrous import systems (e.g. Feo of Escherichia coli) as well as siderophore-based mechanisms. Iron-responsive gene transcription through the regulator Fur is largely responsible for the control of bacterial iron uptake (2). As reviewed by Eide (3) and Askwith and Kaplan (4), studies in yeast have further characterized the role of transport proteins (e.g. Fet4 and Ftr1), ferrireductases (e.g. Fre1 and Fre2), and oxidases (e.g. Fet3 and Fet5) in the membrane transport of iron and also have revealed iron-responsive transcriptional control involving the element Aft1. Like microbes and yeast, plants too display iron-regulated uptake (e.g. IRT1) (5). Finally, advances made through functional expression cloning have most recently identified two mammalian iron transport systems. DCT1/Nramp2 mediates Fe(II) uptake (6) and is thought to be important for iron assimilation by intestinal and erythroid cells, since defects in its gene promote microcytic anemia in the mk mouse (7) and Belgrade (b) rat (8). In contrast, SFT facilitates the import of nontransferrin-bound iron presented as Fe(II) or Fe(III) (9, 10). The latter appears to be first reduced in a copper-requiring process prior to SFT-mediated translocation of Fe(II) across the membrane bilayer (10). Gunshin et al. (6) have reported the presence of DCT1/Nramp2 message in rat intestine, kidney, thymus, and brain, with low levels detected in testis, liver, colon, heart, spleen, skeletal muscle, lung, bone marrow, and stomach. This profile appears to overlap with the appearance of SFT transcripts, which have been found in human intestine, spleen, thymus, prostate, testis, ovaries, and peripheral blood lymphocytes, with low levels observed for colon (9). However, while DCT1/Nramp2 transcripts are known to be increased in the intestine of iron-deficient animals (6), regulation of SFT expression in response to iron levels has yet to be characterized.

The critical need for iron transport regulation can be most readily recognized by the pathological consequences observed when control is lost in the human disease hemochromatosis. This genetic disorder promotes increased intestinal absorption and progressive tissue deposition of iron resulting in cirrhosis of the liver, hepatic carcinoma, congestive heart failure, endocrinopathies, and premature death. The recent elucidation of the gene for this disease led to the discovery that defects in a nonclassical major histocompatibility complex (MHC) class I protein, HFE, are responsible for the iron overload exhibited by patients (11). Although the mechanistic basis for the disease remains obscure, the fact that β₂-microglobulin knockout mice display characteristics of iron overload associated with hemochromatosis patients confirms the relationship of an HMC class I-like molecule with iron metabolism (12, 13). It is estimated that 1 in 10–20 individuals carry the defective HFE allele and that 1 in 200–400 Caucasians are homozygous for the disease; thus, it is the most common defective genetic trait known in humans, more prevalent than cystic fibrosis, phenylketonuria, and muscular dystrophy combined. The recent confirmation of its prevalence has prompted some to refer to hemochromatosis as “the genetic disorder of the 21st century” (14).

We have investigated control of SFT expression by iron levels and as shown by the results presented here, we observe that iron chelation enhances accumulation of SFT transcripts and that SFT protein and message levels both decline when cells are exposed to high iron. Remarkably, however, we find that SFT mRNA is significantly higher in liver from hemochromatosis patients despite massive iron deposition within this tissue. Because mucosal uptake of Fe(III), but not Fe(II), is stimulated in the β₂-microglobulin knockout mouse (15), it is likely that a ferrireductase, an Fe(II)/Fe(III) transporter, or a complex contributing both functions is up-regulated when HFE function is compromised. Thus, our findings suggest that up-regulated expression of the Fe(II)/Fe(III) transporter SFT may contribute to the etiology of hemochromatosis.

