Iron Prevents Ferritin Turnover in Hepatic Cells*

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It has long been assumed that iron regulates the turnover of ferritin, but evidence for or against this idea has been lacking. This issue was addressed using rat hepatoma cells with characteristics of hepatocytes subjected to a continuous influx of iron. Iron-pretreated cells were pulsed with [35S]Met for 60 min or with 59Fe overnight and harvested up to 30 h thereafter, during which they were/were not cultured with ferric ammonium citrate (FAC; 180 μM). Radioactivity in ferritin/ferritin subunits of cell heat supernatants was determined by autoradiography of rockets obtained by immunoelectrophoresis or after precipitation with ferritin antibody and SDS-PAGE. Both methods gave similar results. During the +FAC chase, the concentration of ferritin in the cells increased linearly with time. Without FAC, the half-life of 35S-ferritin was 19–20 h; with FAC there was no turnover. Without FAC, the iron in ferritin had an apparent half-life of 20 h; in the presence of FAC there was no loss of 59Fe. Without FAC, concentrations of ferritin iron and protein also decreased in parallel. We conclude that a continuous influx of excess iron can completely inhibit the degradation of ferritin protein and that the iron and protein portions of ferritin molecules may be coordinately degraded.

Ferritins are large, multisubunit proteins, well known as the principal sites for storage of excess iron in cells. Almost ubiquitous in living organisms, ferritins also provide a means of rapidly sequestering iron ions that might otherwise promote the formation of reactive oxygen species. Each ferritin molecule can hold thousands of iron atoms in innocuous form. In addition, iron influx stimulates the synthesis of ferritin protein, so that additional sites for non-toxic iron storage are available. The response of ferritin synthesis to iron influx is also exceptionally rapid, because it is mainly translational and utilizes existing mRNA for ferritin (rather than additional ferritin gene transcription, which would take more time) (1–3). The mechanism by which iron regulates ferritin mRNA translation, involving an iron-responsive element (IRE)† in the 5′-untranslated region (4, 5), led to the further discovery of IREs in other proteins of iron metabolism and the identification of IRE-binding proteins (IRP1 and IRP2), which coordinate regulate iron metabolism in cells (5–11). This opened a window of understanding into new (non-transcriptional) ways in which cellular processes can be regulated. The ferritin response to iron influx can thus be viewed as a protective rapid response system, allowing immediate formation of additional ferritin in which to store the additional iron. Elucidation of the mechanisms involved has (rightfully) preoccupied the field of ferritin research for some time. This may in part account for the dearth of information on turnover of ferritin, where much has remained unexamined.

If ferritin is to function as a protective mechanism for storage of excess iron, it also would make sense for iron to reduce ferritin protein degradation, so that ferritin molecules would be preserved for iron binding. Accumulation of proteins can occur not just through stimulation of synthesis but also through inhibition of their degradation. Thus, for example, arginase (12) and tryptophan oxygenase (13) accumulate through stabilization when needed. In the latter case, substrate stabilization (by tryptophan) is involved (13). So it would not be surprising to find that iron stabilizes ferritin. However, the matter has not been adequately studied, and the few reports that have examined the issue have given conflicting results.

In the seminal original report of Drysdale and Munro (1), who first alerted the field to translational regulation of ferritin by iron, some data on the turnover of ferritin were included but were difficult to interpret. In these studies, ferritin was followed in the livers of rats that were and were not treated with iron during the turnover phase of 3 days. Not only was there little or no information on the variability of the data, but assuming that they were not variable, one could draw the conclusion that iron treatment can both enhance and hinder ferritin protein turnover. Later studies by Treffrey et al. (14), also in rats that were and were not treated with iron (400 μg/100 g body weight) at 12-h intervals, suggested that iron treatment made no difference. Based upon data for groups of four rats at 3 time points, the half-life of [14C]HCO3- labeled liver ferritin, with and without iron, was about 70 h. The report of Khogo et al. (15), which focused on the synthesis and turnover of different isoforms of liver ferritin, did include turnover data for a few rats given and not given two iron injections (over 70 h). They used the double radioisotope injection approach and found that ratios of 14C to 3H radioactivity in ferritin (derived from injection of radioactive leucine 2 and 67 h before sacrifice, respectively) were somewhat higher in the iron-treated rats, suggesting a faster rate of turnover. (However, the data were highly variable and could not be analyzed statistically.) Whole animal studies have the inherent difficulty of maintaining elevated intracellular labile iron pools, and it would seem logical that elevated pools would need to be maintained to demonstrate that iron is (or is not) influencing ferritin turnover. Thus, cultured cells might provide a better means of testing the possibility that iron plays such a role.

