Mouse Retinal Dehydrogenase 4 (RALDH4), Molecular Cloning, Cellular Expression, and Activity in 9-cis-Retinoic Acid Biosynthesis in Intact Cells*

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This study describes cDNA cloning and characterization of mouse RALDH4. The 2.3-kb cDNA encodes an aldehyde dehydrogenase of 487 amino acid residues, about two-orders of magnitude more active in vitro with 9-cis-retinal than with all-trans-retinal. RALDH4 recognizes as substrate 9-cis-retinal generated in transfected cells by the short-chain dehydrogenases CRAD1, CRAD3, or RDH1, to reconstitute a path of 9-cis-retinoic acid biosynthesis in situ. Northern blot analysis showed expression of RALDH4 mRNA in adult mouse liver and kidney. In situ hybridization revealed expression of RALDH4 in liver on embryo day 14.5, in adult hepatocytes, and kidney cortex. Immunohistochemistry confirmed RALDH4 expression in hepatocytes and showed that hepatocytes also express RALDH1, RALDH2, and RALDH3. Kidney expresses the RALDH4 protein primarily in the proximal and distal convoluted tubules of the cortex but not in the glomeruli or the medulla. Kidney expresses RALDH2 in the proximal convoluted tubules of the cortex but not in the distal convoluted tubules or glomeruli. Kidney expresses RALDH1 and RALDH2 in the medulla. The enzymatic characteristics of RALDH4, its expression in fetal liver, and its unique expression pattern in adult kidney compared with RALDH1, -2, and -3 suggest that it could meet specific needs for 9-cis-retinoic acid biosynthesis.

All-trans-retinoic acid (atRA)1 induces a variety of biological responses by modulating gene expression to control differentiation or entry into apoptosis of diverse cell types in numerous organs (1–3). atRA seems to function as the major RAR ligand in vivo and satisfies all known retinoid endocrine functions (4–6). 9cRA has been identified as an RXR ligand in cells treated with atRA and serves as a high-affinity ligand for both RAR and RXR in vitro (7, 8). RXR forms heterodimers with numerous nuclear receptors, including RAR, vitamin D receptor (VDR), and peroxisome proliferator-activated receptor (PPAR). The heterodimers seem to require only the non-RXR ligands for maximum activation, if present in sufficient concentrations. Nevertheless, 9cRA increases heterodimer activation in vitro when non-RXR ligand concentrations fall below maximum. 9cRA and its analogues may affect disease progression, including noninsulin-dependent diabetes mellitus and specific cancers (9, 10). If endogenous 9cRA has important functions in vivo, its biosynthesis likely would be controlled. Understanding control would require detailed knowledge of the enzymes that catalyze 9cRA biosynthesis and their expression loci.

RA biosynthesis from retinol proceeds via two reactions with retinal as an intermediate (11). Only one mouse SDR, RDH1, functions efficiently with all-trans-retinol, but at least three mouse SDR, RDH1, CRAD1, and CRAD3, function efficiently with 9-cis-retinol (12–15). Four different RALDH have been identified that convert all-trans- or 9-cis-retinal into RA. All belong to the ALDH superfamily, which consists of at least 86 eukaryotic members (16). ALDH1A1 (human ALDH1 (17, 18), mouse AHD2 (19), rat RALDH2 (20–23)) catalyzes conversion of all-trans- and 9-cis-retinal into atRA and 9cRA with similar efficiencies (Km/K0.5) (24). ALDH1A2 (human ALDH11 (25), mouse/rat RALDH2 (26, 27)) also catalyzes dehydrogenation of all-trans- and 9-cis-retinal into RA but functions about 4-fold less efficiently with 9-cis- than with all-trans-retinal (11, 24). ALDH1A3 (mouse RALDH3 (28)) catalyzes dehydrogenation of all-trans-retinal efficiently but not that of 9-cis-retinal.2 A fourth candidate, the human ALDH12 (not the same enzyme as Δ1-pyrroline-5-carboxylate, which also has been designated ALDH12/ALDH8A1 (29, 30)), has considerable activity with 9-cis-retinal but negligible activity with all-trans-retinal (31). It is the only known ALDH more efficient for 9-cis-retinal than for all-trans-retinal.

