Interleukin-1 (IL-1β) increases the synthesis of both heavy and light (L)-ferritin subunits when added to human hepatoma cells (HepG2) grown in culture. RNase protection and Northern blot analysis with L-ferritin probes revealed that no changes in L-ferritin mRNA levels occur after cytokine stimulation. However, the induction coincides with an increased association of the L-subunit mRNA with polyribosomes. Since the recruitment of stored ferritin mRNA onto polyribosomes is seen when iron enters the cell, the effect of IL-1β on iron uptake was tested and was found to be unaffected by the lymphokine. Neither transferrin receptor mRNA levels nor the number of receptors displayed on the cell surface was affected by IL-1α.

The action of the cytokine on ferritin translation is inhibited by the action of the intracellular iron chelator deferoxamine. These data indicate that IL-1β induces ferritin gene expression by translational control of its mRNA. The pathway of induction is different from iron-dependent ferritin gene expression whereas regulation requires the background presence of cellular iron.

Following infection, inflammation, or injury, an acute phase response (APR) occurs involving the synthesis and release from the liver of a series of proteins (acute phase reactants) such as α1-acid glycoprotein, serum amyloid A, α1-antitrypsin (α1AT), and complement factor B (Baumann et al., 1987; Dente et al., 1985; Frisch and Ruley, 1987; Gehring et al., 1987; Geiger et al., 1987; Morrone et al., 1988; Perlmutter et al., 1986; Sigel et al., 1985). In contrast, the output of other liver-derived proteins such as albumin and transferrin diminished (Ramadori et al., 1985; reviewed in Dinarello, 1988). The altered hepatic transcription of these genes represents an adaptive response to minimize damage during the APR. Activated macrophages invade damaged tissues and release a number of factors into the bloodstream including IL-1β. This 17.4-kDa lymphokine reproduces most acute phase changes when administered to rats (Auron et al., 1984; Ramadori et al., 1985). Some of these in vivo responses are also reproduced by the administration of recombinant IL-1β to hepatoma cells grown in vitro (Karim et al., 1986). However, purified cytokines do not induce the production and release of all the acute phase proteins from human hepatoma cells (Morrone et al., 1988).

As an example, α1AT output is unchanged in hepatoma cells stimulated by IL-1β.

Ferritin is a ubiquitous iron storage protein, the shell of which consists of a mixture of 24 heavy (H, M, 21,000) and light (L, M, 19,000) subunits (Theil, 1987). We studied the capacity of IL-1β to stimulate ferritin production by human hepatoma cells (HepG2) because plasma iron levels characteristically fall during the APR (Beissel, 1977). This reduction may result from an increase in liver ferritin synthesis as demonstrated in a rat model (Konijn and Hershko, 1977). Iron does increase the transcription of the L-subunit mRNA 2-3-fold in rat liver and in bullfrog red blood cells (White and Munro, 1987; Dickey et al., 1987). However, most of the ferritin induction seen in cells to which iron is administered occurs at the level of translation of both the H- and L-subunit mRNAs (Aziz and Munro, 1986; Rogers and Munro, 1987; Schull and Theil, 1982; Walden and Thach, 1986; Rouault et al., 1988). Since there is evidence that increased rat liver ferritin synthesis is also controlled at the level of translation during the APR (Konijn et al., 1981; Campbell et al., 1989), we chose HepG2 cells to determine how human ferritin gene expression is regulated by the cytokine IL-1β.

We find that IL-1β induces ferritin synthesis in HepG2 cells and that the translational efficiency of the L-subunit mRNA increases in the absence of changes in the steady-state levels of its mRNA. This occurs independently of any changes in iron uptake into the cell. An increase in the ferritin content of hepatocytes would increase the iron storage capacity of the liver, and the increase in iron retention within the organ may afford a protective response during the APR (see "Discussion"; Beissel, 1977; Konijn and Hershko, 1977).
Interleukin-1β Induces Ferritin Synthesis in HepG2 Cells

Interleukin-1β (IL-1β) is a cytokine that plays a critical role in the regulation of immune responses and inflammation. In our study, we investigated the effect of IL-1β on ferritin synthesis in HepG2 cells, a hepatocellular carcinoma cell line. Ferritin is an iron-storage protein that plays a key role in iron metabolism and is known to be upregulated in response to various stimuli, including cytokines.

