The Human Type 2 Iodothyronine Deiodinase Is a Selenoprotein Highly Expressed in a Mesotheioma Cell Line*

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Types 1 and 3 iodothyronine deiodinases are known to be selenocysteine-containing enzymes. Although a putative human type 2 iodothyronine deiodinase (D2) gene (hDio2) encoding a similar selenoprotein has been identified, basal D2 activity is not selenium (Se)-dependent nor has D2 been labeled with 75Se. A human mesothelioma cell line (MSTO-211H) has recently been shown to have ~40-fold higher levels of hDio2 mRNA than mesothelial cells. Mesothelioma cell lysates activate thyroxine (T4) to 3,5,3'-triiodothyronine (T3) with typical characteristics of D2 such as low Km (T4) 1.3 nm, resistance to propylthiouracil, and a short half-life (~30 min). D2 activity is ~30-fold higher in Se-supplemented than in Se-depleted medium. An antiserum prepared against a peptide deduced from the sequence of the putative D2 mRNA (4) precipitates a 75Se protein of the predicted 31-kDa size from 75Se-labeled mesothelioma cells. Bromoadenosine 3'-5'-cyclic monophosphate increases D2 activity and 75Se-p31 -2.5-fold whereas substrate (T4) reduces both D2 activity and 75Se-p31 –2-3-fold. MG132 or lactacystin (10 μM), inhibitors of the proteasome pathway by which D2 is degraded, increase both D2 activity and 75Se-p31 3-4-fold and prevent the loss of D2 activity during cycloheximide or substrate (T4) exposure. Immunocytochemical studies with affinity-purified anti-hD2 antibody show a Se-dependent increase in immunofluorescence. Thus, human D2 is encoded by hDio2 and is a member of the selenoiodinase family accounting for its highly catalytic efficiency in T4 activation.

It also revealed a requirement for a stem loop structure in the 3'-untranslated region, the Sec insertion sequence (SECIS) element (2), which is found in all eukaryotic selenoprotein mRNAs described to date (3).

The most recently cloned deiodinase is the type 2 (D2), a propylthiouracil (PTU)-resistant, low Km (T4) obligate outer ring deiodinase that catalyzes T4 to T3 conversion (4, 5). The major open reading frame of the hD2 cDNA encodes a putative ~31-kDa protein with high similarity of the Sec-containing active center of the putative D2 enzyme with those of D1 and the other member of this group, type 3 iodothyronine deiodinase (D3) (6). Furthermore, a SECIS element has been identified in the extreme 3'-untranslated region of both the human and highly homologous chicken Dio2 genes (7, 8). Human, mouse, rat, chicken, and frog D2 all contain a putative in-frame UGA codon in the deduced amino acid sequence of the active center (position 133 in hD2) and therefore all are considered to be selenoenzymes (8).

Despite this evidence, there is vigorous disagreement that D2 is a selenoprotein, with some investigators claiming that Dio2 encodes a “virtual” or artificial selenoprotein that is not expressed in humans or rats (9–14). Three major arguments support this position, namely 1) the failure of Se deficiency to reduce D2 catalytic activity either in vivo or in vitro (9, 15, 16), 2) the inability to identify a 75Se-labeled protein of the expected size in cells expressing D2 (13), and 3) the inability to identify immunoreactive protein by Western analysis, immunoprecipitation (IP), or immunocytochemistry using antibodies prepared against peptides deduced from the sequence of the putative D2 mRNA (4). An alternative scenario put forward is that D2 is a large protein complex (200 kDa) containing one or more 29-kDa substrate-binding subunits (p29), an ~60-kDa cAMP-induced activation protein, and one or more catalytic subunits (12). Rat p29 was identified in astrocytes by N-bromoacetetyl-T4 labeling (17–19), has no enzymatic activity, and is highly similar to Dickkopf-3 (20). Although many of these apparent discrepancies could be explained by low expression of a highly efficient enzyme, reservations as to the identity of D2 are expressed even in recent reviews of the subject (21, 22).

A mesothelioma cell line, MSTO-211H, was recently shown to express large amounts of Dio2 mRNA by microarray analysis (accession number U53506), offering a potential system to resolve the issue of D2 identity (23).

