Chapter 2
Skin Stearoyl-CoA Desaturase Genes

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Introduction

The hair follicle and its associated sebaceous gland constitute the skin pilosebaceous unit, the biogenesis of which occurs during embryogenesis. In certain skin areas such as eyelids, nipples, prepuce, and labia minora, sebaceous glands may form and function in the absence of hair follicles, but all hair follicles form and function normally in association with sebaceous glands. Although significant advances have been made in our understanding of hair biology during the last decade, cellular and molecular differences of sebaceous glands between various species and skin sites within an organism are poorly understood. Furthermore, it is currently unknown whether differences in sebaceous glands are related to the heterogeneity of hair follicles. It has been hypothesized that during evolution sebaceous glands arose first in the animal kingdom before hair follicles came into existence (Stenn et al. 2008). If this hypothesis is true, it can be logically concluded that sebaceous glands must have played some crucial role in the evolution of hair follicles. In fact, in vitro and in vivo studies suggest that sebaceous glands are important for normal formation or functioning of hair follicle (Williams and Stenn 1994; Allen et al. 2003). Given the relationship between sebaceous glands and hair follicles, an obvious interesting question that arises is what happens to skin and or hair follicles if sebaceous glands have defects in differentiation and as a result do not function properly. Such questions may be addressed with appropriate animal models (Porter et al. 2002; Lunny et al. 2005; Yager et al. 2012). A spontaneous mutant mouse, asebia (*ab*), is known to exist that serves as an excellent model for sebaceous gland deficiency.

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The recessive asebia mutation originated spontaneously in a colony of BALB/cCrglGa mice (Gates and Karasek 1965). The name asebia (*ab*) was initially given to mutant mice as it was believed that they lacked sebaceous glands; however, subsequent closer examination revealed that in fact sebaceous glands were not absent but hypoplastic, and other related glands (meibomian, perianal glands, and ceruminous glands) are affected to various extents in *ab* mice (Josefowicz and Hardy 1978; Pennycuik et al. 1986; Compton et al. 1989; Sundberg et al. 2000). Studies of dermal-epidermal recombination fetal grafts suggested that the functional defect in mutant mice was in the epidermis and not the dermis (Pennycuik et al. 1986). Other prominent features of *ab* mutant mice are their scant subcutaneous fat and corneal opacities.

Identification of *Scd1* Gene Defect in the *Asebia* Mouse by Positional Cloning

An allelic spontaneous mutation, *ab^J*, was identified at the Jackson Laboratories and was mapped to mouse Chromosome 19 (Sweet and Lane 1977). Later another allelic mutation, *ab^{2J}*, arose spontaneously at the Jackson Laboratories on the inbred mouse strain DBA/1LacJ and its characterization was reported by Sundberg et al. 2000. Differences in appearance of mutant and normal mice and their skin histology are shown in Fig. 2.1. Whereas well-differentiated sebaceous glands are obvious in normal mouse skin section, they are not apparent in *ab^{2J}* skin section. The gene
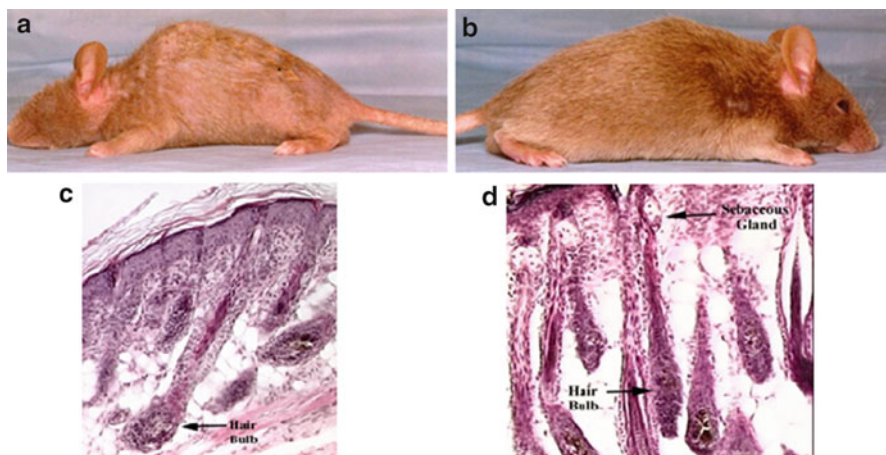

