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The role of fatty acid desaturases in epidermal metabolism

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Abbreviations: SCD, stearoyl-CoA desaturase; FADS, fatty acid desaturase

The lipid composition of skin is important to a variety of functions served by this organ. Therefore, skin expresses multiple enzymes that synthesize and metabolize lipids. An important class of lipid metabolism enzymes expressed in skin is the lipid desaturases. Various isoforms of stearoyl-CoA desaturase, a delta-9 desaturase, as well as a delta-6 desaturase alter the lipid composition of the skin, thereby affecting skin barrier homeostasis and consequently, whole body energy balance. This review will focus on the role of fatty acid desaturases in maintaining epidermal metabolism.

Introduction

As the largest organ in the body, the skin serves a whole host of functions, the most important of which is to act as a protective barrier between the organism and the external environment. This barrier function has two separate components: the permeability barrier and the antimicrobial barrier.[1-4] The permeability barrier function of skin prevents loss of heat and water across the skin's surface, thereby preventing dehydration, as well as helping to maintain body temperature and body weight in homeotherms. The skin permeability barrier consists of the outer layer of the epidermis, the stratum corneum, made up of differentiated keratinocytes and corneocytes. Another important component of the stratum corneum is the extracellular matrix which is enriched in neutral lipids such as cholesterol, ceramides and free fatty acids.[1-4] The array of functions served by skin require the synthesis of large amounts of lipids, including cholesterol, phospholipids, triglycerides, ceramides, cholesterol esters and wax esters. These lipids are used as cell membrane components, signaling molecules, and as a source of energy and are constantly turned over due to the continuous shedding of dead keratinocytes from the epidermis.[1-7] Therefore, the different layers of skin express a multitude of enzymes involved in lipid metabolism, including lipid hydrolases, sphingomyelinases, lipases and desaturases.

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Much of what we know regarding the role of desaturases in the skin comes from studies using mouse models with spontaneous or targeted deletions of specific desaturases, especially delta-9 desaturases. With the exception of stearoyl-CoA desaturase-4, which is solely expressed in the heart,[8] all other isoforms of murine delta-9 desaturase have been shown to be expressed in various layers of skin. Stearoyl-CoA desaturase-1 is expressed in the dermal layer mainly in the sebaceous gland but has profound effects on skin metabolism, including the epidermal layer.[9-11] *Scd2* is primarily expressed in the epidermis and is integral to maintaining an intact skin barrier.[12] *Scd3* is expressed predominantly in the sebaceous gland in the dermis, but its role in affecting epidermal metabolism is as yet unclear.[13] Additionally, the delta-6 desaturase, FADS2, has been recently shown to be expressed in the skin, where it plays a role in maintaining skin homeostasis.[14,15]

Stearoyl-CoA Desaturase-1

SCD1 is primarily expressed within undifferentiated sebocytes at the base of the sebaceous gland in the dermal layer, but expression in the epidermis has also been reported, especially under conditions where SCD2, the main epidermal isoform, has been deleted.[12] First identified as the mutation resulting in sebocyte atrophy and alopecia in asebia mice, SCD1 is regulated throughout the hair cycle.[16] Subsequent studies in both asebia mice and mice with a targeted deletion of SCD1 (*Scd1*$^{-/-}$ mice) have established that this enzyme plays a critical role in the maintenance of skin integrity, as well as whole body energy metabolism.[9-11,16-23] *Scd1*$^{-/-}$ mice are lean and resistant to diet-induced obesity and insulin resistance, and they also present with skin abnormalities including sebocyte hypoplasia and severe alopecia. However, the role of the cutaneous phenotype in *Scd1*$^{-/-}$ mice in regulating body weight was not clear until the recent development of a skin-specific *Scd1*$^{-/-}$ animal. Interestingly, deletion of SCD1 from the skin alone recapitulates the lean phenotype of mice lacking SCD1 globally.[11] These skin-specific *Scd1*$^{-/-}$ mice also have increased metabolic rates, stemming from an inability to maintain core body temperature due to loss of sebaceous lipids in the skin coupled with severe alopecia. While sebaceous lipids such as triglycerides and cholesterol esters were drastically reduced in mice lacking skin SCD1, free cholesterol

and ceramides, which are associated with the stratum corneum were significantly increased, possibly as a compensatory mechanism to maintain barrier function in the context of sebocyte hypoplasia.[11]

While it is clear that SCD1 in the skin plays a critical role in maintaining sebaceous lipids, a potential role for SCD1 in regulating the water permeability of the epidermis is as yet unresolved. Asebia J1 mice naturally lacking SCD1 have been shown to have no impairment in their skin permeability,[2] despite significant sebocyte atrophy. However, asebia 2J mice, as well as an additional model of global SCD1 deletion have been reported to have increased skin permeability.[10,17] The differences in phenotypes observed using two different models of SCD1 deficiency suggest that the loss of sebaceous lipids per se is not sufficient to induce a loss of the epidermal permeability barrier. It is possible that secondary changes, including reduced surface free cholesterol, decreased ceramides or increased dermal inflammation mediate the changes in transepidermal water loss observed in some models of SCD1 deficiency.[1,2,10,11,17,24,25]

