Regulation of Reticuloendothelial Iron Transporter MTP1 (Slc11a3) by Inflammation*

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Acute and chronic inflammation cause many changes in total body iron metabolism including the sequestration of iron in phagocytic cells of the reticuloendothelial system. This change in iron metabolism contributes to the development of the anemia of inflammation. MTP1, the duodenal enterocyte basolateral iron exporter, is also expressed in the cells of the reticuloendothelial system (RES) and is likely to be involved in iron recycling of these cells. In this study, we use a lipopolysaccharide model of the acute inflammation in the mouse and demonstrate that MTP1 expression in RES cells of the spleen, liver, and bone marrow is down-regulated by inflammation. The down-regulation of splenic expression of MTP1 by inflammation was also observed in a Leishmania donovani model of chronic infection. The response of MTP1 to lipopolysaccharide (LPS) requires signaling through the LPS receptor, Toll-like receptor 4 (TLR4). In mice lacking TLR4, MTP1 expression is not altered in response to LPS. In addition, mice lacking tumor necrosis factor receptor 1α respond appropriately to LPS with down-regulation of MTP1, despite hypersensitivity to tumor necrosis factor-α signaling, suggesting that this cytokine may not be required for the LPS effect. We hypothesize that the iron sequestration in the RES system that accompanies inflammation is because of down-regulation of MTP1.

Iron is an essential nutrient for growth and development of eucaryotes and most prokaryote species. A normal individual will absorb ~1 mg of elemental iron a day through the duodenum, to match an equivalent daily physiologic loss. The plasma turnover of iron is ~10–20 mg a day and one source of this pool is iron released from the reticuloendothelial system (RES).1 Macrophages of the RES release iron from phagocytosed erythrocytes and return it to the circulation for reuse by the erythroid compartment of the body. Difficulties in environmental iron acquisition limit the growth of microorganisms and some of the major virulence factors associated with bacterial infections are genes encoding more efficient means for acquiring iron from the host. One defense against invading microorganisms involves the sequestration of iron in body compartments not readily accessible to these invaders. The acute phase response to infection is characterized by a number of changes in iron metabolism including acute declines in serum iron, increases in the rate of serum iron disappearance, a decline in serum iron turnover, sequestration of the metal in the RES, and a decline in intestinal iron absorption (reviewed in Refs. 1 and 2). Chronic inflammatory states are also characterized by low serum iron levels, RES iron sequestration, and anemia (3, 4, 5). A number of cytokines including interleukin 1 (IL-1) (6–11), tumor necrosis factor-α (TNF-α) (11–14), and IL-6 (16–18) have been demonstrated to be potentially involved in changes in iron metabolism in animal and human models of acute and chronic inflammation.

During inflammation serum iron levels drop secondary to an increase in the rate of iron clearance from plasma, a decrease in iron mobilization from the RES compartment (the so-called iron exit block) (19–25), and a decrease in iron absorption (23, 26–28). The recent identification and characterization of the duodenal epithelial cell basolateral iron exporter solute carrier family 11a member 3 (SLC11a3), also known as IREG1 (29), ferroportin 1 (30), MTP1 (31) as an iron-regulated protein that is also expressed in the RES, has led to the hypothesis that MTP1 may be the protein responsible for iron export from this compartment. There is ample evidence that MTP1 exports iron from cells. Overexpression of MTP1, by transient transfection, in tissue culture cells has been demonstrated to result in depletion of intracellular ferritin and cytosolic iron levels (31) and MTP1 expression in frog oocytes results in measurable iron efflux (29, 30). In this paper we report that MTP1 expression in the cells of the RES is regulated by acute inflammation. This inflammation-mediated control of MTP1 expression in the RES may be one component responsible for iron sequestration in the RES in both acute and chronic inflammatory states.

** Experimental Procedures

Materials—Lipopolysaccharide (LPS), from Escherichia coli serotype 055:B5, iron-dextran, and pyrrolidinedithiocarbamate (PDTC) were purchased from Sigma and resuspended in saline. Recombinant tumor necrosis factor-α were obtained from PeproTech (Rocky Hill, NJ). Rat anti-mouse F4/80 antigen antibody was obtained from Serotec (Raleigh, NC). The production of the rabbit anti-MTP1 polyclonal antibody has been previously described (31). Alexa dye-conjugated goat anti-rat and anti-mouse F4/80 antigen antibody was obtained from Serotec (Raleigh, NC). The production of the rabbit anti-MTP1 polyclonal antibody has been previously described (31). Alexa dye-conjugated goat anti-rat and goat anti-rabbit antibodies were purchased from Molecular Probes (Eugene, OR). Goat anti-rat/mouse TNF-α was from Calbiochem (La Jolla, CA). For in vivo work anti-TNF-α (clone MP3-XT6) was from Pharmingen (San Diego, CA).