Fig. 2.1 Scaly skin with alopecia in an adult *ab^{2J}* mutant mouse (**a**) and normal fur of nonmutant littermate (**b**). Histology (H&E) skin sections of *ab^{2J}* and nonmutant mouse are shown in (**c**) and (**d**), respectively. While well-developed sebaceous glands, as indicated, are visible in (**d**), they are hypoplastic and not obvious in (**c**)
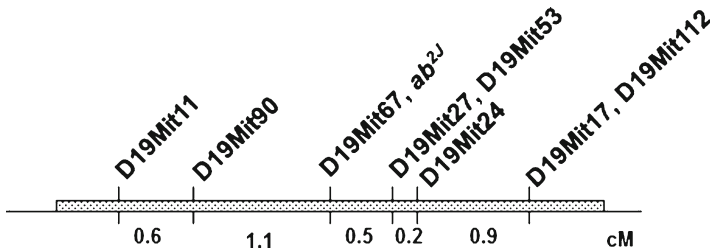
Fig. 2.2 Genetic linkage map of the mouse chromosome 19 region surrounding ab^{2J} locus and the associated microsatellite polymorphic markers that were used to obtain the map from backcross progeny as described by Eilertsen et al. (2000). The marker D19Mit67 is tightly linked to ab^{2J} as indicated. Inter-marker genetic distances are shown in centimorgans (cM). The ab^{2J} mutation is within the 1.6 cM genetic interval defined by D19Mit90 and 19Mit27/D19Mit53

defect in asebia mouse was identified by positional cloning involving two major steps. The first step was obtaining a high resolution genetic and physical map of the locus as reported by Eilertsen et al. (2000), followed by detailed identification and characterization of the genetic lesion in the mutant mouse using a variety of molecular techniques including nucleic acid sequencing (Zheng et al. 1999). These studies mapped the ab^{2J} mutation to mouse chromosome 19 that co-segregated with the polymorphic microsatellite marker D19Mit67 when DNA from 644 backcross mouse progeny were examined as reported by Eilertsen et al. 2000. The critical genetic interval in ab^{2J} mouse was identified to a fairly narrow region of DNA (1.6 cM) as shown in Fig. 2.2. Further detailed molecular analysis ultimately identified underlying genetic defects in both ab^{J} and ab^{2J} mice.