EXPERIMENTAL PROCEDURES

Reagents—MG132 and lactacystin were obtained from Calbiochem (La Jolla, CA) and dissolved in Me2SO. MG132 is a reversible proteasome inhibitor. Lactacystin blocks proteasome activity by targeting the catalytic β-subunit and covalently inhibiting the chymotrypsin- and trypsin-like activities. T4, cycloheximide (CX), and 8-bromoadenosine 3’-5’ cyclic monophosphate (8-Br-cAMP) were from Sigma and were dissolved in 40 mM NaOH (T4) or Me2SO. Protein G plus/protein A

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A-agarose solution was obtained from Oncogene Research Products (Boston, MA). Outer ring-labeled (32P)C1 (specific activity, 4400 Ci/mmol) was from PerkinElmer Life Sciences. Na2[75Se]O3 was kindly provided by the University of Missouri Research Reactor, courtesy of Drs. Marla Berry and Dolph L. Hatfield. All other reagents were of analytical grade.

Cell Culture and D2 Activity—Mesothelioma (MSTO-211H) and mesothelial (MeT-5A) cell lines were obtained from American Type Culture Collection (ATCC; Manassas, VA) and made available through Dr. Rihm. Cells were plated in 60-mm dishes and grown until confluence in RPMI or M-199, respectively, and supplemented with 0–10% fetal bovine serum (FBS). Human embryonic kidney epithelial cells (HEK-293) were obtained from American Type Culture Collection (ATCC; Manassas, VA) and made available through Drs. Marla Berry and Dolph L. Hatfield. All other reagents were of analytical grade.

Procedures for Transfections—In some experiments D2 was transiently expressed in HEK-293. Cells were transfected by the CaPO4 method as described previously (25) with plasmids containing wild type D2 (KD2-SepE), a D2 mutant in which the Sec-133 (but not Sec-266) was replaced by Cys (CysD2), or a CysD2 in which the SECIS element was deleted (CysD2Xba).

75Se Incorporation and D2 IP—This was performed as described previously (25) after cells were labeled with 4–6 μCi of Na2[75Se]O3/dish. The lysis buffer contained 25 mM Tris-HCl (pH 7.4), 300 mM NaCl, 1 mM CaCl2, 0.5% Triton X-100, 0.2 units/ml aprotinin, 1 mM phenylmethylsulfonyl fluoride. The 2,000-rpm supernatant of each cell lysate was incubated for 16 h at 4°C with D2 rabbit antisera 85254 at final dilution of 1:100 (25). 30 μl of protein G plus/protein A-agarose solution were added per tube and incubated under slow agitation for 2 h at 4°C. The IP pellets were washed once with lysis buffer and once with 25 mM Tris-HCl (pH 7.4), 140 mM NaCl, 1 mM CaCl2. Pellets were re-suspended in sample loading buffer and analyzed in 12% SDS-PAGE. In some experiments IP was processed in unlabeled buffer and analyzed in 12% SDS-PAGE. In some experiments IP was processed in unlabeled buffer and analyzed in 12% SDS-PAGE.
Type 2 Deiodinase in Mesothelioma Cells

T₄ with kinetic properties typical of native D₂, namely a Kₘ₄ for T₄ of ~1.0 nM and insensitivity to inhibition by 1 mM PTU as shown in the Lineweaver-Burk plot (Fig. 1A). Neither D₁ nor D₃ activities were detected nor did the transformed normal mesothelial cells (MeT-5A) express D₂ activity (not shown). D₂ activity in MSTO-211H cells was highly Se-dependent. Basal activity was decreased 4-fold by reducing the concentration of FBS containing endogenous selenoproteins (Fig. 1B). That these changes are specifically caused by Se deficiency and not by other components in FBS is evident from the fact that Se supplementation progressively increased D₂ activity at each concentration of FBS, from 2–3-fold at 10% FBS up to ~30-fold when no FBS was present (Fig. 1B). The Lineweaver-Burk plots from cells incubated in the absence of FBS with or without 100 nM Na₂SeO₃ for 24 h shows a ~16-fold increase in Vₘ₃ with no change in the Kₘ₃ (Fig. 1A). A dose-response curve of D₂ activity versus Na₂SeO₃ concentration indicated that the maximum stimulatory effect is obtained at 100 nM. A time-response curve showed that an effect of Se is present after 2 h, but the full effect requires 8 h (not shown). Similar effects of Se to increase D₂ activity were observed in HEK-293 cells transiently expressing Sec-encoding D₂ mRNA. Exposure to 100 nM Na₂SeO₃ for 24 h increased D₂ activity by ~10-fold suggesting this effect is primarily post-transcriptional (Fig. 1B).