Mice—Unless otherwise indicated C57/BL6 mice aged 8–12 weeks of either sex were used for the experiments described. LPS, PDTC, and all
cytokines were prepared in a 100-μl volume of saline and given intra-
peritoneally. Iron-dextran was given in 50–100 μl of saline in two
thigh muscles. Turpentine was administered to anaesthetized animals
as a 50–100 μl subcutaneous injection into the back between the scap-
ulas. Unless noted otherwise, a minimum of 4 animals were used per
experimental condition. Low iron mouse chow was purchased from
Harlan Sprague-Dawley (Indianapolis, IN).

Experimental Infection—Six-week-old male BALB/c mice were
infected intravenously with 1 × 10⁶ Leishmania donovani (MHOM/S.D./
001S-2D) amastigotes in Hanks’ balanced salt solution as previously
described (32). Age-matched control mice received the same volume
of Hanks’ balanced salt solution by the same route of inoculation. At 56
days post-infection, mice were killed and the spleen sections were
prepared in paraffin and paraffin-embedded mouse organ sections using an affinity purified rab-
bit anti-MTP1 polyclonal antibody using the Envision + (Dako Corp.,
Carpenteria, CA) staining kit with Vector VIP or AEC as chromogen
(Vector Laboratories, Burlingame, CA) as described previously (31).

Immunohistochemistry—Immunohistochemistry was performed on
paraffin-embedded mouse organ sections using an affinity purified rab-
bit anti-MTP1 polyclonal antibody using the Envision + (Dako Corp.,
Carpenteria, CA) staining kit with Vector VIP or AEC as chromogen
(Vector Laboratories, Burlingame, CA) as described previously (31).

Immunofluorescence was performed using the affinity purified rabbit
anti-MTP1 polyclonal antibody at 4 μg/ml, and a rat anti-mouse F4/80
antigen antibody (Serotec, Raleigh, NC) at 1:20. Secondary reagents
were Alexa 488-labeled goat anti-rabbit IgG antibody and Alexa 594
goat anti-rat IgG antibody at 1:500 dilution. Sections used for immu-
nofluorescence were fixed with a 50:50 mixture of acetone and methanol
for 20 min at −20 °C. Pictures were obtained on color slide film using an
Olympus BX-60 fluorescence microscope.

Western Blotting—Liver and spleen lysates were prepared by homog-
enization of tissue in phosphate-buffered saline supplemented with
0.5% Triton X-100, 5 mM EDTA, 0.1 mg/ml 4-(2-aminoethyl)benzene-
Olympus BX-60 fluorescence microscope.

PDTC was added at a concentration of 100 μM and a goat anti-rat/
mouse TNF-α antibody at 1:500 dilution. Sections used for immu-
nofluorescence of the Kupffer cells co-localized to the
surface of hepatocytes and in Kupffer cells. The MTP1
expression was based on standard curves prepared from serially diluted mouse mast cell cDNA.

The following sense and antisense sequences were employed: mouse
MTP1, sense, CTACCATTAGAAGGTGACCGCTA, antisense, ACTGGAGAAGCAATGTGATACTG; mouse GAPDH, sense, CAGCTCCGGTGTTCCTA, antisense, TGT CATCATCTGGCAGCT-GT-TCT.

RESULTS

MTP1 Is Expressed in Spleenic, Liver, and Bone Marrow Macrophage Cells—Previous work had indicated that MTP1 is
primarily expressed in the Kupffer cells of the liver and red pul-
ple of the spleen and had a distribution similar to that seen
with the F4/80, a macrophage-specific cell surface antigen (31).
The identification of MTP1 staining cells in the spleen, liver,
and bone marrow as macrophages was confirmed by two-color
double immunofluorescence staining using antibodies to MTP1
and F4/80 antigen in frozen liver, spleen, and bone marrow cell
sections (Fig. 1). In the red pulp of the spleen, there was great
overlap between distribution of MTP1 and F4/80 staining cells.
Interestingly, there were F4/80 positive cells in the white pulp
of the spleen that do not stain with the MTP1 antibody, indic-
ating that not all macrophages express MTP1. In the liver, as
reported previously, MTP1 immunostaining was apparent on
the surface of hepatocytes and in Kupffer cells. The MTP1
immunofluorescence of the Kupffer cells co-localized to the
immunostaining with the F4/80 antigen. In bone marrow cell
cytosins, there were many MTP1 positive cells, and immunostain-
ing also co-localized with F4/80 in most of the cells.

