# The surprising diversity of Δ6-desaturase substrates

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## Abstract

**A single gene encoding a Δ6-desaturase (FADS2) has been isolated and characterized in mammalian species. This Δ6-desaturase plays a major role in the biosynthesis of PUFAs (polyunsaturated fatty acids). It catalyses the rate-limiting desaturation of linoleic acid ($C_{18:2}$ $n-6$) and α-linolenic acid ($C_{18:3}$ $n-3$) required for the biosynthesis of long-chain PUFAs. Moreover, recent studies have provided strong evidence that this Δ6-desaturase also acts on 24-carbon PUFAs of both the $n-6$ and $n-3$ series. Another substrate of this Δ6-desaturase has been identified through complementary works from different investigators. This Δ6-desaturase acts on a saturated fatty acid, palmitic acid ($C_{16:0}$), leading to the newly characterized biosynthesis of hexadecenoic acid ($C_{16:1}$ $n-10$) or sapienate.**

## Introduction

In mammals, at least three distinct desaturase enzymes introduce double bonds at the Δ9, Δ6 and Δ5 positions along the carbon fatty-acyl chains of some fatty acid substrates. Δ9-Desaturase, also named SCD (stearoyl-CoA desaturase), catalyses the rate-limiting step in the biosynthesis of monounsatured fatty acids. In mouse, four isoforms of SCD have been identified [1]. In human, a single SCD gene which is highly similar to mouse genes has been cloned and characterized [2].

Δ6- and Δ5-desaturases govern rate-limiting steps in the biosynthesis of long-chain PUFAs (polyunsaturated fatty acids). The biosynthesis of long-chain PUFAs from $C_{18:2}$ $n-6$ and $C_{18:3}$ $n-3$ involves successive desaturation and elongation steps. The first step is the Δ6-desaturation of the 18-carbon precursors of the $n-6$ and $n-3$ series. The Δ6-desaturase cloned from human [3] and rodents [3,4], i.e. FADS2 [5], was shown to catalyse this initial reaction. The second Δ6-desaturation step from $C_{24:4}$ $n-6$ to $C_{24:5}$ $n-6$ and from $C_{24:5}$ $n-3$ to $C_{24:6}$ $n-3$, initially described by Sprecher and co-workers [6], had to be further explored.

More recently, a palmitoyl-CoA Δ6-desaturase was reported for the first time to be present in mammals [7]. This finding has emerged from detailed study of the prepucial gland of mice with targeted disruption of SCD1, a major isoform of Δ9-desaturase. In this work, the impairment of $C_{16:1}$ $n-7$ biosynthesis in SCD1$^{-/-}$ mice correlated with an increased level of $C_{16:1}$ $n-10$. The palmitoyl-CoA Δ6-desaturase responsible for this increased biosynthesis was not identified.

We investigated the possibility that the rat Δ6-desaturase which acts on 18-carbon PUFA also acts on 24-carbon PUFA and on palmitic acid. Together with results obtained by other investigators, our data demonstrate a remarkable diversity of Δ6-desaturase substrates.

## Δ6-Desaturase acts twice in long-chain PUFA biosynthesis

In long-chain PUFA biosynthesis the conversion step from $C_{22:4}$ $n-6$ to $C_{22:5}$ $n-6$ and from $C_{22:5}$ $n-3$ to $C_{22:6}$ $n-3$ has remained controversial for years. One opinion is that this step depends on a microsomal Δ4-desaturation [8]. Another theory proposed by Sprecher and co-workers [6] is a Δ4-desaturase-independent pathway including two successive elongations producing 24-carbon fatty acid intermediates, followed by a Δ6-desaturation of these 24-carbon fatty acids in the microsomes, and a final chain-shortening in the peroxisomes.

We addressed the possible role of the rat Δ6-desaturase, known to act on $C_{18:2}$ $n-6$ and on $C_{18:3}$ $n-3$, in the conversion of $C_{24:4}$ $n-6$ to $C_{24:5}$ $n-6$ and $C_{24:5}$ $n-3$ to $C_{24:6}$ $n-3$. To investigate this hypothesis, we transiently expressed rat Δ6-desaturase [9] in COS-7 cells. We provided strong evidence in these mammalian cells that a high level of rat Δ6-desaturase expression was correlated with a significant activity on both 18- and 24-carbon PUFAs of the $n-3$ series. Our results also suggested a similar mechanism in the $n-6$ series. In a yeast expression model, de Antueno et al. [10] obtained similar results with the human Δ6-desaturase, homologue to the rat Δ6-desaturase we studied.