In one report, cultured K562 cells were used to examine ferritin turnover (16), but in this case the effect of iron depletion rather than enhanced iron influx was tested. This study...
was not entirely satisfactory with regard to turnover in other ways as well. There was no information on the variability and replicability of the results, and the time period examined was so short that relatively little turnover of ferritin actually occurred. The data, however, suggested that iron deficiency, induced by deferoxamine, enhanced the rate of ferritin protein turnover, so that conversely one might surmise that iron inhibits turnover. Data on the effects of deferoxamine on ferritin concentrations in L-6 skeletal muscle myoblasts (17) were consistent with this concept. An enhancement of turnover by iron depletions was also implied by data from studies in which the concentrations of ferritin (H and L subunits), in developing erythroid cells in culture, were followed during the period of hemoglobin accumulation (which would use the ferritin iron). A reciprocal relationship was observed (18).

In the studies presented here, a rat hepatoma cell line that we have verified has many of the characteristics of normal hepatocytes (19) was used to study ferritin protein turnover and the loss of ferritin iron in the presence and absence of ferric ammonium citrate in the culture medium. The results show unequivocally that iron can completely block turnover of ferritin and suggest that, at least in the case of the $^{59}$Fe-labeled ferritin present in these cells (made in response to iron), the iron and protein portions of the ferritin may turn over together.

**EXPERIMENTAL PROCEDURES**

**Cell Culture**—Rat hepatoma H4-II-E-C3 cells purchased from the American Type Culture Collection (Manassas, VA) were cultured in Dulbecco’s modified Eagle’s medium supplemented with 15% horse and 5% fetal bovine serum, as described previously (19).

**Turnover of Ferritin Protein**—Cells at 90% confluency were cultured overnight in Dulbecco’s modified Eagle’s medium, 5% serum (horse/fetal bovine 3:1) containing iron (FAC, 180 $\mu$M) to stimulate ferritin synthesis, then pulsed for 60 min with $[^{35}S]$Met (50 $\mu$Ci/ml; ICN Nutritional Biochemicals; Costa Mesa, CA) in Met-free RPMI 1640 medium (Life Technologies, Inc.) with FAC, and (after rinsing) then chased by culturing in Dulbecco’s modified Eagle’s medium (with no serum) containing either FAC or deferoxamine mesylate (100 $\mu$M; Sigma). The $\pm$ FAC medium was changed after 12 h, or additional FAC was added, to make sure iron concentrations were maintained. Cells were harvested by trypsinization, homogenized, and heated to 70°C for 10 min, as described previously (19), to obtain heat supernatants that were used to determine radioactivity in ferritin. Aliquots of homogenate were used to determine radioactivity in total protein, and the total protein content of each flask was assayed by the Bradford dye binding assay (Bio-Rad), using bovine serum albumin as the standard, all as described previously (19). Values for radioactivity in ferritin and total protein are given as cpm/106 cells, based upon a cell protein content of 0.7 mg of protein/106 cells, based upon a cell protein content of 0.7 mg of protein/106 cells, based upon a cell protein content of 0.7 mg of protein/106 cells, based upon a cell protein content of 0.7 mg of protein/106 cells.

