short communication

Identification of mouse palmitoyl-coenzyme A Δ9-desaturase

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Abstract **Stearoyl-coenzyme A desaturase (SCD) catalyzes the desaturation of saturated fatty acids to monounsaturated fatty acids in mammalian cells. Currently, there are four known enzymatic isoforms (SCD1–SCD4) in the mouse genome. The physiological roles for multiple SCD isoforms and their substrate specificities are unknown at present. We report here distinct substrate specificities for the mouse SCD isoforms. Each SCD isoform was able to complement the *ole1* mutation in *Saccharomyces cerevisiae* through heterologous expression of transgenic SCD. Fatty acid analysis showed that mouse SCD1, SCD2, and SCD4 desaturate both C18:0 and C16:0, whereas mouse SCD3 uses C16:0 but not C18:0. We identify SCD3 as a mammalian palmitotyl-CoA Δ9-desaturase, and its existence in mouse helps explain distinct physiological roles for each SCD isoform.**—Miyazaki, M., S. M. Bruggink, and J. M. Ntambi. **Identification of mouse palmitoyl-coenzyme A Δ9-desaturase. *J. Lipid Res.* 2006.** 47: **700–704.**

Supplementary key words stearoyl-CoA desaturase • oleate • palmitoleate • substrate specificity

Δ9-desaturase is a fatty acid-modifying enzyme in the biosynthesis of monounsaturated fatty acids. Because this enzyme commonly introduces a *cis* double bond at the 9,10 position of stearoyl-CoA to form oleoyl-CoA, it has been commonly known as stearoyl-coenzyme A desaturase (SCD) (1–5). Four SCD isoforms (SCD1–SCD4) have been characterized in mice (6–9). All mouse SCD genes are colocalized to chromosome 19 (9).

Despite the fact that the four SCD isoforms share >75% nucleotide and amino acid sequence identities, they differ in their 5′-flanking promoter, which results in divergent tissue-specific expression (2). SCD1 is expressed in lipogenic tissues, including liver and adipose tissue (8). SCD2 is expressed primarily in the brain and neuronal tissue, particularly during the neonatal mylenation period (6). SCD3 expression is restricted to sebocytes in skin, preputial gland, and Harderian gland (9–11). SCD4 is expressed predominantly in heart (7). Mouse SCD1 and SCD2 are the best characterized isoforms because of the availability of SCD1 and SCD2 knockout mice ($SCD1^{-/-}$ and $SCD2^{-/-}$) (12, 13). Adult $SCD1^{-/-}$ mice exhibit a decrease in the synthesis of esterified lipids, including triglycerides, cholesteryl esters, and wax esters. As a consequence, $SCD1^{-/-}$ mice are protected against adiposity and liver steatosis, but they develop alopecia and close eye fissure (12, 14, 15). In contrast, SCD2 mice have a defect in skin permeability barrier formation and show a decrease in the synthesis of lipids during early development but not at late stages of development (13). These results have suggested that although SCD1 is crucial in adult mice, SCD2 controls lipid metabolism in early life.

Currently, it is unknown why multiple SCD isoforms exist in mammalian genomes. Both the tissue-specific expression and the resulting phenotypes of SCD1 and SCD2 mouse isoform knockouts suggest that each isoform has a distinct physiological role; however, it is not clear how the enzymes accomplish the different roles biochemically. Liver microsomes from $SCD1^{-/-}$ and $SCD2^{-/-}$ mice displayed a decrease in the conversions of both 18:0-CoA and 16:0-CoA to 18:1-CoA and 16:1-CoA, respectively, suggesting that SCD1 and SCD2 synthesize oleate (18:1Δ9) and palmitoleate (16:1Δ9) (12, 13). However, microsomes from the Harderian gland of $SCD1^{-/-}$ mice still displayed very high SCD activity toward 16:0-CoA, despite the undetectable level of activity toward 18:0-CoA (10), suggesting the existence of 16:0-CoA-specific Δ9-desaturase in the Harderian gland of mouse. Although each isoform explicitly desaturates at the Δ9 position of saturated acyl-CoAs, it is clear that both 16:0 and 18:0 fatty acids can be used as substrates.

To determine the physiological basis of each mouse SCD isoform, we conducted substrate specificity assays to ascertain isoform preferences for 16:0 and 18:0 acyl-CoAs. We demonstrate in this study that SCD1, SCD2, and SCD4

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Abbreviations: PCD, palmitoyl-coenzyme A Δ9-desaturase; SCD, stearoyl-coenzyme A desaturase.