After probing skin RNA blots from ab^{J} and ab^{2J} mutant and normal mice with DNA probes derived from genes and expressed sequence tags (ESTs) from mouse chromosome 19 critical region, one gene probe derived from *Scd1* showed a lack of *Scd1* RNA expression on skin RNA blots from ab^{J} and ab^{2J} mice in contrast to normal mice (Zheng et al. 1999). Although this was good suggestive evidence that the *Scd1* was most likely the gene that was mutated in *ab* mice, more in-depth analysis of Southern and Northern blots, RT-PCR and DNA sequence analysis from mutant and normal mice, subsequently revealed that the *Scd1* gene expression was indeed disrupted due to mutations in *Scd1* gene in both ab^{J} and ab^{2J} mice although the nature of genetic lesions was different. Whereas a large deletion of DNA (exon 1–4) is responsible for gene inactivity in ab^{J} mice, a more subtle deletion of 18 nucleotides at exon 2 and intron 2 boundary was identified in ab^{2J} mice (Zheng et al. 1999). The gel electrophoresis of RT-PCR products from skin and liver RNA samples indicated the expected band of 787 base-pairs derived from *Scd1* RNA of the normal mouse, but mutant samples had either multiple bands due to aberrant RNA splicing in ab^{2J} or no bands at all due to larger genomic deletions in ab^{J} (Fig. 2.3a). DNA sequencing of RT-PCR products established that all three aberrantly spliced transcripts had in-frame stop codons in ab^{2J} (Fig. 2.3b). Deletion of 18 nucleotides in ab^{2J} causes loss of the 5′ splice site (GT) at the exon 2–intron 2 boundary used for *Scd1* RNA splicing. As a consequence of this 5′ splice site deletion, genomic DNA
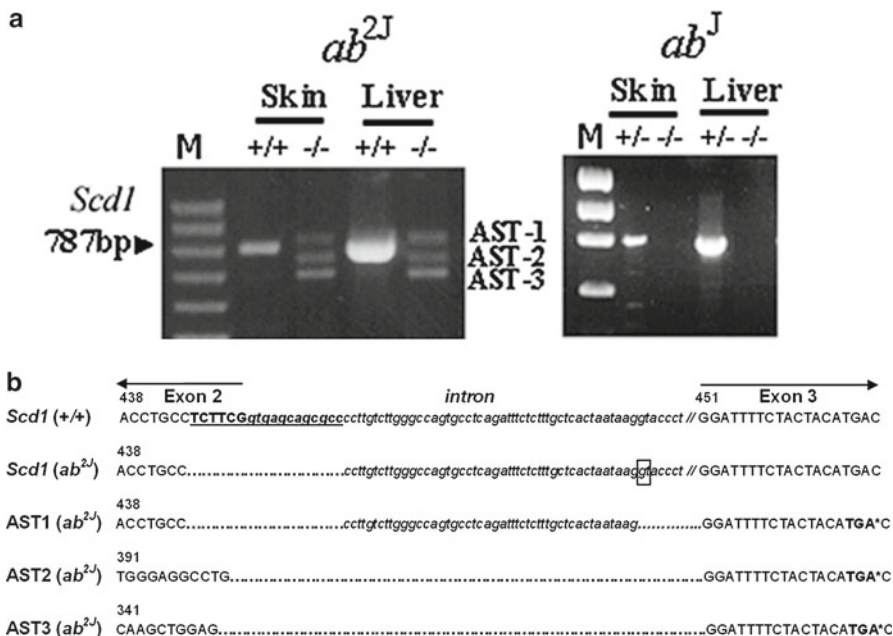
Fig. 2.3 (**a**) Characterization of RT-PCR products from mutants ab^J, $ab^{2,J}$ and nonmutant tissues on agarose gel. *M* marker ladder. AST-1, AST-2, and AST-3 are three aberrantly spliced transcripts from ab^{2J} tissues. *Arrowheads* indicate *scd-1*-specific transcript. +/+=nonmutant; −/−=mutant; +/−=heterozygote that is phenotypically normal. Reproduced from Zheng et al. (1999) *Nat Genet* 23:268–270. (**b**) Comparison of DNA sequences from genomic DNA of nonmutant (+/+), ab^{2J} mouse and cDNA derived from aberrantly spliced transcripts (AST-1, AST-2, and AST-3) from ab^{2J} mouse. *Asterisk* indicates in-frame stop codons. The GT dinucleotide used as cryptic 5′ splice for the generation of AST-1 is shown as boxed within the intron 2 of genomic sequence of *Scd1* (ab^{2J}). The exon sequences are in the *upper case* and intronic sequences are in the *italics* and *lower case*. The eighteen-nucleotides, encompassing exon 2 and intron 2 junction, that are deleted in ab^{2J} mutant are shown in **bold** and underlined in *Scd1* genomic sequence (+/+). *Dots* reflect deletions and // indicates intronic sequence present in the genomic DNA but not shown in the figure. The sequence numbering is same as that of the published cDNA (Ntambi et al. 1988. *J Biol Chem* 263:17291–17300)

codes for the aberrantly spliced transcript (AST-1) in ab^{2J} by utilizing a 5′ cryptic splice site (GT) within the intron as shown in Fig. 2.3b. The AST-1 from ab^{2J} has an insertion of 47 nucleotides from intron 2 as reflected by its larger sized RT-PCR product in comparison to that derived from the nonmutant mouse samples and confirmed by DNA sequencing (Fig. 2.3). Smaller sized RT-PCR products derived from aberrantly spliced transcripts, AST-2 and AST-3, apparently use other upstream 5′ cryptic sites and as a result generate smaller sized RT-PCR products (Fig. 2.3). None of the aberrantly spliced transcripts in ab^{2J} can code for Scd protein since all of them have in-frame stop codons (Fig. 2.3b). The fact that the *Scd1* gene mutation is responsible for the asebia phenotype was also supported by *Scd1* gene knockout studies as reported by Miyazaki et al. (2001). Details of how the *Scd1* gene defect

in asebia impacts sebum synthesis or controls sebaceous gland morphogenesis and function are still. However, the role of various members of fatty acid desaturase gene family in skin has been reviewed recently (Sampath and Ntambi 2011).