Here, we report cDNA cloning and characterization of a new mouse ALDH, RALDH4, and its mRNA and protein expression patterns in the adult and embryo. We reconstituted 9cRA biosynthesis in intact cells to compare the activity of mRALDH4 to the other two mouse RALDH (RALDH1 and RALDH2) that recognize 9-cis-retinal and to assess ability of the three RALDH to generate 9cRA from 9-cis-retinal produced in intact cells by the retinol dehydrogenases mCRAD1, mCRAD3, and mRDH1. We found that RALDH4 functions in intact cells to generate 9cRA when co-expressed with CRAD1, CRAD2, or RDH1 and has a unique expression pattern in kidney compared with the other RALDH.

1 The abbreviations used are: atRA, all-trans-retinoic acid; CRAD, cis-retinoid/androgen dehydrogenase; e, mouse embryo day; RACE, rapid amplification of cDNA ends; RALDH, retinal dehydrogenase(s); RA, 9-cis-retinoic acid; RAR, retinoic acid receptor(s); mRDH1, mouse retinol dehydrogenase type 1; RXR, retinoid X receptor(s); SDR, short-chain dehydrogenase/reductase(s); CHO, Chinese hamster ovary.

2 Min Lin and J. L. Napoli, unpublished data.
FIG. 1. Amino acid sequences of mouse and rat RALDH4 and the human ortholog. Underscoring indicates residues that differ in each species. Boldface identifies the 23 invariant residues in the ALDH superfamily. The box shows the peptide used to generate antibodies.

Mouse RALDH4

| Amino acid sequence comparisons of mouse RALDH |
|------------------------|------------------------|
| GenBank™ accession numbers are provided in parentheses. |

**TABLE I**

| Molecule | RALDH4 (AF510322) | RALDH1 (P24459) | RALDH2 (Q6E418) | RALDH3 (AAF07246) |
|-----------|------------------|-----------------|------------------|------------------|
| % similarity | 48/39 | 48/39 | 75/67 | 78/70 |
| 100/100 | 4/100 | 2/100 | 3/100 |
| 50/39 | 50/39 | 50/39 | 50/39 |
| 48/38 | 48/38 | 48/38 | 48/38 |
| 48/39 | 48/39 | 48/39 | 48/39 |
| 79/71 | 79/71 | 79/71 | 79/71 |
| 75/67 | 75/67 | 75/67 | 75/67 |
| 78/70 | 78/70 | 78/70 | 78/70 |
| 100/100 | 100/100 | 100/100 | 100/100 |

**Reconstitution in Intact Cells**—The day before transfection with LipofectAMINE 2000 (Invitrogen), CHO-K1 cells were seeded into 6-well plates. 24 h after transfection, the medium was replaced with fresh medium (1 ml/well) containing 1 μM 9-cis-retinol. After 1 h of incubation, cells and medium were extracted to quantitite 9cRA.

**In Situ Hybridization**—The same probe used for Northern blot hybridization was cloned into pGEM-T (Promega) for sequencing.

**Western Blot and Immunohistochemistry**—Rabbit antibodies were raised against peptides designed from mouse RALDH4 (residues 406–419, DSEEVETRNSFR), RALDH1 (residues 434–455, TKLDLKAITVSS), RALDH2 (residues 482–493, REYSEKTVTTYK), and RALDH3 (residues 446–459, KNLKDALKLAAL). Each was purified by affinity chromatography using peptide coupled to N-hydroxy-
Slides were incubated with 1.5% blocking serum at room temperature. pcDNA3/RALDH2 (open bars), pcDNA3/RDH1 (filled bars). Bottom panel, in a separate experiment, CHO cells were transfected with pcDNA3/RAD1 (0, 0.25, 0.5, and 1 µg) and 0.5 µg of pcDNA3/RALDH1 (D, open bars), pcDNA3/RALDH2 (E, striped bars), pcDNA3/RALDH4 (F, filled bars; 0.25, 0.5, and 1 µg vector only). Data are pmol 9cRA generated per well in 1 h of incubation from 1 µM 9-cis-retinol (means ± S.D., n = 3). Western blots are shown below each graph. The top rows show expression from the varied vectors; the bottom rows show expression from the fixed vectors.