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Experimental Procedures

HeLa cells were grown in Dulbecco’s modified Eagle’s medium supplemented with 300 g/liter 1-glutamine, 10% fetal bovine serum, 50 units/ml penicillin, and 50 μg/ml streptomycin as detailed previously (10). HepG2 cells, obtained from American Type Tissue Collection (Manassas, MD), were grown in α-minimal essential medium containing 10% fetal bovine serum, 50 units/ml penicillin, and 50 μg/ml streptomycin. Cells were subcloned with addition of 65 μM Fe-NTA (1:1) to the culture medium for the times shown. These conditions are not necessarily selective for nontransferrin-bound iron uptake, but transferrin-independent iron transport has been demonstrated in studies employing Fe-NTA (16–18), as well as Fe-citrinate (18, 19), Fe-acetate (19–23), and Fe-dithylthreitolaminepentacetic acid (24). Fe-NTA was chosen for this investigation, because NTA is membrane-impermeable and provides a stably chelated form of Fe(III); others have shown a 4-fold increase in cellular iron content under these experimental conditions (25). This level of Fe-NTA (65 μM) had no apparent toxicity based on cell viability and growth. Although confluent cells down-regulate SFT expression in response to iron, the extent of down-regulation is greater in dividing cells and therefore all results shown are from experiments performed on subconfluent cultures except where noted. Tissue from hemochromatosis patients and control individuals was obtained from the NIH-funded Liver Tissue Procurement and Distribution System directed by Dr. Harvey Sharp (Fairview University Hospitals and Clinics, Minneapolis, MN).

Total cellular RNA was isolated using RNAzol B according to the manufacturer’s direction (Tel-test, Friendswood, TX). For Northern analyses, the samples were electrophoresed on denaturing formaldehyde-agarose gels, transferred to Nitran (Schleicher & Schuell), UV-crosslinked, then probed with randomly primed 32P-labeled SFT cDNA under high stringency conditions. Blots were washed twice with 6 × SSPE (1 × SSPE: 0.18 mM sodium chloride, 10 mM sodium phosphate, 1 mM EDTA) containing 0.5% SDS at room temperature, twice with 1 × SSPE containing 0.25% SDS at 37 °C, followed by a final wash in 0.1 × SSPE containing 1% SDS for 30 min at 65 °C. Blots were exposed to film 5–14 days for autoradiography. Ribonuclease protection assays utilized a cDNA fragment of SFT containing the entire 3′-non-coding region (9) subcloned into pBSK(−) (Stratagene, La Jolla, CA) such that complete digestion could be verified by the difference in electrophoretic mobility of the protected fragment. Twenty μg of total RNA was hybridized to this probe (5 × 106 cpm) for 16 h at 50 °C. Nonhybridized probe was digested with a combination of ribonuclease A (40 μg/ml) and ribonuclease T1 (2 μg/ml) for 60 min at 30 °C; nucleases were subsequently digested with proteinase K (125 μg/ml) at 37 °C for 15 min. After phenol/chloroform extraction, the hybridized probes were precipitated with ethanol and heat-denatured at 85 °C for 5 min prior to electrophoresis on a 6% polyacrylamide-8 M urea gel. The gel was then dried and exposed to film for autoradiography. Molecular biology reagents were obtained from Boehringer Mannheim and U. S. Biochemical Corp. The data shown are from individual experiments and represent results obtained on multiple occasions under various experimental conditions for the different cell lines and tissue specimens.

Results and Discussion

To investigate regulation of SFT expression, Northern analysis was performed with total RNA from HeLa cells grown under low, normal, and high iron conditions (Fig. 1). Treatment with the iron chelator desferrioxamine to deplete cellular iron increases SFT transcript levels, while iron-loading induces down-regulation. As shown in Fig. 2A (top panel), SFT transcript levels were barely detectable in control HeLa cells 16 h after the addition of 65 μM Fe-NTA to culture in medium supplemented with 65 μM Fe-NTA. Western analysis confirms the loss of SFT synthesis over precisely the same time frame (Fig. 2B), indicating that levels of the transport protein closely correlate with the amount of its transcript. Down-regulation of SFT message in response to high iron is completely reversible, and basal levels are restored when HeLa cells are returned to normal culture conditions (data not shown; see below).

Transferrin receptor synthesis also is down-regulated in response to iron-loading. When cellular iron content is low, the binding of iron-responsive regulatory protein (IRP) to iron-responsive elements (IREs) present in the 3′-untranslated region protects the receptor message against degradation. The loss of IRP mRNA binding activity under high iron conditions leads to destabilization and transcript decay (26). Under our experimental conditions, loss of transferrin receptor mRNA upon iron-loading is significantly slower than the time course observed for SFT mRNA reduction (Fig. 2A), suggesting that the latter is regulated via different mechanisms.