Impact of *Scd1* Gene Defect in Mouse

Scd1 mutation causes several distinct changes in mouse when compared to heterozygote or normal mice. Adult homozygous asebia mice develop generalized alopecia, scaly skin, and have a hunched back. The hair shafts formation occurs normally, but they are sparse and matted (Josefowicz and Hardy 1978; Compton et al. 1989; Sundberg 1994). In adult asebia mice, hair follicles protrude deep in subcutis and hair cycles (anagen, catagen, and telogen) last longer than those in the controls (Josefowicz and Hardy 1978; Pennycuik et al. 1986). A subtle abnormality in mutant mice hair shaft includes retention of inner root sheath (IRS) above sebaceous gland that causes the plugging of the hair canal (pilary canal). The abnormally long hair follicles deep in dermis in mutant mice are believed to exist as a consequence of the retention of this cornified cell plug in the pilary canal that impedes the normal exit of hair shaft (Sundberg et al. 2000). The protrusion of hair shaft deep within the skin causes foreign body reaction with the resultant dermal scarring and eventual destruction of the hair follicle itself resulting in progressive alopecia with age in mutant mice. These observations underscore the importance of the sebaceous gland in controlling normal hair shaft growth and hair shaft-sheath interactions. Other studies also suggest that the separation of the hair shaft from the sheath is dependent on an intact mid-follicle/sebaceous gland (Williams and Stenn 1994; Gemmell and Chapman 1971; Williams et al. 1996). Given the similarity between hair follicle destruction observed in ab^{2J} mouse and human scarring alopecia, the asebia mouse has been postulated to be a good model for the pathogenesis of some forms of human scarring alopecia (Sundberg et al. 2000). Besides hair follicle abnormalities, asebia mice have thickened epidermis and dermis which is marked by increased vascularity and cellular infiltrate of mast cells and macrophages (Brown and Hardy 1988, 1989). Dermal inflammation and epidermal hyperplasia in mutant mice are believed to be due to macrophages containing lipid crystals (Brown and Hardy 1988). Skin surface lipid analysis of the asebia mutant mouse showed a marked reduction in sterol esters and cholesterol with apparently total loss of diol diesters compared to littermate controls (Wilkinson and Karasek 1966; Sundberg et al. 2000).

Although adult mutant mice are easy to distinguish visibly from normal mice, they are very difficult to distinguish phenotypically from littermate controls at the time of birth until approximately 1 week of age when hair fibers emerge from the follicles. Histological examination of skin reveals the presence of very small sebaceous glands in mutant skin as compared to controls (Sundberg et al. 2000). Ultrastructural studies of the glands indicate fewer lipid droplets, intracellular abnormalities such as impaired mitochondrial development and dilated smooth endoplasmic reticulum (Josefowicz and Hardy 1978).

The fact that disruption of *Scd1* expression in asebia mice causes dramatic phenotypic changes highlights the importance of this enzyme for normal skin function including sebaceous gland differentiation. How exactly the enzyme or its product is able to control the fate of sebaceous gland morphogenesis is unknown at present. Stearoyl-CoA desaturase (Scd) is a key iron-containing membrane-bound enzyme that catalyzes the rate-limiting step of oxidative conversion of saturated fatty acids to monounsaturated fatty acids, involving the insertion of a cis-double bond between the C9 and C10 positions in the acyl-CoA derivatives of saturated fatty acids such as palmitic and stearic acids to produce palmitoleoyl and oleoyl-CoA, respectively (Tocher et al. 1998; Paton and Ntambi 2009). This process is dependent upon electron flow from NAD(P)H through NADH-cytochrome b5 reductase to cytochrome b5, to Scd and finally to molecular oxygen that is reduced to water. Unsaturated fatty acids are not only involved in energy metabolism, but also in lipid-activated signal transduction (Shinomura et al. 1991; Kasai et al. 1998). Hence, one can conclude that monounsaturated fatty acids or their metabolite products, through an unknown mechanism, affect some pathways that are crucial for the normal differentiation of sebaceous gland and other related glands.