Inflammation Results in Down-regulation of MTP1 Expression
in the Reticuloendothelial Cells—A murine LPS model of the acute phase reaction was used to examine the connection
between MTP1 expression in the RES compartment of the body
and inflammation. Experimental mice were treated with 100 μg of LPS and changes in MTP1 expression were assessed
16–18 h later (Fig. 2A). Immunohistochemical staining using an anti-MTP1 antibody of sections of spleen from LPS-treated

![FIG. 1. MTP1 co-localizes with macrophage marker F4/80. Sections of frozen mouse spleen (first row), frozen liver (second row), and bone marrow cell cytosin (third row) were stained with antibodies against MTP1 and F4/80 as indicated. Secondary reagents were Alexa 488-conjugated goat anti-rabbit and Alexa 594 goat-conjugated anti-rat secondary antibodies. Photographs were taken using appropriate green and red filters. Photographs illustrating merging of red and green fluorescence were done by double exposure. Arrows indicate F4/80 positive but MTP1 negative cells. Original magnification was ×200–400.](image-url)
mice demonstrated diminished MTP1 staining of spleen macrophages compared with control mice. To study the response of Kupffer cell MTP1 expression to LPS administration, mice were treated with 1–2 mg of iron-dextran to induce Kupffer cell MTP1 expression (31) and 7–10 days later treated with LPS. In iron-treated mice, LPS injection resulted in down-regulation of MTP1 in the Kupffer cells. Additionally, MTP1 was also down-regulated in bone marrow cells with LPS treatment. Last, duodenal MTP1 expression was induced with feeding of a low iron diet to mice and subsequent LPS administration to these iron-deficient mice also resulted in down-regulation of duodenal MTP1 expression compared with controls.

The regulation of MTP1 in the spleen in a mouse model of a more chronic infectious disease was examined. The spleens of mice infected with *L. donovani* for 8 weeks were examined for MTP1 expression by immunohistochemistry using paraffin-embedded tissue and the anti-MTP1 antibody. Infected mice demonstrated diminished MTP1 staining in the spleen in comparison to control mice (Fig. 2B). Tissues from two infected and two control animals were examined. These data demonstrate that MTP1 was also down-regulated in a more chronic inflammatory state induced by an infection.

Western blotting of liver and spleen samples from LPS-treated and control mice confirmed the decreased tissue expression of MTP1 secondary to LPS administration (Fig. 3). The down-regulation of MTP1 expression by LPS was apparent in Western blots of immunoprecipitated MTP1 from spleen (Fig. 3, left panel) and liver lysates (Fig. 3, right panel). In most, but not all experiments at least two or more distinct bands were apparent in the immunoblots of spleen and liver lysates. The first was a smear occurring at 60,000–65,000 and the second was of higher molecular weight appearing at 110,000–130,000. The appearance of the 60,000–65,000 and the higher molecular weight bands were specific to immunoprecipitation with the anti-MTP1 antibody and blotting with the anti-MTP1 antibody. The peptide used to purify the anti-MTP1 antisera blocked the appearance of the bands. The higher molecular weight bands were present in most experiments and the ratio of these bands to the 60,000–65,000-band varied from experiment to experiment. The 60–65-kDa-band is most likely MTP1.

Preliminary data indicates that the larger bands do not represent either glycosylation or ubiquitination intermediates of MTP1. Anti-ubiquitin antibodies do not recognize the higher molecular weight bands by Western blotting and treatment with N-linked carbohydrate endoglycosidases does not alter the mobility of these higher molecular weight bands (data not shown). The larger bands probably represent a fraction of MTP1 that is modified, aggregated, or exhibits an aberrant migration.