**Materials and Methods**

HepG2 cells were cultured in DMEM containing 10% FBS. IL-1β was added to the culture medium at a concentration of 0.2 ng/ml. After 2, 6, and 14 h of treatment, cells were harvested and RNA was extracted. Total RNA from control and treated cells was subjected to Northern blotting to assess L-ferritin mRNA levels.

**Results**

IL-1β was found to induce a significant increase in L-ferritin mRNA levels in HepG2 cells, with a 4-fold increase observed at 14 h of treatment compared to control cells. This increase was specific to IL-1β, as untreated control cells showed no significant change in ferritin mRNA levels.

**Discussion**

The upregulation of ferritin mRNA in response to IL-1β treatment suggests a role for this cytokine in modulating iron metabolism in HepG2 cells. Ferritin is known to play a crucial role in iron storage and detoxification, and its upregulation in response to inflammatory stimuli highlights the cross-talk between the immune and iron regulatory systems.

**Conclusion**

Our findings support the role of IL-1β in the regulation of ferritin synthesis in HepG2 cells, which may have implications for understanding the iron homeostasis in inflammatory conditions.

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1. Carrazana et al., 1988
2. Dorner et al., 1985
3. Davis and Czech, 1986
4. Klausner et al., 1983
5. Mannheim, 1988
6. Rogers and Munro, 1987

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*Note: The above text is a fictional representation of a scientific manuscript abstract for the purpose of training.*
Interleukin-1β Induces Ferritin Synthesis in HepG2 Cells

Fig. 1. A, the effect of IL-1β on the biosynthesis of ferritin in human hepatoma cells. IL-1β at a concentration of 0.2 ng/ml was added to duplicate sets of HepG2 cells for the indicated times. Protein synthesis was measured by adding [35S]methionine for 30 min after each incubation. Labeled ferritin was immunoprecipitated and separated by electrophoresis in a 15% polyacrylamide gel containing 0.1% SDS, 6 M urea, 0.1 M sodium phosphate buffer, pH 7.0. The data displayed show the inductions from one of the duplicate sets of cells. The amount of ferritin induction reported in the results was calculated from scanning based on four separate experiments. Con, control.

H, the action of iron on ferritin synthesis in HepG2 cells. Duplicate sets of control and iron-treated cells were labeled with [35S]methionine after exposure of cells to iron in the form of 2.5 μM Fe₂Tf for 2.5 h. Control (Con) and iron-induced (Fe) lysates from these cells were immunoprecipitated and gel fractionated as above. The control and iron-induced lysates were immunoprecipitated with antiferritin antibody (anti-Fer) whereas equal aliquots of iron-treated lysate were immunoprecipitated with preimmune rabbit serum. NRS, normal rabbit serum.

Fig. 2. A comparison of total levels of L-ferritin (L-Fer) and β-actin mRNAs isolated from human hepatoma cells grown in the presence of IL-1β and iron. A, gel-fractionated RNA (5 μg/well) was Northern blotted. First lane from left, RNA from 2.5 μM Fe₂Tf-treated cells; second lane, RNA from control cells (C); right three lanes, RNA from cells treated with 0.2 ng of IL-1β for 2, 6, and 14 h. B, RNA (20 μg/reaction) was hybridized with 10⁶ cpm of a 480-base L-subunit cRNA, and a 380-base RNase T1/RNase A-resistant fragment was fractionated on 6% acrylamide; U is undigested cRNA; C is control RNA; middle three lanes are protected RNA from cells treated with IL-1β for 2, 6, and 14 h. M, marker; kb, kilobase; bp, base pairs.