**RESULTS**

**Turnover of Ferritin in the Rat Hepatoma Cells**—To study the turnover of ferritin protein and its subunits, and the effect of iron on this process, cells were pretreated overnight with FAC to stimulate ferritin synthesis and accumulation and then pulsed for 60 min with $[^{35}S]$Met (in Met-free medium), after which radioactivity in ferritin was followed for 29–30 h. Two methods were employed to follow the loss of radioactivity in ferritin protein over time, which gave comparable results. In one case, the radioactivity in ferritin was separated from that in other proteins by subjecting samples of heat supernatants, obtained from cell homogenates, to rocket immunoelectrophoresis, with specific ferritin antibody in the gel, and measuring the radioactivity in the rockets by densitometry of autoradiographs (see “Experimental Procedures”). In the other case, heat supernatants were precipitated with ferritin antibody and protein A beads, and radioactivity in the washed precipitates was determined by direct counting and by autoradiography after SDS-PAGE. Examples of data obtained by both techniques are given in Fig. 1.

Fig. 1A shows a sample autoradiograph of ferritin immunoelectrophoresis rockets for sets of three different cultures obtained at two different time points (6 and 30 h) after incorporation of $[^{35}S]$Met into ferritin. As shown here, radioactivity in the actual rockets (as opposed to residual activity in the wells) clearly decreased with time, and this was quantitated by densitometry in the PhosphorImager (see “Experimental Procedures”). (Radioactive iron in ferritin was also detectable and quantifiable by this method (Fig. 1B).) Fig. 1C shows an example of a portion of an autoradiograph and corresponding stained gel obtained with immunoprecipitates subjected to SDS-PAGE, again showing triplicate sets of samples from two different time points (6 and 30 h). The radioactive L and H subunits (left part of figure) are clearly visible and are virtually the only bands on the gel. (Note that radioactivity in the H subunits disappeared more rapidly (see below).) The stained gel (shown on the right) also shows the H and L subunits, along with the immunoglobulin subunits in the immunoprecipitate. Radioactivity in the immunoprecipitates was quantitated directly, as well as by autoradiographs to determine turnover of iron in the subunits.

As shown in Fig. 1D, rates of turnover were very similar when determined by the two methods. During a 27-h “chase,” after labeling the ferritin with $[^{35}S]$Met, there was a substantial loss of radioactivity in ferritin. The upper curve was obtained from the rockets and the lower curve from direct counting of immunoprecipitates. The data fit first order curves, and...
Effect of Iron on Ferritin Protein Turnover

By using both methods, the effects of having iron in the culture medium during the chase period was examined and compared with that for cells cultured in the absence of FAC during the chase. In the case of the iron-treated cultures, new FAC was added at about the half-way point (12–13 h after the [35S]Met pulse) to make certain there was excess iron available throughout. The data in Fig. 2A show that iron was continuing to enter the cells.
throughout the treatment period, because there was a linear increase in cellular ferritin concentration with time. In contrast, the cells not "chased" with iron in the medium decreased their content of ferritin. (There was deferoxamine in the –FAC medium, which would remove extra iron.)

Fig. 2B shows that the presence of iron during the chase phase (+FAC) completely prevented turnover of the ferritin protein. There was no loss of [35S]Met radioactivity that had been incorporated during the pulse. This contrasted with a loss of more than half of the radioactivity in cells cultured without FAC (Fig. 2B, –FAC), as already described. Thus, iron had a marked stabilizing effect on ferritin protein. Fig. 2C shows that iron had no significant effect on the turnover of cell protein as a whole. Radioactivity in total cell protein decreased 10–20% over the period examined, whether or not cells were cultured with added FAC. Thus, in the absence of added iron and presence of deferoxamine, ferritin was turning over faster than hepatoma cell protein as a whole. Radioactivity in ferritin represented from 0.4 to 0.8% of the total radioactivity in cell protein (0.6 ± 0.1%; mean ± S.D., n = 9). Based on examination of the SDS-PAGE autoradiographs (for example, Fig. 1C, showing data for 6 and 30 h), it appeared that ferritin rich in H subunits was turning over a bit faster than that rich in L subunits. Radioactivity in the two subunits was about equal soon after the pulse, but little remained in the H subunit at the end of the period examined.

