

## Special Focus Review

## Sebaceous gland lipids

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**Abbreviations:** Sq, squalene; PUFAs, polyunsaturated fatty acids; 16:0, palmitic acid; 16:1  $\Delta$ 6, sapienic acid; 18:2  $\Delta$ 5,8, sebaleic acid**Key words:** sebum, squalene peroxide, acne, diet

The principal activity of mature sebaceous glands is producing and secreting sebum, which is a complex mixture of lipids. Sebum composition is different among species and this difference is probably due to the function that sebum has to absolve. In human sebum there are unique lipids, such as squalene and wax esters not found anywhere else in the body nor among the epidermal surface lipids. Moreover, they correspond to major components supplying the skin with protection. However, the ultimate role of human sebum, as well the metabolic pathways regulating its composition and secretion rate, are far from a complete understanding. Increased sebum secretion is considered, among all features, the major one involved in the pathophysiology of acne. Along with increased sebum secretion rate, quali- and quantitative modifications of sebum are likely to occur in this pathology. Understanding the factors and mechanisms that regulate sebum production is needed in order to identify new targets that can be addressed to achieve a selective modulation of lipid biosynthesis as a novel therapeutic strategy to correct lipid dysregulations in acne and other disorders of the pilosebaceous unit.

### Sebum

The principal activity of mature sebaceous glands is producing and secreting sebum, which is a complex mixture of lipids. This is a holocrine secretion formed by the complete disintegration of glandular cells into the follicular duct of pilosebaceous unit. Sebum discharge represents a major step in the final stages of differentiation of sebaceous specialized cells, namely sebocytes, and it is the result of accumulation of cytoplasmic lipid droplets and subsequent cell disintegration and release of their content into the follicle.

Sebum composition is different among species and this difference is probably due to the function that sebum has to absolve. Among the functions attributed to sebum in humans there is photoprotection, antimicrobial activity, delivery of fat-soluble anti-oxidants to the skin surface and pro- and anti-inflammatory activity exerted by specific lipids.<sup>1</sup> However, the ultimate role of human sebum, as well

**Table 1 Components of skin surface lipids**

	Sebum %	Epidermal lipids %
<b>Glycerides</b>	30–50	30–35
<b>FFA</b>	15–30	8–16
<b>WE</b>	26–30	-
<b>SQ</b>	12–20	-
<b>CE</b>	3.0–6.0	15–20
<b>CH</b>	1.5–2.5	20–25

Glycerides; Free Fatty Acids (FFA); Wax Esters (WE); Squalene (SQ); Cholesterol Esters (CE); Cholesterol (CH).

as the metabolic pathways regulating its composition and secretion rate, are far from a complete understanding.

Human sebum consists of squalene, esters of glycerol, wax and cholesterol, as well as free cholesterol and fatty acids (Table 1). Triglycerides and fatty acids, taken together, account for the predominant proportion (57.5%), followed by wax esters (26%) and squalene (12%). The least abundant lipid in sebum is cholesterol, which with its esters, accounts for the 4.5% of total lipids.<sup>2</sup> The most characteristic products of sebaceous secretion are squalene and wax esters. They are unique to sebum and not found anywhere else in the body nor among the epidermal surface lipids. Moreover, they correspond to major components supplying the skin with protection. Squalene is a linear intermediate preceding cholesterol in its biosynthesis. Interestingly, in the sebaceous gland, the squalene produced is not converted into lanosterol, halting the completion of the biosynthetic pathway leading to cholesterol. The reason cholesterol is not synthesized in the sebaceous gland, favoring squalene accumulation, is still unclear. Possible explanation for the squalene buildup in the sebaceous gland may be linked to an overexpression or an increase in the activity of squalene-synthase in the cells; or it may be related to decreased level or activity of the enzymes involved in the conversion to cholesterol.<sup>3</sup> In addition, taking into account the peculiarity of squalene, it may be considered as a marker for sebocytes differentiation and thus for sebogenesis.<sup>4</sup> Other features unique to sebum are the branched chain fatty acids and lipids with particular pattern of unsaturation. The  $\Delta$ 6 desaturase enzyme (fatty acid desaturase-2) catalyzes a “sebaceous-type” reaction of desaturation that leads to particular compounds.<sup>5</sup> It is the major desaturase found in the sebaceous gland, and it is detectable mainly in differentiated sebocytes, which occupy the suprabasal layers of the sebaceous gland and have