In LPS-treated mice, hypoferremia was induced more rapidly than changes in splenic MTP1 protein expression. Serum iron was diminished as early as 2 h after LPS administration (Fig. 4A); whereas, there was no change in MTP1 expression at this time point (Fig. 4B). Diminished MTP1 expression was noted at 6 h after LPS administration and this decline persisted as long as 72 h (data not shown). These data indicate that the early hypoferremia because of LPS administration precedes MTP1 protein down-regulation and is not likely to be caused by changes in MTP1 expression. Other mechanisms, such as an increased clearance of blood iron may be more important in the development of the initial hypoferremia.

**Fig. 2.** Down-regulation of MTP1 in mouse spleen, liver, and duodenum is induced by LPS administration and chronic infection. A, immunohistochemistry using the anti-MTP1 antibody was performed as outlined above on paraffin-embedded tissue sections of spleen, liver, bone marrow, and duodenum of mice treated with 100 µg of LPS 18 h prior to sacrifice. Mice used for liver immunohistochemistry staining were treated with an intramuscular injection of 1 mg of iron-dextran 1 week prior to LPS treatment. Mice used for duodenal sections were given an iron-free diet for the month preceding LPS injection. B, paraffin-embedded spleens of mice infected with *L. donovani* and control animals were analyzed for MTP1 content by immunohistochemistry using an anti-MTP1 antibody.

**Fig. 3.** Immunoblot analysis of MTP1 protein expression in LPS-treated mouse spleen and liver. Representative immunoprecipitation followed by immunoblotting using an anti-MTP1 antibody of spleen (left panel) and liver lysates (right panel) prepared from control and LPS-treated mice was done as described. The band on the gel at 45–50 kDa is IgG heavy chain. Data shown is for two mice for each condition.

Toll-like Receptor 4 Signaling Is Required for MTP1 Down-regulation by LPS—Mice lacking a functional LPS receptor, the Toll-like receptor 4 (TLR4), such as the C3H/HeJ mouse strain are resistant to the lethal effects of LPS and fail to mount an acute phase response to LPS challenge and do not demonstrate a decline in serum iron (33, 34). Although C3H/HeJ mice are resistant to induction of the acute phase response with LPS, they are known to be sensitive to other inflammatory mediators. We examined the response of splenic MTP1 to LPS in the C3H/HeJ mouse strain (Fig. 5). LPS-mediated down-regulation of MTP1 in the spleen was abrogated in the C3H/HeJ compared with the LPS-sensitive C3H/HeJ-FeB strain. A turpentine injection model of acute inflammation (23, 27, 35) was used to determine whether MTP1 down-regulation was specific for TLR4 or could be achieved by other stimuli in the C3H/HeJ mice. Turpentine injection of C3H/HeJ mice results in sterile inflammation and the response has been associated with a decline in serum iron and induction of the acute phase response (33, 34). C3H/HeJ mice treated with turpentine demonstrated marked down-regulation of MTP1 expression in the spleen compared with untreated controls. These results indicate that inflammatory stimuli other than LPS can induce down-regulation of MTP1 in the spleen by a non-TLR4 dependent mechanism.

**TNF-α Does Not Induce MTP1 Down-regulation in the Spleen**—Many of the acute effects of LPS are mediated by induction of expression of proinflammatory cytokines such as TNF-α, interferon-γ, IL-6, and IL-1. The response of MTP1 in

**FIG. 3.** Immunoblot analysis of MTP1 protein expression in LPS-treated mouse spleen and liver. Representative immunoprecipitation followed by immunoblotting using an anti-MTP1 antibody of spleen (left panel) and liver lysates (right panel) prepared from control and LPS-treated mice was done as described. The band on the gel at 45–50 kDa is IgG heavy chain. Data shown is for two mice for each condition.