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use both C16 and C18 saturated acyl-CoAs. SCD3 desaturates 16:0-CoA but not 18:0-CoA.

MATERIALS AND METHODS

Cloning of full-length mouse SCD cDNAs

The full coding regions of mouse SCD isoforms (mSCD1, M21280; mSCD2, M26269; mSCD3, AF272037; mSCD4, AY430080) were generated by PCR using mouse tissue cDNAs as templates and 5′ primers, which contain a sequence of N-terminal hemagglutinin epitope tag and a *Eco*RI restriction enzyme site, and 3′ primers, which contain a stop codon and a *Xho*I restriction enzyme site. The resulting PCR product was cloned into either a yeast expression vector, p426GPD (16), or a mammalian expression vector, pcDNA3 (Invitrogen).

Functional analysis

The p426GPD constructs harboring the mouse SCDs were transformed into *Saccharomyces cerevisiae* strain L8-14C (17) (provided by Dr. Charles Martin, Rutgers University), which contains a disruption of the yeast Δ9-desaturase gene OLE1 using the lithium acetate standard method (18). This *S. cerevisiae* strain requires unsaturated fatty acids for growth. The transformed yeast cells were plated onto a synthetic dextrose medium containing 1% Tergitol NP-40, 0.5 mM oleic acid, and 0.5 mM palmitoleic acid but lacking uracil. To test the genetic complementation of the mutant yeast strain, transformed yeast cells were plated onto yeast peptone dextrose (YPD) medium lacking unsaturated fatty acids. Plates were incubated at 30°C for 3 days.

HeLa cells were cultured at 37°C in a humidified 5% CO_2 atmosphere in Dulbecco's modified Eagle's medium supplemented with 10% (v/v) fetal bovine serum and penicillin/streptomycin. The cells were resuspended in cytomix buffer (120 mM KCl, 0.15 mM $CaCl_2$, 25 mM HEPES/KOH, pH 7.6, 2 mM EGTA, and 5 mM $MgCl_2$), and 400 μl of suspension was transferred to a 0.4 cm electroporation cuvette (Invitrogen). Thirty-five micrograms of pcDNA3 DNA harboring one of the mouse SCD constructs was transfected into HeLa cells. Plasmid DNA was added to the cell suspension in the cuvette and mixed. The mixture was then exposed to a single electric pulse of 300 V with a capacitance of 1,000 μF using an Invitrogen pulse system. The cells were allowed to recover in culture medium at 37°C (5% CO_2 atmosphere) for 48 h before harvesting and SCD activity assays.

Fatty acid analysis

Yeast cells were grown in liquid YPD medium lacking unsaturated fatty acids for 3 days. Cells were pelleted and washed twice with water, followed by suspension in 0.5 ml of 2 M NaOH in methanol. The mixture was then heated to 80°C for 1 h and acidified with formic acid. Fatty acids were extracted according to Bligh and Dyer's method (19) and transmethylated with 1 ml of 14% BF_3 in methanol (Sigma). The resulting fatty acid methyl esters were extracted with hexane and analyzed by gas-liquid chromatography (12, 20, 21). Exogenous saturated fatty acids (0.2 mM) were added into YPD in the presence of 1% Tergitol NP-40 (Sigma). The double bond positions of the monounsaturated fatty acid methyl ester were determined by GC-MS analysis of the dimethyl disulfide derivatives (11, 22).

Δ9-desaturase activity

Microsomes were purified from HeLa cells by differential centrifugation and resuspended in a 0.1 M potassium phosphate buffer (pH 6.8). Δ9-desaturase activity was assayed at 25°C for 7 min with either [^{14}C]stearoyl-CoA or [^{14}C]palmitoyl-CoA, 2 mM NADH, and 100 μg of microsomal protein (12).

Immunoblot analysis

Yeast protein extract was electrophoresed by 8% SDS-PAGE and transferred to a nitrocellulose membrane (Millipore). The membrane was blocked at room temperature for 1 h in TBS containing 0.1% Tween 20 containing 1% BSA and then incubated at room temperature with 100 ng/ml anti-hemagglutinin monoclonal antibody (clone 3F10; Roche) in TBS containing 1% BSA for 1 h. After washing with TBS containing 0.1% Tween 20, the membrane was incubated with a 1:20,000 dilution of horseradish peroxidase-conjugated anti-rat IgG (Sigma) for 30 min at room temperature. The signal was visualized with the ECL Western blot detection kit (Pierce).