Cloning of *Scd3*, a Gene with Restricted Expression in Skin

Until late 1990s, only two members of *Scd* gene family were known to express in mouse tissues. A novel member of the *Scd* gene family was subsequently discovered while work on DNA sequencing of cDNA clones derived from asebia and normal skin was in progress. This novel member was named *Scd3* and characterization of this gene was reported by Zheng et al. 2001. Nucleotide sequence analysis of cDNA clones indicated that the *Scd3* transcript has 91 and 88 % identity with *Scd1* and *Scd2* coding sequences, respectively, with very limited homology in noncoding regions, suggesting independent control of gene expression in these genes. The amino acid identity of the Scd3-deduced protein sequence, compared to Scd1 and Scd2, is 88.7 % and 84.9 %, respectively. The Scd3 protein sequence of 359 amino acids, like the other two family members (Sdc1, Scd2), possesses four transmembrane domains and all the conserved histidine residues typically found in the desaturases and hydroxylases of several species. *Scd3* gene exists in close proximity to *Scd1* and *Scd2* genes on chromosome 19 as revealed by in situ hybridization and PCR analysis of BAC clones (Zheng et al. 2001).

Expression of Mouse *Scd* Gene Family in Sebaceous Glands and During Hair Cycle

RNA in situ hybridization of frozen mouse skin sections using a *Scd-1* specific probe demonstrated that *Scd-1* expression could be observed in the sebaceous gland but not in the hair follicle or any other cutaneous structure of wild-type mouse skin
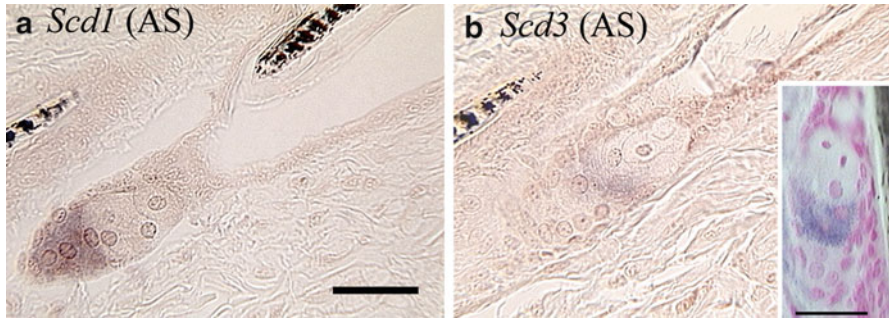
Fig. 2.4 RNA in situ hybridization of mouse skin sections comparing expression of *Scd1* and *Scd3* in the sebaceous gland. The same sebaceous gland is shown on both (**a**) and (**b**) as pictures were derived from two consecutive sections of mouse skin hybridized separately with the *Scd1* and *Scd3* probes. The inset shows an independent section where the slide was stained with hematoxylin and eosin (H&E) after obtaining *Scd3*-specific signal. *AS* antisense probe. The bar is 30 μM. Reproduced from Zheng et al. (2001) *Genomics* 71:182–91 with permission from the publisher (Elsevier)

(Zheng et al. 1999, 2001). *Scd-1* RNA expression was observed in sebaceous glands of skin irrespective of hair cycle stage as reported by Zheng et al. 1999. Similar to *Scd1* expression, *Scd3* expression by in situ RNA hybridization was observed to be restricted to sebaceous glands only (Fig. 2.4). However, the interesting feature of expression of the two genes (*Scd1* and *Scd3*) was that they did not co-express in the same region of sebaceous gland as observed from their expression in two consecutive tissue sections by in situ hybridization. This difference in gene expression may be attributed to the sebocytes of different stages of differentiation and also highlight the independent roles of *Scd1* and *Scd3* in different sebocytes within the sebaceous gland.