HeLa cells were exposed to desferrioxamine in the presence or absence of actinomycin D to study the effects of the transcription inhibitor on the accumulation of SFT mRNA. As shown in Fig. 3, the SFT message is significantly reduced in both control and desferrioxamine-treated cells upon treatment with this drug, indicating that the transcript half-life is <16 h. Time course experiments revealed a t1/2 of ~6 h for SFT mRNA isolated from cells treated with or without desferrioxamine, confirming no significant change in decay rate upon iron chelation (not shown). Although desferrioxamine-induced up-regulation of SFT mRNA levels appears to be sensitive to actinomycin D, it is important to note that our data do not directly discriminate between transcriptional and post-transcriptional events mediating SFT down-regulation under high iron conditions. However, because the IRE hexanucleotide consensus sequence, which contributes to a stem-loop structure recognized by IRPs, does not appear within the 3′-untranslated region of SFT (9), it is unlikely that modulation of SFT synthesis involves stabilization of its message through IRP-controlled mechanisms.

Hemochromatosis is the common genetic disorder known and results in massive iron deposition in the parenchyma of liver, kidney, pancreas, and other tissues (11, 14). Because of the functional role in iron transport implicated for SFT and the observed iron-dependent regulation of its expression, it was of interest to study levels of SFT in liver from hemochromatosis patients. Based on the results discussed above, a prediction would be that SFT transcripts are down-regulated in the disease state. Unexpectedly, ribonuclease pro-

FIG. 1. SFT transcript levels are modulated in response to cellular iron content. Northern blot analysis of total RNA (50 μg/lane) isolated from control HeLa cells, cells grown in medium supplemented with 65 μM Fe-NTA for 16 days, and cells treated with 50 μM desferrioxamine overnight. Briefly, RNA was isolated, electrophoresed on denaturing formaldehyde-agarose gels, and transferred as described under “Experimental Procedures.” Randomly primed probes were hybridized overnight at 42 °C in 50% formamide containing 5 × Denhardt’s solution; the blot was then washed twice with 6 × SSPE-0.5% SDS for 15 min at room temperature, twice in 6 × SSPE-0.2% SDS at 37 °C, then once in 0.1 × SSPE-0.1% SDS for 30 min at 65 °C. Shown are the autoradiographic results obtained for 32P-labeled probes using SFT or 36B4 cDNA as templates for random priming; the latter ribosomal protein is expressed constitutively and confirms equivalent loading in all lanes. In addition to the native 1.5-kilobase message observed for SFT, a 2.4-kilobase band is detected as reported previously (9). Levels of the latter are not regulated by iron depletion or iron loading, although the cross-hybridization of this species with the SFT probe suggests homology between these two transcripts.
Expression of SFT

Fig. 2. SFT and transferrin receptors are down-regulated in response to iron-loading. A, Northern analysis of total RNA (50 μg/lane) as described for Fig. 1 is presented to demonstrate the time course of down-regulation of SFT transcripts compared with transferrin receptor message (TfR) in HeLa cells. At time 0, culture medium was supplemented with 65 μM Fe-NTA, and cells were grown for the times shown prior to RNA isolation. Detection of transferrin receptor transcripts was as described previously (36). B, Western analysis of membrane protein from HeLa cells exposed to 65 μM Fe-NTA for the times shown (0–72 h). Briefly, confluent cells from a 100-mm dish were harvested in phosphate-buffered saline containing 1 mM EDTA, then washed three times with ice-cold phosphate-buffered saline and suspended in 25 mM HEPES, pH 7.4, 85 mM sucrose, 100 mM KCl, and 20 mM EGTA. After disruption of the cells by repeated freeze/thaw, post-nuclear supernatants were collected and membrane was then isolated by ultracentrifugation with a Sorval RP100AT3 rotor at 95,000 rpm for 7–10 h. Protein pellets were suspended in 25 mM HEPES, pH 7.4, 85 mM sucrose, 100 mM KCl, and 20 mM EGTA, and suspensions were boiled for 5 min. One-hundred μg of membrane protein was loaded in each lane and electrophoresed on a 6% polyacrylamide gel under non-reducing conditions. After transfer to nitrocellulose, the blot was blocked, washed, and cut to probe with anti-SFT 4 subunit antisera (1:200 dilution) and -Na,K-ATPase antisera (1:5000) as indicated in the figure. Following incubation with secondary antibody conjugated with horseradish peroxidase (1:2000), the staining pattern shown was developed by enhanced chemiluminescence (ECL) according to the manufacturer’s directions (Amersham Pharmacia Biotech). The anti-LA antisera has been characterized previously (9). The anti-Na,K-ATPase antisera, which is specific for the α-subunit, was a generous gift of Dr. Lorraine Santy (Harvard). The latter can be detected as a broad band on nonreducing gels, but aggregates under reducing conditions. For this experiment, detection of the α-subunit serves as a sample-loading control for each gel lane.