**FIG. 3.** Contribution of mRALDH4 to 9cRA acid biosynthesis in intact cells. Top panel, CHO cells were transfected with pcDNA3/RALDH4 (0, 0.25, 0.5, and 1 µg, left to right) and 0.5 µg of one of three vectors that express SDR, which generate 9-cis-retinol from 9-cis-retinol. A, pcDNA3/CRAD1 (open bars). B, pcDNA3/CRAD3 (striped bars); C, pcDNA3/RD1 (filled bars). Bottom panel, in a separate experiment, CHO cells were transfected with pcDNA3/CRAD1 (0, 0.25, 0.5, and 1 µg) and 0.5 µg of pcDNA3/RALDH1 (D, open bars), pcDNA3/RALDH2 (E, striped bars), pcDNA3/RALDH4 (F, filled bars; 0.25, 0.5, and 1 µg vector only). Data are pmol 9cRA generated per well in 1 h of incubation from 1 µM 9-cis-retinol (means ± S.D., n = 3). Western blots are shown below each graph. The top rows show expression from the varied vectors; the bottom rows show expression from the fixed vectors.

**Fig. 4.** mRNA expression of mRALDH4 in adult and embryo. Adult tissues screened included: heart (1); brain (2); spleen (3); lung (4); liver (5); skeletal muscle (6); kidney (7); testis (8). Embryo samples assayed included: e7 (9); e11 (10); e15 (11); e17 (12). Blots were reprobed with β-actin (lower panels). α- or γ-Actin account for the faster-migrating bands.

**Fig. 5.** In situ hybridization of RALDH4 in mouse embryo. Silver grain signals represent hybridization of antisense cRNA against RALDH4; red signals represent nuclei stained by propidium iodide. Sense cRNA showed no signals (data not shown). A, RALDH4 signal was not detected within the heart or liver primordia of the e10.5 mouse. B, view of e14.5 embryo thoracic region showing low but specific expression of RALDH4 in liver. No signal was detected in lung, heart, mesentery, or other tissues. White arrows indicate liver. Magnifications are 10× for panel A and 4× for panel B.

**Fig. 6.** In situ hybridization of RALDH4 in adult mouse liver and kidney. Hybridization signals are represented by silver grains; nuclei were visualized with propidium iodide. A, antisense cRNA reveals robust RALDH4 transcript levels throughout liver. B, sense cRNA does not show significant hybridization in liver. C, antisense cRNA shows strong RALDH4 expression within the kidney cortex and low-to-absent expression within the medulla. D, sense cRNA does not show significant hybridization in adult kidney. Magnification is 4× in all panels.

**RESULTS**

cDNA Cloning of Mouse RALDH4—Amplification by RACE of the 5'- and 3'-untranslated region of the expressed sequence tag clone IMAGE 987012 produced a cDNA of 2.3 kb that included 50 nucleotides upstream of the ATG start site, continued through the polyadenylation signal, and concluded with 22 adenosine residues (data not shown). The deduced amino acid sequence showed high identity with a human RALDH (90%) and with the partial sequence of a rat RALDH (91%) and...
contained all 23 invariant residues of the ALDH superfamily (Fig. 1). The mouse ALDH, designated RALDH4, shows no more than 50% amino acid sequence similarity with mouse RALDH1, -2, and -3 (Table I) (19–23).