**A** Spleen Liver Bone Marrow Duodenum

**B** Control L. Donovani

**FIG. 2.** Down-regulation of MTP1 in mouse spleen, liver, and duodenum is induced by LPS administration and chronic infection. A, immunohistochemistry using the anti-MTP1 antibody was performed as outlined above on paraffin-embedded tissue sections of spleen, liver, bone marrow, and duodenum of mice treated with 100 µg of LPS 18 h prior to sacrifice. Mice used for liver immunohistochemistry staining were treated with an intramuscular injection of 1 mg of iron-dextran 1 week prior to LPS treatment. Mice used for duodenal sections were given an iron-free diet for the month preceding LPS injection. B, paraffin-embedded spleens of mice infected with *L. donovani* and control animals were analyzed for MTP1 content by immunohistochemistry using an anti-MTP1 antibody.
spleens was assessed in C57Bl6 mice administered TNF-α. Intraperitoneal injection of mice with 1 μg of rTNF-α had no effect on MTP1 expression assessed by IHC on spleen sections using an anti-MTP1 antibody (Fig. 6). In addition, the response of MTP1 in the spleen to LPS was assessed in B6.129-Tnfrsf1α<sup>tm1Mak</sup> mice, which lack expression of TNF-α receptor type 1a and are hyporesponsive to TNF-α stimulation (36). The mice that were treated with LPS and a neutralizing anti-TNF-α antibody responded to LPS by down-regulation of splenic MTP1 indicating that TNF-α stimulation is not required for this effect (Fig. 6). Furthermore, administration of PDTC, a well-characterized inhibitor of NF-κB activation and TNF-α production (37), to mice prior to treatment with LPS did not alter the change in MTP1 expression induced by LPS (data not shown).

**MTP1 mRNA in Adherent Spleen Cell Fractions Is Down-regulated by LPS in Vitro**—To determine the mechanism of regulation of MTP1 expression by LPS, spleen and liver MTP1 mRNA expression was examined by real-time RT-PCR of total RNA from animals treated with LPS and untreated controls. There was a 2–3-fold down-regulation of MTP1-specific PCR product in spleen and liver samples from LPS-treated animals compared with control mice (Fig. 7A). To better determine whether there may be a change in macrophage-specific MTP1 mRNA secondary to LPS treatment (as opposed to total spleen MTP1 mRNA), splenic macrophages were enriched by adherence to plastic and these cells were treated with LPS, PDTC, or rTNF-α. Total RNA was isolated from these cells and MTP1 and GAPDH mRNA levels were assessed using RT-PCR. In *in vitro* LPS treatment resulted in down-regulation of MTP1 mRNA expression relative to GAPDH expression in the splenic adherent cells (Fig. 7B). The addition of PDTC, an inhibitor of NF-κB, did not abrogate the effect of LPS. In addition, direct addition of TNF-α to the adherent cells did not result in down-regulation of MTP1 mRNA. The data indicate that LPS results in down-regulation of MTP1 mRNA in adherent mouse spleen cells and that this action of LPS is probably independent of NF-κB activation and TNF-α synthesis.

**DISCUSSION**

MTP1 is a metal transporter that exports iron from the cytosol to the outside of cells and was initially identified as the duodenal epithelial basolateral iron transporter (29–31). MTP1 has also been demonstrated to export iron when expressed in tissue culture cells and *Xenopus* oocytes. In addition, there is genetic evidence that MTP1 is involved in iron export from the yolk sac of zebrafish embryos. The recent identification of MTP1 mutation leading to hemochromatosis in man adds further weight to the hypothesis that MTP1 is involved in iron homeostasis (38, 39). RES cells are responsible for the recycling of iron from the breakdown of heme from senescent erythrocytes and MTP1 has been hypothesized to be the key iron exporter in these cells. Supporting this hypothesis is the observation that MTP1 is expressed in the RES macrophages of the spleen (29–31), Kupffer cells (29–31), bone marrow, and
lymph node histiocytes. Although there has been no direct demonstration of MTP1-mediated iron export from RES cells, the ability of MTP1 to export iron from other cell types and its involvement in iron export from the duodenal epithelial cells and the zebrafish yolk sac support the supposition that MTP1 may export iron derived from senescent erythrocytes from the RES cells and back into the blood for reutilization by the erythroid compartment.

Chronic and acute inflammation are well characterized conditions in which iron metabolism is altered. These changes in iron metabolism are characterized by a drop in serum iron, an increase in the rate of plasma iron disappearance, a decline in the rate of plasma iron turnover, RES cell iron sequestration, and hyperferritinemia (reviewed Refs. 1–5). In vivo studies of animal models of acute inflammation secondary to LPS or turpentine administration have demonstrated several mechanisms for the decline in serum iron. LPS and turpentine induce an accelerated clearance of iron from blood, thought to be because of an increase in transferrin-dependent uptake of iron by hepatocytes and other cells (13, 14, 23, 24, 40–42). Release of lactoferrin by inflammatory cells may also be a contributing factor to this acute decline (43), but this hypothesis has been challenged more recently (7, 9). Other changes in iron metabolism because of inflammatory stimuli include a decline in RES and hepatocyte cell iron turnover; and the decrease in RES cell iron turnover results in an accumulation of iron in the RES compartment (29–25, 40–42, 44). The mechanism for the RES iron sequestration is not known, although an inflammation-induced increase in ferritin synthesis has been hypothesized to play a role (35). A decrease in intestinal iron absorption as a consequence of LPS or turpentine administration has also been demonstrated suggesting another possible mechanism for the more chronic effects of inflammation on iron metabolism (23, 26–28).