Fig. 3. Actinomycin D blocks up-regulation of SFT in response to iron chelation. Northern analysis of total RNA (50 μg/lane) for HeLa cells treated overnight with or without 50 μM desferrioxamine in the presence or absence of 1 μg/ml actinomycin D. Equivalent loading was confirmed visually by ethidium bromide staining prior to hybridization.

SFT protein in patient liver as well (not shown). One explanation for these observations is that liver cells differentially regulate SFT expression, and to examine this possibility, the properties of SFT expression in HepG2 cells were investigated. This well differentiated human hepatoma cell line synthesizes transferrin, expresses the transferrin receptor, and distributes iron between intracellular pools in a manner similar to liver. Nonetheless, ribonuclease protection experiments confirm the loss of SFT transcripts when HepG2 cells are grown in medium supplemented with 65 μM Fe-NTA for 4 days (Fig. 4, lane 11 versus lane 12). This effect is entirely reversible: basal levels of SFT are observed in cells cultured in high iron medium for 4 days, then returned to normal medium for 4 days (lane 13), cells grown in normal medium for 4 days and then grown in medium supplemented with 65 μM Fe-NTA for 4 days (lane 14). To quantitate differences between patient and controls, bands were excised, and counts/min were measured by scintillation counting. After correction for background, the control group yielded values (+S.D.) for the protected fragment of 74 ± 11.2 cpm, while patient values (+S.D.) were measured to be 369 ± 67.9 cpm.

Fig. 4. Expression of SFT in patients with hemochromatosis, control individuals, and HepG2 cells. RNase protection analysis was performed as detailed under “Experimental Procedures” using 5 × 106 cpm of 32P-labeled transcripts. Shown are assays to compare the extent of RNase protection obtained upon hybridization with 20 μg of total RNA isolated from liver of patients diagnosed with hemochromatosis (lanes 1-6) and for control individuals (normal tissue pathology reported) (lanes 7-10). The control lane indicates extent of digestion without addition of sample RNA and probe lane indicates initial size of the 32P-labeled in vitro transcripts used for these assays (300 cpm loaded onto gel). Also shown are results obtained for 20 μg of total RNA isolated from HepG2 cells cultured under the following matched experimental conditions: no treatment (lane 11), cells exposed to 65 μM Fe-NTA for 8 days (lane 12), cells grown in medium supplemented with 65 μM Fe-NTA for 4 days and then returned to normal medium for 4 days (lane 13), cells grown in normal medium for 4 days and then grown in medium supplemented with 65 μM Fe-NTA for 4 days (lane 14). To quantify differences between patient and controls, bands were excised, and counts/min were measured by scintillation counting. After correction for background, the control group yielded values (+S.D.) for the protected fragment of 74 ± 11.2 cpm, while patient values (+S.D.) were measured to be 369 ± 67.9 cpm.
sibility that up-regulation of SFT message levels is indicative of a specific liver detoxification response that is necessary for the clearance of excess iron incorporated due to enhanced dietary absorption. Unfortunately, the recent elucidation of the disease gene, HFE, yields little insight about how the reciprocal relationship between storage and transport of iron is lost in hemochromatosis. HFE is an MHC class I-like molecule that appears to be expressed in nearly all tissues (11); the defective allele contains a mutation that alters Cys282 such that newly synthesized protein can not stably associate with β2-microglobulin for appropriate assembly and function (29, 30). Consistent with the loss of HFE function, the β2-microglobulin knockout mouse displays characteristics of iron overload resembling the human disease (12, 13) as well as those described for the HFE knockout mouse (31).

It is known that HFE associates with the transferrin receptor (32, 33), and a role for the receptor in HFE trafficking has been suggested (34). Gross et al. (34) further found that cells overexpressing HFE have increased levels of transferrin receptors but reduced levels of ferritin, supporting the idea that HFE modulates the level of iron within the cell. However, whether the absence of this factor alters expression of iron transport and storage factors or whether SFT expression is directly modulated by HFE remains unknown. Duodenal samples from hemochromatosis patients do display greater Fe(III) reducing and uptake activity compared with controls (35). 

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