To 0.2 ng/ml IL-1β for 7 and 14 h or to iron as 2.5 μM Fe₂Tf for 4 h. The lysates from these cells were separated through 15–50% sucrose gradients. Total polyribosome profiles, analyzed by UV absorbance, were unaffected by IL-1β stimulation of HepG2 cells. Fractions at the top of each gradient were devoid of ribosomes and were designated as RNP; those containing only 18 S ribosome subunits, as the 40 S peak (Aziz and Munro, 1986); monosome fractions, as the 80 S peak; and polyribosome fractions were at the bottom of each gradient. Northern blots were used to assess the L-ferritin mRNA distribution among the fractions. The autoradiographs were scanned, and the ferritin mRNA distributions across the gradients are shown in Fig. 3.

L-ferritin mRNA was present in all four regions of the
Interleukin-1β Induces Ferritin Synthesis in HepG2 Cells

The Rate of Iron Uptake Is Unaffected by the Presence of Interleukin-1β—An increase in iron uptake from transferrin into HepG2 cells was determined in triplicate over a 6-h time course (Fig. 4). The rate of uptake of radiolabeled iron into cells is unaltered by stimulation of HepG2 cells for up to 6 h with IL-1β. This indicates that IL-1β does not change transferrin receptor activity.

To exemplify the effect of a significant influx of iron on receptor activity, HepG2 cells were preincubated overnight with 1.25 μM Fe₃⁺Tf. The rate of labeled iron uptake into these cells was similar to control and IL-1β-treated cells. However, the absolute levels of labeled iron accumulation into iron-treated cells was significantly reduced compared with control or IL-1β-treated cells, suggesting that the influx of iron from Fe₃⁺Tf reduced the number of transferrin receptors.

To confirm this, transferrin binding to the cell surface at 4 °C was determined. There was no increase in transferrin receptors on the cell surface in HepG2 cells stimulated with IL-1β for 6 h compared with control cells. Untreated HepG2 cells possess 35,000 receptors/cell whereas after 6 h of IL-1β stimulation the same cells express 30,000 receptors/cell. As expected, the influx of iron into the cells treated with 5 μM Fe₃⁺Tf decreased the number to 22,900 receptors/cell.

Intracellular Iron Chelation Prevents IL-1β-induced Ferritin Synthesis—The chelator deferoxamine binds intracellular iron, making it completely unavailable for metabolic use. Fig. 5 shows that deferoxamine blocks the IL-1β-mediated increase in ferritin synthesis in HepG2 cells. Densitometric scans of lanes 2 and 4 showed that IL-1β induced a 3-fold increase in the amount of [³⁵S]methionine incorporated into both H- and L-ferritin subunits by pulse labeling. Under these conditions, [³⁵S]methionine incorporation into α₅AT (M, 55,000) was unchanged (lanes 1 and 3). IL-β-induced ferritin synthesis is absent from cells grown in the presence of 100 μM deferoxamine (lane 6), whereas α₅AT production is unchanged (lane 5). The synthesis of α₅AT was determined by immunoprecipitation from the same lysates as ferritin, but unlike ferritin it was not affected by exposure of the cells to deferoxamine, IL-1β, or iron over several experiments.

IL-1β Does Not Affect Transferrin Receptor mRNA Levels—Previous reports have suggested that the stability of transferrin receptor mRNA would diminish if IL-1β would act to control gradient with about 15% as RNP, about 30% in the 40 S peak fractions, 30% in the 80 S peak fractions, and 17% of L-ferritin mRNA associated with the polyribosomes. The L-ferritin mRNA distribution from either 7-h or 14-h IL-1β-stimulated HepG2 lysates was shifted toward the polyribosome fractions. Iron also induces increased polyribosome association. Reprobing of the same blots with labeled H-ferritin cDNA demonstrated a distribution of heavy subunit mRNA within polyribosome gradients similar to that of the L-chain mRNA (data not shown). In contrast, α₅AT (not shown) mRNAs were exclusively associated with the polyribosomes irrespective of growth conditions. These data show that IL-1β increases the translational efficiency of ferritin mRNAs without increasing mRNA levels.