**Enzymatic Properties**—Initial assays were done with 10 mM substrate and the 800 g supernatant of transfected CHO cells. mERALDH4 had high enzymatic activity with 9-cis-retinal (2.5 ± 0.2 nmol/min/mg protein; means ± S.D., n = 3), lower activity with 13-cis-retinal (0.6 ± 0.06), and very low activity with all-trans-retinal (0.03 ± 0.002). Kinetic constants were determined in two independent assays under initial velocity conditions with the most efficient substrate, 9-cis-retinal. The average $K_m$ value was 2.3 ± 0.3 μM (± S.E.) and the average $V_{max}$ value was 3.4 ± 0.1 nmol/min/mg (Fig. 2, top). Disulfiram and citral inhibited mRALDH4 activity with IC$_{50}$ values of 5.3 and 31 μM, respectively (Fig. 2, bottom). Acetaldehyde inhibited weakly (IC$_{50}$ value 9.6 mM).

mRALDH4 functioned in reconstituted paths of 9cRA biosynthesis in intact cells, with 9-cis-retinal generated in situ by mCRAD1, mCRAD3, or mRDH1 (Fig. 3). CRAD1 and CRAD3 were about equivalent in generating 9-cis-retinal, as predicted by their kinetic constants (13, 14), whereas RDH1 was less efficient, consistent with its greater efficiency with all-trans-retinol than 9-cis-retinol (15). RALDH4 was less efficient than RALDH1 or RALDH2 in generating 9cRA from 9-cis-retinal produced by CRAD1. Western blots showed that differences in protein expression did not contribute markedly to the differences in activities.

**mRNA Expression of Mouse RALDH4**—Northern blot showed intense expression of mRALDH4 mRNA in liver and kidney (Fig. 4). No signals were detected in six other tissues screened. Northern blot also showed expression at e15 and e17 but no signal at e7 or e11, indicating initiation of RALDH4 expression after e11 and on or before e15.

**In Situ Hybridization**—No mRALDH4 mRNA signal was detected in the e10.5 embryo, consistent with the Northern blot data (Fig. 5). At e14.5, expression was detected in liver but not in kidney or elsewhere except for low but consistent signals in some blood cell populations (data not shown). In the 4-week-old male mouse, RALDH4 mRNA was expressed throughout the liver and intensely in the kidney cortex (Fig. 6).
Expression of RALDH Protein in Adult Liver and Kidney—To test whether the anti-peptide antibodies were specific, Western blot analyses were done with lysates of CHO cells transfected with each RALDH construct. Each RALDH was detected as a 54-kDa band, and each antibody reacted specifically with its corresponding enzyme (Fig. 7).

Immunohistochemical staining of adult mouse liver sections showed that many but not all hepatocytes throughout the liver express the four RALDH (Fig. 8). No pattern emerged for RALDH expression in any particular liver section. Frequent signals for RALDH1 were detected in cells with lipid droplets (Fig. 8, panel 1, arrow). Signals for RALDH2 and 3 were much less frequent in cells with lipid droplets, and signals for RALDH4 did appear in cells with lipid droplets. The epithelial cells of the bile ducts and the endothelial cells of blood vessels showed no specific signal for any of the four enzymes. Negative controls (no primary antibody) showed no staining (Fig. 8C).

Immunohistochemistry showed that kidney expresses RALDH4 primarily in the cortex in the proximal and distal convoluted tubules, overlapping with its mRNA expression (Fig. 9A). RALDH4 was not detected in glomeruli (Fig. 9, B and C). RALDH1 produced weak signals close to background in the cortex (Fig. 9D) but showed strong signals in the medulla, localized to the straight segments of loops of Henle (Fig. 9F), collecting tubules (Fig. 9G), and thin segments of loops of Henle (Fig. 9H). RALDH2 was detected in the cortex in proximal convoluted tubules but not in distal convoluted tubules or glomeruli (Fig. 9E). RALDH2 also was detected in the medulla in collecting tubules (Fig. 9I) and straight segments of loops of Henle (Fig. 9J). Negative controls (no primary antibody) showed no signals (Fig. 9K). No RALDH3 signals were detected in kidney.