Statistical analysis

All data are expressed as means ± SEM. An unpaired Student's *t*-test was used to determine significance.

RESULTS

To study the function of mouse SCD genes (SCD1–SCD4), the open reading frames of the genes were subcloned in the episomal yeast expression vector p426GPD, which encodes uracil prototrophy under the constitutive glyceraldehyde-3-phosphate dehydrogenase promoter. The resulting plasmid was used to transform L8-14C, a Δ9-desaturase (OLE1)-deficient yeast strain. As shown in **Fig. 1**, yeast transformed with plasmids containing each SCD were able to grow on YPD plates lacking unsaturated fatty acids, indicating that the mouse Δ9-desaturases were functional in yeast by their ability to complement the *ole1* mutation. The fatty acid compositions of transformants as determined by gas-liquid chromatography are shown in **Table 1**. Yeast expressing mSCD1 and mSCD2 had similar fatty acid compositions and converted 85% and 77% of 18:0 to 18:1Δ9 and 51% and 36% of 16:0 to 16:1Δ9,

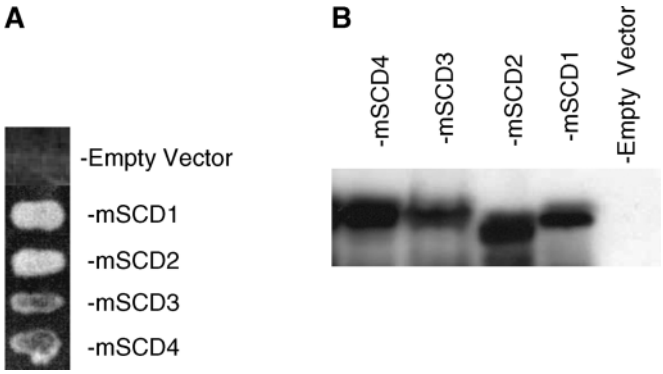

Fig. 1. Growth of yeast *ole1* mutant strain L8-14C containing mammalian Δ9-desaturases. A: L8-14C plated onto medium lacking unsaturated fatty acids. B: Western blot analysis of yeast L8-14C expressing mammalian Δ9-desaturases. Ten micrograms of total protein was subjected to 10% SDS-PAGE. mSCD, mouse stearoyl-coenzyme A desaturase.

TABLE 1. Fatty acid composition of total lipids in L8-14C transformants

SCD Isoform	Fatty acid composition					Percent conversion of 16:0	Percent conversion of 18:0
	16:0	16:1n-7	18:0	18:1n-9	18:1n-7		
	%						
SCD1	49.9	27.9	3.3	18.3	0.6	36.4	84.8
SCD2	41.6	42.9	3.3	11.2	1.0	51.4	77.3
SCD3	42.7	40.0	16.2	0.0	1.1	49.0	0.3
SCD4	60.1	5.9	27.8	5.6	0.6	9.7	16.8

SCD, stearoyl-coenzyme A desaturase. Data represent the content of each fatty acid in percentage of total fatty acids (n = 5). Standard errors of the mean were all <10% and are omitted for clarity.

respectively. mSCD4 used 8% of 16:0 and 13% of 18:0, but the conversion rates were lower than those of SCD1 and SCD2. Therefore, the mouse SCD1, SCD2, and SCD4 enzymes desaturate 16:0 and 18:0 to 16:1Δ9 and 18:1Δ9, respectively, although the three enzymes preferably use 18:0 compared with 16:0. SCD3 converted 49% of 16:0 to 16:1Δ9, but the conversion of 18:0 to 18:1Δ9 was <2%, suggesting that this isoform prefers C16:0 as a substrate. Immunoblot analysis with a hemagglutinin antibody showed that all Δ9-desaturase proteins were expressed in yeast at the expected size (Fig. 1B). The Δ9 positions of the double bond in all monounsaturated fatty acids were determined by GC-MS analysis of the dimethyl disulfide derivatization. As expected, the mass spectra of 16:1 and 18:1 in yeast expressing any SCD showed the characteristic Δ9 unsaturated fragment ions at *m/z* 217 and 185 (data not shown).