**Effect of Iron on Ferritin-Iron Turnover**—In separate experiments, the release of 59Fe from ferritin was also followed and compared with the turnover of ferritin protein measured in parallel cultures. The iron in ferritin was labeled by exposing cells to tracer 59Fe overnight, during the pretreatment with FAC. The data in Fig. 3 show that measured this way, turnover of 35S and 59Fe in the ferritin was the same. In cells cultured without added FAC, the 59Fe in ferritin decreased markedly and exponentially during the period examined (Fig. 3A), with an apparent half-life of about 20 h. Data obtained on the same samples by the immunoprecipitation method confirmed there was a large difference in radioactivity in ferritin, with and without FAC, a 2.5-fold difference at 30 h. Fig. 3B shows that the pattern of decrease in 35S-labeled ferritin was identical. The 35S half-life of 19 h calculated was the same as that described for the earlier experiments (Figs. 1D and 2B). Thus, the protein and iron portions of the ferritin appeared to be turning over at the same rate. The continuing presence of iron in the medium during the period in which turnover of ferritin was examined prevented not just the turnover of ferritin protein but also prevented the release of iron from ferritin. No 59Fe was lost from the ferritin in those cultures where iron continued to be present in the medium (+FAC, Fig. 3A). As before, there was no effect of iron treatment on 35S radioactivity in total cell protein (data not shown).

The actual iron content of the ferritin and the rate of loss of actual ferritin iron and protein (not measured with 35S) in the absence of FAC were also measured and calculated. The iron content of the ferritin was constant during the turnover phase from 6 to 30 h. It averaged 0.15 μg of Fe/μg of protein (± 0.05; mean ± S.D.; n = 12), a typical value for intracellular liver ferritin (22), and was identical to that determined on ferritin isolated from these hepatoma cells in separate studies. The concentration of ferritin in the cells and the ferritin iron declined in parallel. In this set of experiments, a linear extrapolation of the data indicated that all of the ferritin would be gone by about 50 h. On the basis of an exponential decline, a half-life of 23 h was calculated. Thus, the rate of decline in actual content of the ferritin (23) was examined prevented not just the turnover of ferritin protein but also prevented the release of iron from ferritin.
Effect of Iron on Ferritin Turnover in Hepatic Cells

Ferritin concentration was almost the same as the rate of ferritin degradation determined with $^{35}$S. This implies that without continued FAC and with deferoxamine, the cells were mainly degrading ferritin, and there was relatively little (if any) new synthesis of ferritin occurring. This also implies that the iron released from ferritin was not being removed from the pool any new synthesis of ferritin occurring. This also implies that with ferritin degradation (perhaps in lysosomes). With additional iron influx, there was no release of iron or degradation of ferritin protein. Thus, the two phenomena appeared to be coordinated. This was also seen when the declines in cellular concentrations of ferritin iron and protein were determined and compared; they decreased in parallel. Moreover, the rate of decline (based on exponential calculations) was very close to that of actual ferritin protein turnover measured with $^{35}$S, 23 versus 19–22 h.

Most of the ferritin being degraded was that which had been synthesized during the overnight exposure to ferric ammonium citrate and $^{59}$Fe. During that period, it seems that the $^{59}$Fe in ferritin achieved a kind of “equilibration” with the non-radioactive iron in ferritin, so that it “turned over” in the same manner as ferritin protein during the degradative phase. Thus, we can imagine that during the overnight labeling, there was incorporation of $^{59}$Fe into ferritin molecules of a variety of “ages” and therefore stages of core formation. The loss of $^{59}$Fe from this “mixed core” population was then followed and found to have the same half-life as that of ferritin protein. The $^{59}$Fe in ferritin cores did not leave more rapidly than the protein was degraded, implying that it was released in coordination with ferritin degradation (perhaps in lysosomes). In vivo as well as in vitro, the “last in” atoms of iron in the cores would have to be released first, but in vivo, dissolution of the whole cores could be very rapid. (Indeed, it is known that once proteins have entered lysosomes, their degradation is accomplished within minutes (24).)