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reached a full lipid synthetic capacity, providing a functional marker of activity and differentiation of sebocytes.<sup>5</sup>  $\Delta 6$  desaturase preferentially converts palmitic acid (16:0) to sapienic acid (16:1,  $\Delta 6$ ), which is unique to the human sebum and represents ca. 25% of the total fatty acids. Elongation of sapienic acid by 2-carbon unit and further unsaturation leads to the formation of sebaleic acid (18:2,  $\Delta 5,8$ ), which is also peculiar of human sebum. The ratio between  $\Delta 6$  and  $\Delta 9$  unsaturated fatty acids has been proposed as an index of maturation of sebaceous cells and of metabolic process associated to it.<sup>6</sup>

## Sebum Alterations in Acne

*Acne vulgaris* is a disease of the pilosebaceous unit resulting from the interplay of different factors: seborrhoea, *P. acnes* colonization, hyperkeratinization of the follicular duct and release of inflammatory mediators. Increased sebum secretion is considered, among all features, the major one involved in the pathophysiology of acne. On average, acne subjects excrete more sebum than normal ones and secretion rates correlate well with the severity of clinical manifestations.<sup>7</sup> Along with increased sebum secretion rate, qualitative and quantitative modifications of sebum are likely to occur. Decreased concentration of linoleic acid has been observed in skin surface lipids of acne patients. In particular, its level has been found significantly reduced in wax esters making it reasonable to assume that linoleic acid is directly involved in the sebaceous lipid synthesis.<sup>8</sup>

Moreover, experimental data suggest that it is incorporated in epidermal lipids of the infundibulum. In experimental models, linoleic acid is preferentially transformed into two carbons precursors in the sebaceous gland by entering the  $\beta$ -oxidation reaction at the acyl-side chain, which yields to acetyl-CoA. The latter product feeds the biosynthetic pathway leading to squalene and wax esters synthesis.<sup>9</sup> It seems that  $\beta$ -oxidation of linoleic acid is specific of sebocytes and that it is correlated with their differentiation. A diminished amount of linoleic acid has been proposed as a factor predisposing to comedones formation.<sup>10</sup> Moreover, low level of linoleic acid also produces impairment of the epidermal barrier function, which might account for increased permeability of comedonal wall to inflammatory substances.<sup>11</sup> Other lipids have been proposed as having involvement in the development of comedone lesions. In particular the attention has been pointed to the increase of other fatty acid and by-products of squalene peroxidation.<sup>12-14</sup> Following UV exposure, squalene undergoes massive photodegradation. Irradiation of human skin leads to a squalene decomposition of about 60% similar to that observed in vitro.<sup>15</sup> Upon oxidative challenge, squalene is readily oxidized giving rise to different squalene peroxidation by-products exerting harmful activities in skin cell cultures and in vivo, including keratinocytes cytotoxicity,<sup>15</sup> histologic changes and immunosuppression.<sup>16</sup> According to Kohno et al. the primary peroxidation product in human skin surface lipids is squalene monohydroperoxide.<sup>17</sup> Squalene peroxide has been demonstrated to be comedogenic: in animal experiments, comedones have been triggered by exposing rabbit ears to irradiated squalene. A positive correlation was found between degree of squalene peroxidation and size of the comedones elicited. In addition, marked hyperplasia and hyperkeratosis of the epithelium in follicular infundibulum and marked proliferation of sebaceous glands were observed.<sup>13</sup> The all saturated squalene form (squalane), squalene itself and synthetic peroxides with different backbone structures, exerted a negligible comedogenic effect and did

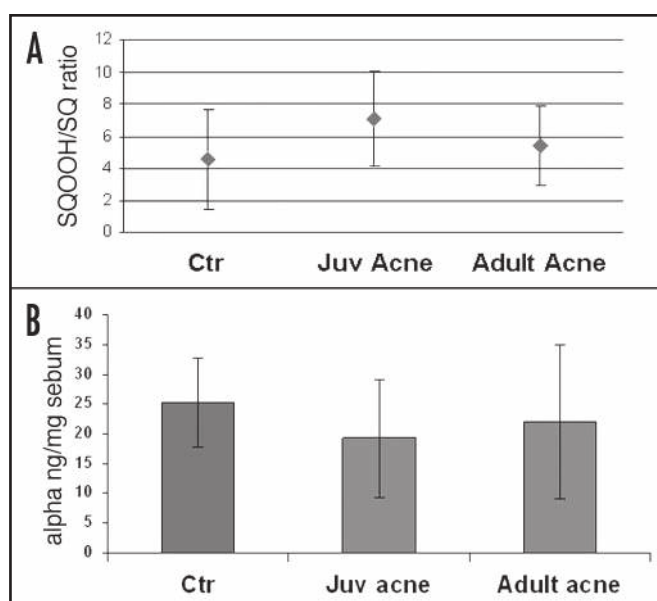


Figure 1. Acne sebum presents a higher level of squalene peroxide when compared with the level found in sebum of control subjects (A). Moreover, a decreased amount of vitamin E was associated with the increase of squalene peroxidation degree (B). These findings are emphasized for juvenile acne with respect to adult acne. Juvenile acne has, in fact, a greater inflammatory character.