To confirm that the MSTO-211H cells express a selenoprotein containing a deduced D₂ epitope, cells were labeled with Na₂[⁷⁷Se]Ο₃ for 24 h and processed for D₂ IP using an anti-hD₂ peptide antiserum (82524) (25). Mesothelial (MeT-5A) cells were used as negative controls. Four ⁷⁷Se-labeled bands of ~70, 58, 25, and 18 kDa (but not 31 kDa) are present in the SDS-PAGE of total cell lysates of MSTO-211H or MeT-5A cells (Fig. 1C, b). These ⁷⁷Se-labeled proteins are increased by incubation with 100 nM Na₂SeO₃ in MSTO-211H cells but are decreased in MeT-5A (Fig. 1C, b). SDS-PAGE analysis of the anti-D₂ IP of the MSTO-211H cell lysate revealed an ~31-kDa ⁷⁷Se-labeled doublet band (p31) of the predicted size of hD₂, the intensity of which is increased ~2-fold in the presence of 100 nM Na₂SeO₃ (Fig. 1C, c and d). A doublet is seen when hD₂ cDNA is transiently expressed because of the presence of a second UGA at the 3’-end of the open reading frame that can be translated either as a Sec or as a stop codon (28). The content of all other ⁷⁷Se-labeled proteins is reduced in the anti-D₂ IP pellets (Fig. 1C, c). IP of non-labeled cell lysates reduced D₂ activity ~20%, and ~½ of this activity can be recovered from the washed IP pellet (Fig. 1D). Addition of the antiserum to the cell lysate did not inhibit D₂ activity nor did exposure to preimmune serum or protein A-Sepharose (not shown). Despite these IP results, we were unable to consistently visualize D₂ by Western blot analysis of MSTO-211H cells using affinity-purified anti-D₂ antibody (AP-45618).

Fluctuation in ⁷⁷Se-p31 Levels Parallel D₂ Activity in MSTO-211H Cells—The hD₂ gene contains a canonical cAMP-response element-binding protein-binding site about 90 base pairs 5’ to the most 5’-transcription start site (29). D₂ activity increases in cells treated for 6 h with 8-Br-cAMP in a dose-dependent fashion (Fig. 2A). To test whether there is a correlation between 8-Br-cAMP-induced D₂ activity and p31, cells treated with 1 mM 8-Br-cAMP were labeled with ⁷⁷Se and processed for D₂ IP. The intensity of the ⁷⁷Se-p31 band increased ~2.5-fold in 8-Br-cAMP-treated cells (Fig. 2F). No effects of insulin (0.1–5 μM) or tumor necrosis factor-α (0.01–10 ng/ml) on D₂ activity were detected (data not shown).

Both endogenous and transiently expressed D₂ have a short-life (~<1 h) that is reduced further by exposure to substrates such as 3,3',5'-triiodothyronine or T₄ (24, 25, 30–32). This is explained by ubiquitin conjugation and subsequent proteasomal degradation of the ubiquitinated D₂ (25, 26). Treatment of cells with 100 μM CX for 1 h resulted in a rapid loss of D₂ activity, compatible with a D₂ half-life of ~<30 min (Fig. 2B). The decrease in D₂ activity was prevented by the proteasome inhibitor, MG132 (10 μM) (Fig. 2B). Furthermore, exposure to MG132 increased D₂ activity up to ~4-fold, with similar results obtained with 10 μM lactacystin (Fig. 2C). Remarkably, anti-D₂ precipitable ⁷⁷Se-p31, but not other labeled proteins, was also specifically increased by treatment with MG132 (Fig. 2D). Exposure to substrate (0.01–10 μM T₄ in 10% FBS) for 1 h caused a concentration-dependent reduction in D₂ activity of up to ~10-fold (Fig. 2D), which again was blocked by MG132 (Fig. 2E). This was accompanied by a reduction in the anti-D₂ precipitable ⁷⁷Se-p31 (Fig. 2F).

MSTO-211H and MeT-5A cells were also analyzed by immunocytochemistry using an affinity-purified anti-D₂ antibody (AP-45618). In MSTO-211H cells incubated in serum-free medium for 24 h, the cytoplasm showed mild staining for D₂ (Fig. 3A). Treat-
ment with 100 nM Na₂SeO₃ for 24 h substantially increased the intensity of the staining without changing the distribution pattern (Fig. 3B). No fluorescence was detected in MSTO-211H cells incubated with secondary antibody alone (Fig. 3C) or in Na₂SeO₃–treated MeT-5A cells incubated with affinity-purified anti-D2 antibody (d). Panel e is a phase contrast of a typical MSTO-211H cell co-stained with anti-D2 antibody (f) and GRP78/BiP protein (g). The superimposition of the same fields is shown in h, where the inset represents the distribution spectrum of image pixels. Cell types are indicated in the upper left corner. Bar = 50 μm.