DISCUSSION

This report shows that a fourth mouse ALDH, RALDH4, recognizes retinoids as substrates. Mouse RALDH4 likely represents an ortholog of human ALDH12 because the two share 90% amino acid identity, have similar Km values for 9-cis-retinal (3.2 μM for ALDH12), do not catalyze all-trans-retinal dehydrogenation well, and are expressed intensely in the adult only in liver and kidney (31). Characterization of mouse RALDH4 extends insight into retinoid metabolism by demonstrating its generation of 9cRA in intact cells in cooperation with any one of three mouse SDR (CRAD1, CRAD3, RDH1) and by showing that its mRNA and protein expression patterns differ from the other RALDH. In contrast to RALDH4, the e14.5 mouse liver expresses RALDH1 mRNA weakly and does not express RALDH2 or RALDH3 mRNA (33, 34). This early intense expression of RALDH4 in fetal liver suggests a function in fetal hemopoiesis. This is significant because mouse embryos that lack RXRs have decreased erythropoietin expression and impaired erythropoiesis between e10.25 and e14.5 (35). These observations may provide insight into the mechanism for the synergistic effects of vitamin A and iron supplementation on erythropoiesis and relief of nutritional anemia relative to iron supplementation alone (36).

RALDH1 accounts for at least 90% of the all-trans-retinal and 9-cis-retinal dehydrogenase activities in adult rat/mouse liver and kidney (18, 19, 24). RALDH2, -3, and -4 contribute the remaining activity, without apparent domination by any one. Multiple RALDH expressed in hepatocytes, albeit not necessarily in the same hepatocytes, may allow differential regulation or may reflect the status of the cell cycle or differentiation state. Distinctive functions for each isozyme are suggested by the observation that adult mouse kidney cortex expresses RALDH2 and -4, whereas the medulla expresses RALDH1 and -2. Adult mouse kidney expresses RDH1 protein in both the cortex and medulla, which could provide 9-cis-retinal for 9cRA production by RALDH.4 The lack of a protein signal for RALDH3 in kidney contrasts with detection of RALDH3 mRNA in the collecting ducts of the renal papilla in fetal and adult mouse (34). It is not clear whether this reflects a technical problem or weak translation of RALDH3 mRNA and/or rapid turnover of RALDH3 protein in adult kidney.

Citril inhibits retinal metabolism catalyzed by rat RALDH1 and -2 and chick RALDH3 with IC50 values of 1, 12, and 3.5 μM, respectively, compared with the IC50 value of 25 μM with mRALDH4 (20, 23, 28). Areas affected morphologically by citral have been considered loci of RA biosynthesis and signaling, even though no data indicates that citral inhibits RALDH and/or any ALDH specifically. The aldehyde functional group of citral could impair actions of many proteins through Schiff’s base formation unrelated to active site binding. Acetaldehyde inhibition of all RALDH suggests potential impairment of RA generation through two mechanisms, competition at active sites and acetylation of lysine residues. In summary, this study describes cDNA cloning and characterization of mouse RALDH4, an enzyme active with endogenously generated 9-cis-retinal in intact cells. RALDH4 has different expression during embryonic development and in the adult kidney compared with three other mouse RALDH. RALDH4 can function with any one of CRAD1, CRAD3, or RDH1 to reconstitute a path of 9cRA biosynthesis in cells. These data are consistent with a distinct contribution of RALDH4 to retinoid metabolism.

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* The standardized ALDH nomenclature approved by HUGO has named 17 human ALDH genes, but the human ALDH with 9-cis-retinal dehydrogenase activity reported in Ref. 31 as ALDH12 was not among them. The trivial name ALDH12 has been assigned to Δ4-pyrroline-5-carboxylase (16).

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