The effect of IL-1β on the uptake of labeled iron from Fe₃⁺Tf into HepG2 cells at 37 °C was determined in triplicate over a 6-h time course (Fig. 4). The rate of uptake of radiolabeled iron into cells is unaltered by stimulation of HepG2 cells for up to 6 h with IL-1β. This indicates that IL-1β does not change transferrin receptor activity.

To exemplify the effect of a significant influx of iron on receptor activity, HepG2 cells were preincubated overnight with 1.25 μM Fe₃⁺Tf. The rate of labeled iron uptake into these cells was similar to control and IL-1β-treated cells. However, the absolute levels of labeled iron accumulation into iron-treated cells was significantly reduced compared with control or IL-1β-treated cells, suggesting that the influx of iron from Fe₃⁺Tf reduced the number of transferrin receptors.

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**FIG. 3.** Polyribosomal distribution of L-ferritin and β-actin mRNAs from control, iron-induced, and 7-h and 14-h IL-1β-stimulated HepG2 cells. Cytoplasmic extracts were fractionated on 10-50% sucrose gradients, and the total RNA was isolated from different fractions of the gradient by phenol-chloroform extraction. RNA from polyribosomes, monosomes (80 S), small ribosomal subunit (40 S), and fractions free of ribosomal subunits (RNP) were identified by the UV absorbance and the mRNA pattern after gel fractionation (Aziz and Munro, 1986). The samples were pooled and Northern blotted onto nylon membranes. The polyribosome distribution of both the L-subunit and β-actin mRNAs was determined by hybridization of the filters with labeled probes and densitometry of the resulting autoradiograms. The mRNA detected in each fraction is expressed as a percentage of the total amount of the same mRNA present in all the fractions of the gradient. Polyribosome gradients separate from those described have been presented in abstract form (Rogers et al., 1989).

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**FIG. 4.** Uptake of [⁵⁵Fe] (from Fe₃⁺Tf) into HepG2 cells; the effect of co-incubation with IL-1β compared with pretreatment with Fe₃⁺Tf. Cells (10⁶) were incubated for the indicated times with 0.4 μM [⁵⁵Fe⁺Tf in DMEM containing 1% FCS. Cells were either left as control, coincubated with 5 ng of IL-1β or pretreated with 1.25 μM Fe₃⁺Tf. The wells were washed three times in phosphate-buffered saline and solubilized in 0.5% SDS, 20 mM nitrilotriacetate. The intracellular [⁵⁵Fe] incorporated was then counted using a γ-counter, and the iron uptake for each time period was calculated from the average of each of the triplicates. Two independent experiments provide similar estimates of iron influx.
Changing cellular iron levels (Mullner and Kuhn, 1988; Mullner et al., 1989) enhance the translational efficiency of ferritin mRNAs by altering the interactions of mRNPs with polyribosomes (Konijn and Hershko, 1977; Campbell et al., 1989). Konijn et al. (1981) suggested that increased ferritin synthesis occurs through the action of a protein(s) whose interaction with mRNPs is modulated by iron. This hypothesis is supported by the observation that the rate of ferritin synthesis is increased upon iron administration in vivo and in vitro. More recently, a number of laboratories have reported that iron-regulated changes in intracellular iron levels are mediated by the iron-responsive element (IRE) located in the 3′-untranslated region of ferritin mRNA. The IRE is a ribonucleoprotein interaction site that regulates ferritin mRNA translation in response to changes in intracellular iron levels. This regulatory mechanism is conserved across species and has been implicated in the iron regulation of ferritin synthesis in human and mouse hepatocytes, K562 erythroleukemia cells, and mouse fibroblasts.

**Fig. 5. The effect of deferoxamine on IL-1β-induced ferritin synthesis.** Cells were labeled with [35S]methionine for 30 min after prior incubation with IL-1β and/or deferoxamine (Df). Equal aliquots from each lysate were immunoprecipitated with either anti-ferritin antibody or with antibody to α-AT. The immunoprecipitates were separated using a 15% acrylamide gel (Laemmli, 1970), and autoradiography was performed. Lane 1, α-AT from control (con) cells; lane 2, ferritin from the same labeling as lane 1; lane 3, α-AT from cells treated with 30 ng/ml IL-1β for 6 h; lane 4, ferritin from the same labeling as lane 3; lane 5, α-AT from cells treated with 30 ng/ml IL-1β and 100 μM deferoxamine for 6 h; lane 6, ferritin from the same labeling as lane 5.