## SCD1 disruption reveals a new substrate of Δ6-desaturase

Recent findings, by Ntambi and Miyazaki [11], using a mouse model with disruption of SCD1 gene expression have highlighted the role of *de novo* oleate production and the physiological roles of SCD1. Their characterization of this

**Key words:** Δ6-desaturase, FADS2, palmitic acid, polyunsaturated fatty acid (PUFA).
**Abbreviations used:** PUFA, polyunsaturated fatty acid; SCD, stearoyl-CoA desaturase.
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mouse model also revealed for the first time the presence of a palmitoyl-CoA Δ6-desaturation in animals [7]. They demonstrated a Δ6-desaturation in the preputial gland, a sebaceous gland of the urogenital tract, of SCD1$^{-/-}$ mice in which $C_{16:1}$ $n-10$ content was markedly increased.

To investigate the putative involvement of Δ6-desaturase (FADS2) in this synthesis, we incubated COS-7 cells expressing rat Δ6-desaturase with palmitic acid ($C_{16:0}$). Transfected cells were able to synthesize $C_{16:1}$ $n-10$, while non-transfected cells did not produce any $C_{16:1}$ $n-10$. Thus rat Δ6-desaturase which acts on the 18- and 24-carbon PUFAs (FADS2) is also able to catalyse palmitic acid Δ6-desaturation [12]. We also performed similar incubation of COS-7 cells expressing both Δ6-desaturase and SCD1 Δ9-desaturase with palmitic acid. In these experimental conditions, we showed that conversion of $C_{16:0}$ to $C_{16:1}$ $n-10$ was limited while the conversion of $C_{16:0}$ to $C_{16:1}$ $n-7$ was greatly increased. Thus we propose that $C_{16:1}$ $n-10$ biosynthesis may occur in tissues with a high level of Δ6-desaturase (FADS2) expression and a low level of SCD1 expression, such as in human sebaceous glands [13]. Consistent with this proposal, the palmitoyl-CoA Δ6-desaturase identified in SCD1$^{-/-}$ mice is likely to be FADS2, which was detectable at similar levels in the preputial glands of both wild-type and SCD1$^{-/-}$ mice. The lack of SCD1 may lead to a tissue-specific adaptative increase in $C_{16:1}$ $n-10$, preventing palmitate accumulation.

## A new biological significance of Δ6-desaturase activity?

Ge et al. [13] also identified human FADS2 as the major fatty acid desaturase in human sebaceous glands capable of catalysing palmitate ($C_{16:0}$) Δ6-desaturation to sapienate ($C_{16:1}$ $n-10$). In human, sapienate is the major fatty acid in sebaceous gland [14]. Thus these authors proposed that FADS2 plays an important role in sebum production, possibly sebocyte differentiation in human and skin homoeostasis.

An inherited deficiency in Δ6-desaturase (FADS2) has been reported in the skin fibroblasts of a young patient [15]. Shortly after her birth, abnormal serum $C_{20:4}$ $n-6$ and $C_{22:6}$ $n-3$ levels were detected and a severe clinical picture, including corneal ulceration, growth retardation, feeding intolerance and skin abnormalities, was reported [15]. $n-6$ and $n-3$ PUFA dietary supplementation of this young patient led to amelioration of her growth retardation. However, some skin, nail and hair abnormalities were not sensitive to this $n-6$ and $n-3$ PUFA dietary supplementation. If $C_{16:1}$ $n-10$ biosynthesis is important for human skin, a $C_{16:1}$ $n-10$ supply should be considered in the case of altered Δ6-desaturase activity.

## Conclusion

The Δ6-desaturase is considered as a key enzyme required for numerous vital functions involving distinct PUFAs and other PUFA-derived bioactive lipids. It seems that the biological importance of Δ6-desaturase activity should also be considered for its newly identified role in the control of the biosynthesis of a monoenoic fatty acid ($C_{16:1}$ $n-10$), particularly in tissues with low Δ9-desaturase activity.

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