It is a well-known fact that hair follicle undergoes cyclic changes of growth (anagen), regression (catagen), and quiescence (telogen). The duration of each stage of the cycle is characteristic of both the hair type and species. Given the close association of sebaceous gland and hair follicle as mentioned earlier, it is of interest to know if hair cycle-induced changes in skin also impact expression of the *Scd* gene family. Such changes can be observed in natural or induced (plucked hair) hair cycles. As shown in Fig. 2.5a, steady-state levels of *Scd-1* transcript change over the natural hair cycle. The level of *Scd1* transcript was very low in skin at day 1 post-birth, but its expression increases considerably in the skin derived from mouse in anagen of the first hair cycle (day 8) and then decreases in regression/resting phases of hair cycle followed by increase in the next growth phase of the second hair cycle (days 28 and 35). *Scd-1* expression is much lower in the telogen hair cycle (days 21 and 42). In contrast to *Scd1*, *Scd2* did not show hair cycle-dependent changes in expression in the skin. This phenomenon of enhanced *Scd1* gene expression in skin with hair follicles in the anagen phase followed by decreased expression in skin containing telogen hair follicles was also observed in induced hair cycles (Fig. 2.5b). These results as reported by Zheng et al. (1999, 2001) do not answer the question if
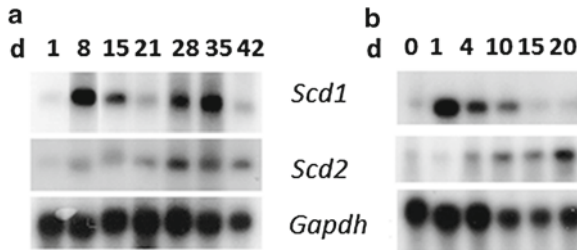
Fig. 2.5 Changes in *Scd-1* expression during spontaneous and induced hair cycles. (**a**) RNA blots of the samples from spontaneous hair cycle obtained from dorsal skin RNA of mice normal mice (DBA/1LacJ) at the age of mice in days (d) as indicated were probed with *Scd1*, *Scd2,* or Gapdh (control)-specific probes. (**b**) RNA blots of the samples from induced hair cycle14 procured from dorsal skin of normal mice (C57BL/6) probed with the same probes as in (**a**). Day 0 (d 0) and day 1 (d 1) represent telogen (quiescent) and early anagen (growth), respectively. The anagen phase ends at about day 18. Adapted from Zheng et al. (1999) *Nat Genet* 23:268–270
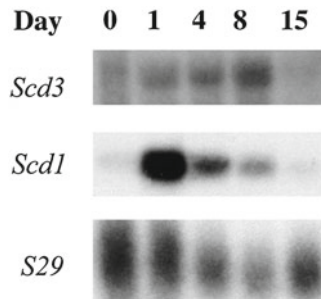

Fig. 2.6 Mouse hair cycle-dependent expression of *Scd3* in comparison to *Scd1*. RNA samples from the skin of 8-week-old mice with hair follicles in quiescent phase (telogen—day 0) and at days 1, 4, 8, and 15 after induction of follicular growth (anagen) by hair depilation were analyzed by RNA blots and probed with *Scd1*- and *Scd3*-derived probes. S29 is a ribosomal protein control probe. Reproduced from Zheng et al. (2001) *Genomics* 71:182–91 with permission from the publisher (Elsevier)

the changes in expression of skin *Scd-1* over the hair cycle are because of changes in *Scd1* expression in the sebaceous gland alone, or whether other tissues such as subcutaneous fat cells also contribute to these changes. Interestingly, in comparison to *Scd1*, *Scd3* transcript level increases gradually during induced hair cycle reaching the highest level at day 8 of anagen (late anagen), and then decreases at catagen (regression phase), which is day 15 of the induced hair cycle (Fig. 2.6). *Scd1* expression is very high in early anagen but relatively low in late anagen. These data also highlight the fact that *Scd1* gene expression is much higher compared to *Scd3* in mouse skin, particularly in early anagen phase (day1) of the induced hair cycle.