The rate of decline in actual ferritin iron and protein concentrations may have been a little slower than that of radiolabeled ferritin, although it seems unlikely that the difference in apparent half-life (23 versus 19–22 h) was really significant. Assuming that it was, the difference would indicate that, although degradation was clearly predominating, there was nevertheless also some continued synthesis of new ferritin. A slightly slower fall in ferritin iron (versus the release of $^{59}$Fe from prelabeled ferritin iron cores) cannot be explained on the basis that the $^{59}$Fe in ferritin was actually “chased out” of the cores (because the last atoms in are the first out; see Ref. 25).

However, it might indicate that iron released from $^{59}$Fe-rich ferritin was preferentially lost from the cell, over less $^{59}$Fe-rich iron associated with other cell proteins, and that the latter was above the normal during the culture (chase) period examined, when ferritin turnover was blocked. In contrast, ferritin protein turned over fairly rapidly in cells where FAC was no longer in the medium, and deferoxamine was present to prevent further iron influx. (In those cells, ferritin levels did not rise and in fact fell over time.) The half-lives of 19–20 h obtained are not very different from the 12–h value reported previously for cultured K562 cells (16). The turnover was, however, considerably more rapid than that measured in vivo by us (18) and others (14, 23) for livers of male and female rats, where half-lives ranged from 1.9 to 4 days. Our data indicating that H-rich ferritin was turning over more rapidly than L-rich ferritin agree with the earlier report of Khogo et al. (15) who examined liver ferritin isoforms in rats. It contrasts with reports for erythroid cells (16, 18), where L and H subunits appeared to be turning over at the same rate.

Our additional finding that iron treatment also prevented release of ferritin iron has several implications as well. The observation that the iron in ferritin was being released (or not being released) in parallel with the turnover of the protein portion of ferritin suggests that these two parts of ferritin might be degraded together. In other words, degradation of the protein part of ferritin might accompany the release of its iron or vice versa. In the absence of continued iron influx (and presence of deferoxamine), $^{59}$Fe was released at the same rate as ferritin protein was being degraded. With additional iron influx, there was no release of iron or degradation of ferritin protein. Thus, the two phenomena appeared to be coordinated. This was also seen when the declines in cellular concentrations of ferritin iron and protein were determined and compared; they decreased in parallel. Moreover, the rate of decline (based on exponential calculations) was very close to that of actual ferritin protein turnover measured with $^{35}$S, 23 versus 19–22 h.

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incorporated into the new ferritin still being made. Iron released from degradation of ferritin protein might thus re- ceptively be available for binding and sequestration by deferox- amine. Overall, the data seem most consistent with the concept that there is coordination of turnover of ferritin iron and pro- tein and that release of ferritin iron may depend upon degra- dation of the protein, at least in this cell type under the condi- tions examined.

If degradation of the ferritin protein “shell” is necessary for the release of iron from ferritin in vivo, ferritin degradation may be occurring in the lysosomes. Indeed, studies by two different research groups, with fibroblasts (26) and K562 cells (27), have implicated lysosomes in ferritin turnover. Although ubiquitin-dependent proteolysis has dominated more recent work on cellular protein degradation, it has long been known that lysosomes account for the bulk of cellular protein degra- dation (28–30), including degradation of cytosolic proteins. Several pathways for entry of cytosolic proteins into lysosomes have been identified (28–32), including a specific mechanism involving the recognition of KFERQ-like sequences in the protein target, plus cytosolic and lysosomal chaperones and a receptor (31, 32). Coordinate degradation of ferritin protein and release of its iron may, however, not occur in all cell types, as the turnover of ferritin iron in K562 cells appeared to be accel- erated by deferoxamine treatment, whereas that of ferritin protein appeared to be unchanged (16). (However, the changes reported in those studies were small and could not be evaluated statistically.)

Regarding earlier reports of studies in whole animals in which iron treatment failed to inhibit ferritin turnover (14) or provided evidence for both stimulation and stabilization of ferritin by iron (1), the first was based on a single experiment with four rats at 3 time points, and the second on even fewer data points and no evidence on replicability. Nevertheless, the original study of Drysdale and Munro (1) did conclude that iron stabilizes ferritin, and this is what we have now clearly demonstrated.

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