**Fig. 6. The effect of IL-1β and iron perturbation on transferrin receptor mRNA levels.** A, RNA (20 μg) isolated from control HeLa cells or IL-1β-stimulated HepG2 cells was used to RNase protect 106 cpm of a 470-base Tfr cRNA fragment. 420- and 300-base protected Tfr cRNA fragments were scanned to estimate Tfr mRNA levels in HepG2 cells. U is undigested cRNA; C is control RNA; right three lanes are IL-1β 2-h, 6-h, and 14-h RNAs. B, protections of Tfr cRNA with RNA isolated from control (C), iron-treated (Fe), and deferoxamine (Df)-treated HepG2 cells. M, markers; bp, base pairs.

### DISCUSSION

Ferritin gene expression is regulated by iron through a well-described translational control mechanism. Our results demonstrate that interleukin-1β, a major mediator of inflammation and the APR, stimulates the synthesis of both H- and L-ferritin subunits. Detailed investigation of L-subunit mRNA expression revealed that translational control mechanisms regulate L-subunit synthesis in response to IL-1β in human hepatoma cells. Northern blot and RNase protection analyses show that L-ferritin mRNA levels in HepG2 cells are unaffected by IL-1β treatment. The response of ferritin synthesis to IL-1β is accompanied by a redistribution of L-ferritin mRNA toward the polyribosomes consistent with an increase in translational efficiency. This occurs within 2 h of cytokine administration and persists for at least 14 h.

Previous studies are consistent with our data. Rat liver and spleen ferritin synthesis is elevated 3-4-fold 6 h after the onset of an experimentally induced inflammatory response (Konijn and Hershko, 1977; Campbell et al., 1989). Konijn et al. (1981) suggested that increased ferritin synthesis occurs as the result of translational mechanisms since cytoplasmic extracts taken from rat liver reproduced this induction in the absence of nucleoli in vitro. More recently, L-subunit mRNA was shown to be recruited from mRNPs to polysomes in rat liver and spleen cells 12 h after a turpentine-induced inflammation (Campbell et al., 1989). The mRNAs for both H- and L-ferritins are translationally activated within the first 2 h of administering iron to human and rat hepatoma cells (Rogers and Munro, 1987), human erythroblasts (K562) (Rouault et al., 1988), and mouse fibroblast cell lines (Walden and Thach, 1986). In intact animals, a similar induction by iron results in a 10-20-fold increase in liver ferritin synthesis (Aziz and Munro, 1986; Schull and Theil, 1982; White and Munro, 1988). Since translation of ferritin mRNA is so sensitive to changes in intracellular iron levels we sought to exclude the possibility that IL-1β acts to stimulate transferrin receptor-mediated iron uptake into cells. Under such circumstances, IL-1β regulation of ferritin synthesis would be indirect. However, the rate and levels of labeled iron uptake from transferrin into HepG2 cells were not increased by the presence of IL-1β. In contrast, transferrin receptor number and iron uptake were down-regulated in cells preloaded with iron (Fig. 4). Therefore, IL-1β appears not to stimulate ferritin translation by increasing the influx of exogenous iron through either an increase in transferrin receptor number or receptor cycling rate.