The data presented here demonstrate that acute LPS administration to mice results in down-regulation of MTP1 expression in cells of the RES in the liver, marrow, and spleen in duodenal epithelial cells. Western blotting of total liver and spleen lysates confirmed the decline in MTP1 protein expression. Furthermore, in an infectious model of chronic visceral leishmaniasis, MTP1 was also down-regulated in the infected spleen. The effects of LPS on MTP1 expression are specific for the RES cells and a significant change in staining of blood vessels or kidney cells in response to acute LPS administration was not observed (data not shown). These observations support a hypothesis that the RES cell iron exit block of acute and/or chronic inflammation result from down-regulation of MTP1. The down-regulation of MTP1 in the spleen by LPS was not apparent at 2 h after injection, whereas hypoferremia was present at this time. Other reports have also pointed to a fast onset of hypoferremia with LPS (43, 45). These observations make it unlikely that the LPS-mediated MTP1 down-regulation in the RES is responsible for the initial hypoferremia observed with LPS. The initial hypoferremia probably result from an increased rate of transferrin-mediated uptake of blood iron. It is more likely that MTP1-mediated RES cell iron exit block may serve to maintain the hypoferremia rather than initiate it.

Many of the effects on iron metabolism of LPS are known to be secondary to LPS-induced synthesis of known proinflammatory mediators such as the interleukins and TNF-α. Although it is difficult to draw many conclusions from the literature because of differences in animal models used, doses of cytokines, and the modes of administration among others, numerous reports indicate administration of IL-6 (17), IL-1 (6, 7, 14), and TNF-α (11, 14, 15) in humans and animals result in rapid drops in serum iron but this decline is relatively short-lived compared with that observed with LPS. Chronic administration of TNF-α (11, 15) or IL-1 (10, 15) results in more prolonged hypoferremia. In these studies, the major effects of IL-6 (17), IL-1 (7, 15),

**A**

**B**

**FIG. 7.** Splenic and liver MTP1 mRNA levels decline in response to LPS treatment. A, MTP1 and GAPDH mRNA levels were assayed in total RNA from spleen and liver tissue of control or LPS-treated mice with MTP1 and GAPDH-specific primers using real time RT-PCR as indicated above. Data shown is compiled from four LPS and four control animals from two independent experiments. Ratios of MTP1 mRNA to GAPDH mRNA were calculated and the MTP1/GAPDH mRNA ratio of one control per experiment was set arbitrarily to 100%. Other values are the MTP1/GAPDH mRNA ratios normalized to this one control. B, adherent mouse splenocytes were isolated as indicated above and treated overnight with LPS (5 μg/ml) or LPS and PDTC (100 μM) or TNF-α (10 ng/ml). Total RNA from the treated and control cells was subjected to RT-PCR analysis using MTP1-specific and GAPDH housekeeping gene primers. Ratios of MTP1 mRNA to GAPDH mRNA are calculated and the MTP1/GAPDH mRNA ratio of one control per experiment was set arbitrarily to 100%. Other values are the MTP1/GAPDH mRNA ratios normalized to this one control. The data for the control and LPS animals is from 6 mouse spleens used in three separate experiments. PDTC and TNF-α data represent duplicates of an experiment in which adherent cells were derived from two pooled mouse spleens. * indicates results that have calculated p < 0.05 for differences.
and TNF-α (15) on iron metabolism appear to be an increase in the rate of plasma iron disappearance and an increase in hepcidin gene transcription. Abnormalities in iron homeostasis in chronic renal failure can be observed in many disease states including cancers, rheumatologic conditions, chronic renal failure, and acute and chronic infectious diseases. This work is significant because the data suggest that strategies aimed at abrogating the down-regulation of MTP1 by inflammatory stimuli. Furthermore, new evidence suggests that chronic inflammation may play a role in the pathogenesis of a variety of disease states such as chronic renal failure and heart disease. Down-regulation of MTP1 by chronic inflammation may result in iron sequestration in tissues and predispose to iron-dependent oxidant-dative stresses.

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