To determine whether the mouse SCD isoforms desaturate other saturated fatty acids, we exogenously provided the saturated fatty acids (0.2 mM) to yeast expressing each SCD isoform (**Fig. 2**). SCD1 and SCD2 converted 13% and 14% of 13:0 to 13:1Δ9, 11% and 14% of 14:0 to 14:1Δ9, 43% and 31% of 17:0 to 17:1Δ9, and 30% and 45% of 17:0 to 17:1, respectively. mSCD3 converted 14% of 12:0, 32% of 13:0, and >50% of 14:0 to 12:1Δ9, 13:1Δ9, and 14:1Δ9, respectively. The conversion of 17:0 to 17:1Δ9 was undetectable in yeast expressing SCD3. SCD4 used only 2.9% of 14:0 and 5.7% of 17:0, suggesting that mSCD4 may use other acyl-CoAs as major substrates. None of the SCD isoforms used a C10:0 or C20:0 saturated fatty acid.

To determine whether the mouse SCDs displayed similar substrate specificities in mammalian cells, we recloned

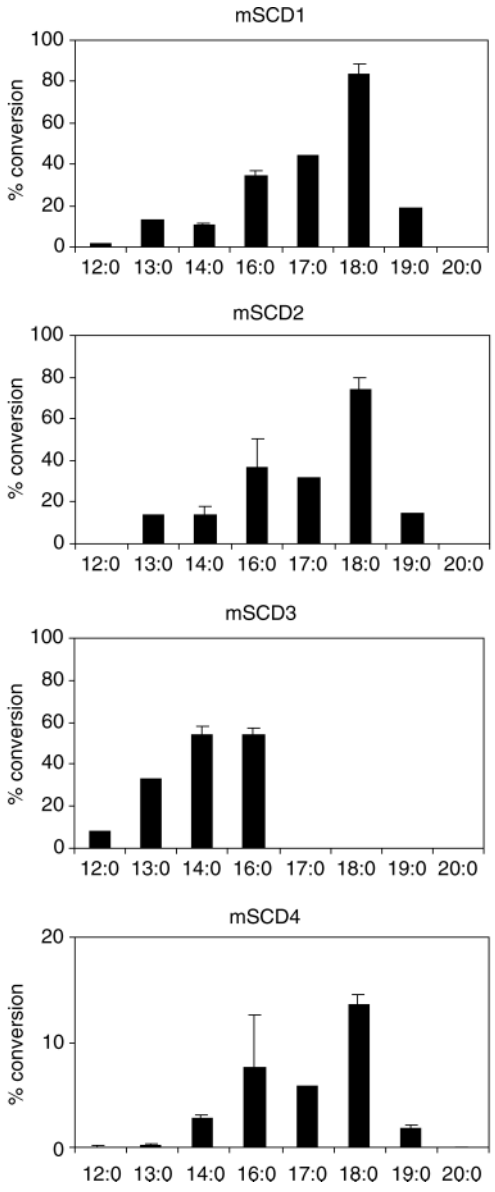

Fig. 2. Conversion of saturated fatty acids to Δ9 monounsaturated fatty acids. Fatty acids (0.2 mM) were added in the presence of 1% Tergitol NP-40, and yeast cells were cultured for 2 days. Values represent mean conversion (%) ± SEM (n = 5).

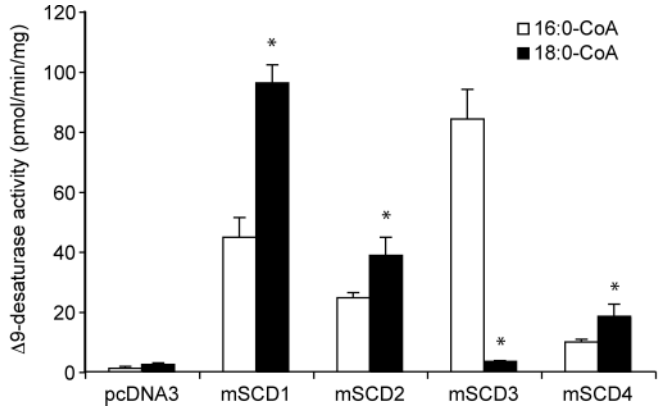

Fig. 3. Δ9-desaturase activity in HeLa cells overexpressing mouse Δ9-desaturases. Microsomal fractions (100 μg) were incubated with either [^{14}C]stearoyl-CoA or [^{14}C]palmitoyl-CoA in the presence of NADH. Each value represents the mean ± SEM (n = 4) * $P < 0.001$ versus 16:0-CoA.