Δ9 desaturase mRNA is expressed in adult mouse and pig sebaceous gland and human hair bulb, whereas Δ6 desaturase mRNA is expressed only in adult human sebaceous gland
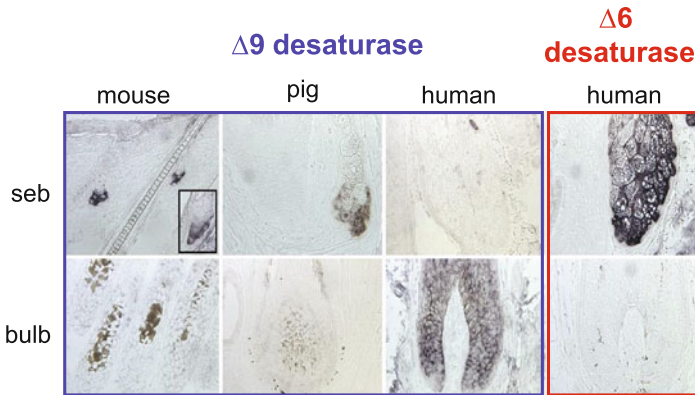
Fig. 2.7 Mouse SCD-1 expression is restricted to the sebaceous gland. Human SCD is weakly expressed in the sebaceous gland, but is highly expressed in the hair follicle bulb and lower hair shaft

Human Skin Desaturases

The human SCD1 gene was cloned by screening a human keratinocyte cDNA library and analysis of 3 h-RACE (rapid amplification of cDNA ends) products from various tissues yielded a 5.2 kb cDNA encoding a 359 amino acid protein with a calculated molecular mass of 41.5 kDa. Analysis of 3 h-RACE products suggested that alternative usage of polyadenylation sites generates two transcripts of 3.9 and 5.2 kb, a result consistent with Northern analysis. Southern analysis demonstrated the existence of two *SCD* loci in the human genome. Chromosomal mapping localized one locus to chromosome 10, and the second locus to chromosome 17. The locus on chromosome turned out to be transcriptionally inactive, fully processed pseudogene. Although the primary sequence and intron–exon structure of *SCD* is phylogenetically conserved, divergence between rodent and human is seen in the number of *SCD* genes and in the generation of alternative transcripts, suggesting a species-specific component of *SCD* regulation of unsaturated fatty acid metabolism.

   In skin, mouse SCD-1 is restricted to and abundantly expressed in mouse sebaceous gland, whereas human SCD is weakly expressed in human sebaceous gland (Fig. 2.7). In skin, human SCD is highly expressed in the hair follicle bulb, lower hair shaft, and in the eccrine sweat gland, suggesting a role in the production of hair and sweat. Pig SCD is similar to mouse with sebaceous gland expression, and similar to human with sweat gland (apocrine) expression. However, pig differs from human in that the hair follicle lacks SCD expression. The differences between species in pilosebaceous expression of SCD do not seem to correlate with the number of SCD genes. The difference in gene number, polyadenylation, and expression

pattern indicate that the SCD genes underwent species-specific selection during evolution, and that species-specific function of the pilosebaceous unit may contribute to this diversification. Among human, pig, mouse, and sheep, humans are the only species to express the delta 6 desaturase in sebaceous glands and if we consider that they are the only species that develop acne, that makes it a valid target for that human-specific disease. As described above, the essential role of the SG in hair follicle growth comes from the asebia mouse, which demonstrated hypoplastic SGs and alopecia, and due to a loss-of-function mutation in the Scd-1 gene; highly and specifically expressed in murine sebocytes (Gates and Karasek 1965; Zheng et al. 1999). From the expression of FAD2 in the human sebaceous gland we could conclude that the delta 6 desaturase may participate towards the differentiation process of sebocytes in adult sebaceous glands since its expression is mainly in suprabasal sebocytes.

Human sebaceous glands (SG's) have unique anatomical and biochemical properties since the sebaceous follicle is characterized by large, multi-lobular SGs that are attached to a hair follicle bearing a small hair shaft (Kligman 1974). But the most striking exceptionality is that the human sebum contains an abundant fatty acid that is unique among the animal kingdom. This fatty acid is named sapienic acid, thus "sapien" is the root of its name, and is a 16 carbon monounsaturated fatty bearing the double bond on the $n10$ or delta 6 position (Nicolaides 1974; Stewart et al. 1986). This fatty acid is implicated in the pathogenesis of acne, a disease that is mainly manifested in humans (Downing et al. 1986; Stewart et al. 1986). The levels of sapienic acid are multiple folds higher than any of its derivatives or isomers or other monounsaturated fatty acids found in sebum, which combined with the lack of SCD expression in human SG suggested that other members of the desaturase superfamily, particularly Δ-6 desaturase (also known as *fatty acid desaturase-2, FADS2*), may be expressed in human SG (Ge et al. 2003; Pappas et al. 2002; Pappas 2009).