Stearoyl-CoA Desaturase 2

SCD2 shares significant sequence homology with SCD1 and is primarily expressed in the brain.[12] Unlike SCD1 which is mainly expressed in the dermal layer of skin, SCD2 is expressed to a greater extent in the epidermis and plays an important role in maintaining an intact skin permeability barrier. Mice with a targeted deletion of SCD2 (*Scd2*$^{-/-}$ mice) have a 70–100% mortality rate within 24 hours of birth, primarily due to alterations in epidermal lipid content and composition.[12] *Scd2*$^{-/-}$ mice have increased skin barrier permeability due to significant decreases in skin cholesterol esters, triglycerides, acylceramides and glucosylacylceramides. While lamellar bodies were present in normal numbers in skin of *Scd2*$^{-/-}$ mice, their internal contents were substantially reduced, and lipid delivery to the stratum corneum was decreased.[12] As anticipated, delta-9 monounsaturated fatty acids were significantly lower in skin lipids of *Scd2*$^{-/-}$ mice. In addition, linoleic acid, the main epidermal fatty acid in mice, was reduced by 80% in the acylceramide fraction and increased by 30% in the phospholipid fraction of skin lipids from these mice. This preferential channeling of linoleic acid towards phospholipid synthesis may be a compensatory mechanism to maintain membrane fluidity in the absence of monounsaturated fatty acids. In addition to changes in lipid content and composition, keratinocyte differentiation was also impaired in *Scd2*$^{-/-}$ mice. Interestingly, SCD1 expression was variably induced in *Scd2*$^{-/-}$ mice, and the degree of induction of SCD1 appeared to determine the chance of survival of *Scd2*$^{-/-}$ mice into adulthood.[12] These findings underscore the importance of in situ delta-9 desaturation in maintaining skin barrier function.

Stearoyl-CoA Desaturase 3

The *Scd3* gene shares 91 and 88% sequence homology in the protein coding sequence with *Scd1* and *Scd2*, respectively. SCD3 displays specificity towards palmitoyl-CoA as a substrate.[13,26] SCD3 expression is limited to the Harderian gland and skin of the mouse, and it is expressed at significantly lower levels than SCD1 in the skin. In the skin, SCD3 expression is limited to the sebaceous gland, but it is only expressed in differentiated sebocytes, unlike SCD1, which is expressed in the undifferentiated cells at the base of the sebaceous gland.[13] Like *Scd1*, the *Scd3* gene is also regulated throughout the hair cycle and is expressed at significantly greater levels in the skin of male rather than female mice.[13] While SCD1 is not required for SCD3 expression, SCD3 expression is dramatically reduced in skin of *Scd1*$^{-/-}$ mice due to the loss of sebocyte differentiation in mice lacking SCD1. However, an independent role for SCD3 in maintaining skin function has not yet been described.

Delta-6 Desaturase

The delta-6 desaturase FADS2 has been ascribed a role in modulating skin lipid composition.[14,15,27] FADS2, which is expressed in multiple tissues including liver, brain and skin, is known to catalyze desaturation of at least five distinct substrates including linoleate, linolenate and palmitate.[28,29] In the sebaceous gland, FADS2 primarily desaturates palmitate to sapienate (16:1n-10), the most abundant fatty acid in human sebum.[15] Consistently, a delta-6 desaturase deficiency has been clinically described to be accompanied by skin abnormalities.[27] Similarly, mice with a targeted deletion of FADS2 exhibit cutaneoous abnormalities, including dermatitis.[14] However, both in the described clinical case as well as in *Fads2*$^{-/-}$ mice, dietary supplementation with arachidonic acid ameliorates the cutaneous phenotypes, at least partially.[14,27] This is in marked contrast to the models of delta-9 desaturase deficiency, i.e., *Scd1*$^{-/-}$ and *Scd2*$^{-/-}$ mice, which show no improvement of alopecia or skin lipid abnormalities despite supplementation of the diet with exogenous monounsaturated fatty acids.

Conclusion

It has become increasingly clear that the lipid composition of the skin is influenced by both sebaceous secretions from the dermal layer as well as enzymes expressed in the epidermis. Desaturases expressed in the various layers of skin exert a profound influence on lipid metabolism in the epidermis and overall lipid composition of the skin. Studies in rodent models suggest that the maintenance of skin lipid content and composition is important to the barrier function of the skin in regulating water and temperature balance in the skin as well as whole body energy homeostasis.

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