DISCUSSION

The Se-supplemented MSTO-211H cells have the highest D2 activity reported to date in a human tissue (~140 fmol/min/mg protein), ~40% higher than in Graves’ thyroid tissue (33). This high D2 expression permits the unequivocal demonstration that endogenous hD2 is a selenoprotein encoded by the Dio2 gene (5). The present results satisfy a number of important criteria establishing the identity of hD2 as the product of the Dio2 gene. Furthermore, they allow confirmation that the endogenous human enzyme behaves as predicted from a number of studies using transiently expressed protein.

The first important criterion to establish D2 as a selenoprotein is to demonstrate its Se dependence. Past studies showed that the elevated D2 in cerebral cortex of thyroidectomized rats is not reduced by Se deficiency (15) and that astroglial cells depleted of Se for 3–5 days did not have lower basal D2 activity (9). Although there was about 50% reduction of the D2 activity in cAMP-treated primary astrocyte cultures after 7 days of Se deprivation, basal D2 activity was still not affected (34). However, the central nervous system is well known to retain Se with high efficiency, which could explain why D2 synthesis is not impaired by Se deficiency (35).

In MSTO-211H cells, on the other hand, Se depletion for 24 h reduced basal D2 activity by ~4-fold. This decrease in D2 activity was specifically reversed by Se supplementation (Fig. 1, A and B). In fact, addition of Se increased D2 activity by ~30-fold in Se-depleted cells, in a dose- and time-dependent fashion, a phenomenon that also occurs in HEK-293 cells transiently expressing D2 (Fig. 1, A and B). Selenium depletion of MSTO-211H cells also markedly reduces the levels of another selenoprotein, glutathione peroxidase (36).

A second criterion met by the present studies is the ⁷⁷Se labeling and immunological recognition of D2. A recent study could not identify the ⁷⁷Se-D2 protein by IP using antibodies that were raised against the COOH terminus of full-length rat D2 or against the catalytic core of the enzyme (13). This is not the case in the present studies (see Fig. 1C and Fig. 2F). Aside from potential differences in the antisera per se, which might be an issue, the D2 activity in rat tissue sonicates or stimulated primary astrocyte cultures are only ~10% of that in MSTO-211 cells. Because of the higher D2 expression, we can demonstrate IP of D2 activity, as well as of a ⁷⁷Se-labeled protein of the predicted size (31 kDa) from MSTO-211H cells (Fig. 1C). This is the first demonstration of endogenous ⁷⁷Se-D2. The ⁷⁷Se-labeled 31-kDa protein is increased by Na₂SeO₃, mirroring changes in D2 activity (Fig. 1C). A correlation between changes in D2 activity and the amount of ⁷⁷Se-p31 is also evident during treatment with proteasome inhibitors (see below), 8-Br-cAMP, or D2 substrate (Fig. 2).
Additional immunological identity criteria were obtained by immunocytotoxicity studies using the affinity-purified anti-D2 antibody. Staining was only present in MSTO-211H cells and was markedly increased by Se supplementation (Fig. 3, A–D). Furthermore, D2 co-localized with the endoplasmic reticulum-specific marker BiP as found previously in HEK-293 and neuroblastoma cells transiently expressing hD2 (Fig. 3, E–H) (27). Despite successful IP of the D2 protein and activity, we were unable to visualize D2 by Western blot analysis presumably because of low antibody affinity for denatured protein, low D2 expression, or both.

A short half-life and the acceleration of endogenous D2 degradation by exposure to substrates observed in pituitary tumor cells and in cells transiently expressing D2 are reproduced in these experiments. A short half-life (<1 h) is characteristic of D2 in all cells studied (11, 24, 31) and is explained by the fact that D2 is the target of selective ubiquitination and proteolysis by the proteasomal system (24–26). This is also the case in MSTO-211H cells, in which D2 activity and 75Se-D2 protein levels were extremely sensitive to inhibitors of the proteasomal pathway (Fig. 2, B–E). It is remarkable that in GH4C1 rat pituitary tumor and transfected HEK-293 cells, treatment with proteasomal inhibitors for 1 h increases D2 activity by only ~20% (24, 25) whereas in the present study a similar treatment resulted in a 3–4-fold increase in activity (Fig. 2C). This can be explained by a more rapid turnover of the enzyme in mesothelioma cells. Furthermore, as in pituitary tumor cells and transfected HEK-293 cells, exposure to T4, the preferred D2 substrate, accelerates the turnover, increasing D2 co-localized with the endoplasmic reticulum (24–26). In addition, it has been shown that normally does not express deiodinase, the other being the high levels of D3 in hemangiomas (38). It will be of interest to determine whether primary mesotheliomas also express high levels of D2 and what, if any, effects of increased rate of T4 to T3 conversion might have in these cells.

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