Concluding Remarks

Based on the dramatic cutaneous pathology observed in asebia mouse, it has become clear that *Scd-1* gene product plays an important role for maintaining normal skin and eye phenotype. Mechanistic understanding of how the *Scd-1* gene product contributes to normal differentiation and function of sebaceous glands or Meibomian glands is unclear at present. Histological studies of normal and asebia mice suggest that the sebaceous gland also plays an important role in dissociating the hair follicle sheath from the outgrowing shaft during hair growth cycle, but molecular basis for this process is again unclear. It is possible that monounsaturated fatty acids or their derivatives may play an important role in sebocyte membrane synthesis, in sebum production, or in sebocyte signaling pathways (Shinomura et al. 1991; Kasai, et al. 1998). Monounsaturated fatty acids have been implicated in maintaining retinol homeostasis based on the observation that skin retinol/retinoic acid and the retinoic acid-induced genes were elevated in *Scd1* gene knockout mice (Flowers et al. 2011).

Fig. 2.8 Tissue-specific expression pattern of *Scd3* from RNA blots. The membrane blots were probed with cDNA probes from the noncoding regions specific for each *Scd* gene. The β-actin probe was used as a control. The exposure times for *Scd3* blot was adjusted more than fivefold in order to achieve comparable signal intensity to that of *Scd1* probed blot. Reproduced from Zheng et al. (2001) *Genomics* 71:182–91 with permission from the publisher (Elsevier)
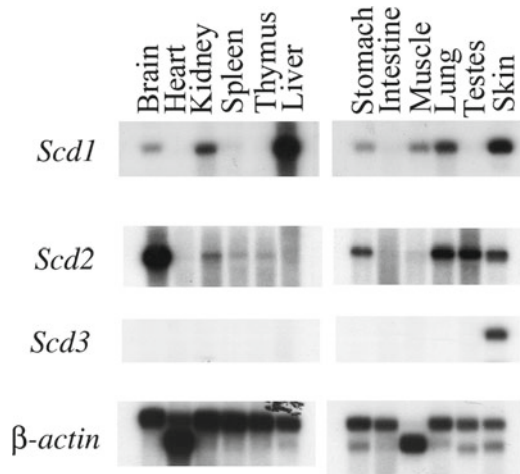
Expression of multiple *Scd* genes has been reported in rodent skin (Zheng et al. 1999, 2001). Although the predicted Scd1 and Scd3 protein sequences have high sequence homologies, it is unknown if there are any differences in the activity of the two gene products. However, differences in the gene promoter sequences suggest different gene control mechanisms that may be responsible for observed tissue specificity with respect to their expression (Fig. 2.8). It is noteworthy that the lack of expression of *Scd1* in asebia mouse does not alter the expression of *Scd3* gene, at least in young mice (Zheng et al. 2001). Decrease of *Scd3* expression with advanced age in mutant mice is most likely related to the destruction of follicles and sebaceous glands due to the scarring of the pilosebaceous units (Sundberg et al. 2000). However, it is obvious that in asebia mutant mice with rudimentary sebocytes, *Scd3* gene expression in young mice cannot compensate for the lack of *Scd1* expression. The spatial expression of *Scd1* and *Scd3* in the mouse sebaceous gland underscores their roles in distinct cellular populations of sebaceous gland. Interestingly *Scd3* gene expression is slightly higher in male skin than in female skin (Zheng et al. 2001). Whether this differential regulation is achieved by androgen-mediated up-regulation in male or estrogen-mediated down-regulation in female mouse is unknown, although an estrogen receptor recognition site was observed in the *Scd3* distal promoter (Zheng et al. 2001).

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