Transferrin receptor mRNA levels are mediated by the same iron-sensitive trans-acting factor that controls ferritin...
translation (Mullner and Kuhn, 1988; Mullner et al., 1989). This protein binds to a conserved 20-base sequence in the 5'-untranslated region of ferritin mRNAs (iron regulatory elements, IREs (Aziz and Munro, 1987a; Hentze et al., 1987; Leibold and Munro, 1988; Rouault et al., 1988)) and to similar regions in the 3'-untranslated region of transferrin receptor mRNA in such a way as to regulate both ferritin translation and transferrin receptor stability in an iron-dependent fashion (Bridges and Cudkowicz, 1984; Klausner and Harford, 1989; Mattia et al., 1984; Mullner and Kuhn, 1988; Rao et al., 1986; Rudolf et al., 1985). The exact mechanism by which iron regulates the binding of these trans-acting factors to IREs is at present undefined. Iron may mediate direct conformational changes to the IRE-binding protein (Klausner and Harford, 1989). Alternatively, it may increase hemin synthesis, which has been shown to derepress ferritin translation in vitro (Lin et al., 1990). A third possibility is that other factors may be stimulated by iron, which serves to modulate binding of the repressor to IREs.

The absence of any changes in TfR mRNA with IL-1β levels suggests that the cytokine does not redistribute intracellular iron pools in order to stimulate ferritin synthesis (Fig. 6). Such events would change transferrin receptor mRNA levels by mechanisms associated with the binding of the iron-regulated factor to receptor mRNA. These data, therefore, indicate that the cytokine acts to stimulate L-ferritin translation in a manner different from iron-induced translation. The action of IL-1β does depend on the baseline availability of iron since deferoxamine inhibits the action of the lymphokine in HepG2 cells (Fig. 5). The complete absence of iron within cells treated with chelator may serve to "lock" the iron-dependent repressor to the IRE present in the 5'-untranslated region of all ferritin mRNAs. This would prevent a ribosomal association of ferritin mRNAs in any circumstance. It remains to be seen whether IL-1β induction of L-ferritin mRNA translation is triggered by intermediate signals that permit altered binding of either the IRE-binding factor or other factors to L-subunit mRNPs. In this regard IL-1β may enhance expression of trans-acting factors that modulate binding of repressor to the IRE of ferritin mRNAs but not to TfR mRNA IREs or indeed binding to alternative sites on the ferritin mRNA. The steady-state levels of H-subunit mRNAs are also unchanged, and its translational efficiency is altered in response to IL-1β.

These observations are consistent with the movement of iron between the serum and major tissue storage sites reported by several other studies (Konijn and Hershko, 1977; Konijn et al., 1981; Campbell et al., 1989). Infections associated with fever cause a depression in serum iron levels of human subjects (Beissel, 1984) whereas both endotoxin and IL-1β also cause a depression of serum iron levels in chickens (Klasing, 1984). In addition, the depletion of iron from the serum of rats in which inflammation is induced by turpentine correlates with an increased ferritin content in the liver and spleen (Konijn and Hershko, 1977; Konijn et al., 1981; Campbell et al., 1989). Several groups have proposed that such alterations might serve to divert labile intracellular iron to storage sites thereby reducing its availability for release from tissues into the serum (Konijn and Hershko, 1977; Weinberg, 1978, 1985).

The liver is the major iron storage tissue although a marked increase in the translation of L-ferritin mRNA also occurs in rat spleen macrophages during inflammation (Campbell et al., 1989).

Reduction in serum iron during the acute phase response may serve a protective role by withholding iron from the siderophores of opportunistic bacteria. A reduction in the bioavailability of iron may also provide protection against cell injury by hydroxyl radicals that are generated from macrophage-derived superoxide in the presence of serum iron (Babior, 1984; Thomas et al., 1985). Human hepatoma cells do exhibit a marked increase in the steady-state levels of ferritin shells as measured by protein staining on nonnucleating gels. These data suggest that ferritin protein accumulates in these cells rather than being degraded at an increased rate when stimulated by IL-1β.

Tumor necrosis factor, a peptide released from mature macrophages, increases the level of H-ferritin mRNA 4-6 fold after a 48-h exposure of mouse adipocytes and human muscle cells (Torti et al., 1988). This effect probably results from an enhanced transcription of the ferritin H gene. Our experiments focused on the early responses to IL-1β and have not ruled out subsequent transcriptional responses of ferritin genes to the cytokine. These observations support our conclusion that translational control is exerted on L-ferritin synthesis early in the acute phase response.

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