the Δ9-desaturases into a mammalian expression vector and transfected them into HeLa cells (human cervical cancer cells), which have very low Δ9-desaturase activity compared with other human cell lines, including HEK-293, HepG2, CHO, MDA, and MCF-7 cells (data not shown). 16:0-CoA and 18:0-CoA were used as substrates because 16:1Δ9 and 18:1Δ9 are the major monounsaturated fatty acids in mammalian cells. The substrate preferences of all of the Δ9-desaturases in mammalian cells are consistent with those found in yeast experiments. HeLa cells overexpressing mSCD1, mSCD2, and mSCD4 used 16:0-CoA and 18:0-CoA, but with 2.2-, 1.6-, and 2.0-fold higher Δ9-desaturase activity, respectively, toward 18:0-CoA than 16:0-CoA. mSCD3 showed high activity toward 16:0-CoA, but its activity toward 18:0-CoA was not detectable (**Fig. 3**).

DISCUSSION

There are four known Δ9-desaturase isoforms in mouse that are required for the biosynthesis of monounsaturated fatty acids, mainly oleate and palmitoleate (2). However, except for rat SCD1 (17), the substrate specificities of mammalian Δ9-desaturases have not been characterized in detail. In addition, the reasons for the existence and tissue-specific expression of the multiple isoforms remain unknown. Using two different models [*1*) a Δ9-desaturase-deficient yeast strain that requires unsaturated fatty acids for growth, and *2*) HeLa cells (human cervical cancer cells), which have very low activity of Δ9-desaturase], we demonstrated that mouse SCD isoforms have different substrate specificities. Based on the results from both experiments, mSCD1 and mSCD2 are capable of using 16:0-CoA and 18:0-CoA, although there was an ~2-fold higher preference toward 18:0-CoA over 16:0-CoA. SCD4 also used both 16:0 and 18:0, but the activity was lower than those of other isoforms. Therefore, the preferential substrates of SCD4 may be undetermined. SCD3 uses C16:0 but not C18:0. Based on this observation, SCD3 should be named palmitoyl-coenzyme A Δ9-desaturase-1 (PCD1).

The substrate recognition of plant acyl-acyl-carrier protein Δ9-desaturase has been studied extensively because of the availability of the crystal structure (23). Using structural prediction and site-specific mutagenesis, the tryptophan at position 118 was shown to control the chain length specificity of plant 16:0-acyl-carrier protein-specific Δ9-desaturase (23). However, all of the tryptophans in the predicted catalytic sites located between the first histidine box and the C terminus are conserved in the mouse Δ9-desaturases. Despite the distinct substrate preferences described above, the presumed catalytic sites of mouse SCDs, particularly between SCD1 and PCD1/SCD3, are very similar (>94%) (7, 9). The amino acid alterations between these two proteins are concentrated in 20 amino acid residues before the third histidine box, suggesting that an amino acid in this portion of the protein might distinguish substrates as a result of their chain lengths. More studies are required to resolve this issue.

Although the reason for the existence of PCD1/SCD3 and its ability to produce shorter chain monounsaturated fatty acids is unknown, it could be attributable to the unique tissue-specific distribution of the SCD genes and the difference in melting point of their monounsaturated fatty acid products. PCD1/SCD3 is highly expressed in skin sebaceous glands, which produce lipid secretions (mainly wax ester) referred to as sebum (9). The most abundant monounsaturated fatty acid in sebum is 16:1 (24). Because skin is poikilothermal, sebum is easily affected by the environmental temperature. The melting point of 16:1Δ9 (0.5°C) is lower than that of 18:1Δ9 (16.2°C). Thus, 16:1Δ9 appears to be more resistant to cold temperature and could be preferentially used by acyl-CoA wax alcohol acyltransferases (AWAT1 and AWAT2) (25) in the synthesis of skin waxes. The skin of $SCD1^{-/-}$ mice exhibits alopecia, atrophy of the sebaceous gland, and decreased sebum production (12, 26). Interestingly PCD1/SCD3 expression was lost in skin sebocytes of $SCD1^{-/-}$ mice (9, 11). These data suggest that 16:1Δ9 synthesized from PCD1/SCD3 is an important fatty acid in the skin functions of wax production and hair growth. In addition, we previously found that Harderian gland sebocytes of $SCD1^{-/-}$ mice have greater SCD activity toward 16:0-CoA than 18:0-CoA, and the reduction in the levels of 16:1Δ9 and its metabolites in the Harderian gland of $SCD1^{-/-}$ mice is less than that of 18:1Δ9 and its metabolites (10). Therefore, we conclude that the residual palmitoyl-CoA desaturase activity in the Harderian gland of $SCD1^{-/-}$ mice is that of PCD1/SCD3.

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