not lead to skin roughness and wrinkling, indicating that squalene monohydroperoxide is specifically involved in the observed skin alterations.<sup>14,18</sup> In addition, in vitro data showed that squalene peroxide beyond induction of HaCaT keratinocytes proliferation, led also to the upregulation and release of inflammatory mediators, which indicate a pro-inflammatory activity of by-products of squalene oxidation.<sup>19</sup> The strategy that skin adopts to limit the potentially harmful effects of peroxidated squalene relies on the vitamin E supply to the skin surface. Vitamin E is found in the skin surface lipids as a significant constituent of human sebum. In sites with elevated sebaceous glands density continuous secretion of vitamin E is detected, which is in tight correlation with the levels of cosecreted squalene.<sup>20</sup> The role played by squalene peroxidation in acne development is strengthened by the observation that skin surface and comedones lipids collected from acne patients are enriched in polar lipids mainly derived from squalene oxidation.<sup>21,22</sup>

More recent data collected in vivo have confirmed these findings and indicated significant differences in sebum composition of acne patients in comparison with healthy subjects with regard to squalene and vitamin E amount. In particular, higher amounts of squalene peroxide and consequently decreased levels of vitamin E level have been detected in acne subjects<sup>23</sup> further supporting the role of squalene peroxidation,<sup>24</sup> and, in general, of lipid peroxidation in acne development (Figure 1).<sup>25</sup> A lower 16:0/16:1 ratio in triglycerides and wax esters has been also found, underlying another kind of alteration characteristic of sebum from acne patients.<sup>23</sup>

Recently it has been reported that acne subjects differ significantly from unaffected subjects for a different ratio between saturated and monounsaturated fatty acids in skin surface triglycerides.<sup>26</sup> Higher sebum outflow, as well as clinical manifestations, seemed to be associated with an increase in the proportion of monounsaturated fatty

acids suggesting a possible role for desaturase enzyme in the sebaceous lipogenesis and acne onset. Low glycemic load diet has been demonstrated to be able to correct the increased sebum production and compositional changes proper of acne, indicating the need to point to diet habits as possible concurrent factors influencing sebaceous gland physiology.<sup>26</sup>

## Sebum, Diet and Acne

There is evidence indicating that dietary factors alter sebaceous gland output. It has been demonstrated that sebum production can be increased by the consumption of dietary fat or carbohydrate.<sup>27</sup> Variations in carbohydrates can also affect sebum composition.<sup>28,29</sup> In turn caloric restriction has been shown to dramatically decrease the sebum secretion rate.<sup>30,31</sup> All these findings suggest that dietary habits, supplying substrates for the sebaceous lipid synthesis, can be involved in the sebum production mechanism.<sup>32</sup> Considering that increased sebum production is a primary component in acne, dietary factors have long been implicated in its pathogenesis. So far data concerning this issue are still controversial. Epidemiological studies have shown that increasing the intake of  $\omega$ -3 fatty acids through a diet rich in fish and seafood results in a lower rates of acne.<sup>33</sup> Intake of  $\omega$ -3 polyunsaturated fatty acids (PUFAs) may affect the inflammatory pathways activation through their inhibitory activity on the pro-inflammatory cytokines secretion and the leukotriene B<sub>4</sub> (LTB<sub>4</sub>) synthesis, mechanisms demonstrated beneficial in acne.<sup>25,34,35</sup> The western diet typically provides a higher supply of  $\omega$ -6 over  $\omega$ -3 PUFAs, with a ratio between 10:1 and 20:1,<sup>33,36</sup> which is higher than the 2:1 ratio found in the non-westernized diet.<sup>37</sup>

From a limited study conducted in ten subjects studied in time frames longer than two months, it resulted that the fluctuations observed in the composition of sebum fatty acids, including branched ones, were unlikely due to changes in the dietary habits or in the metabolism. Instead, variability was observed between the investigated subjects suggesting an interindividual difference in the processing of this particular class of sebaceous lipids.<sup>38</sup> A larger twin study investigating sebum secretion in 40 sets of adolescent acne twins found that differently from dizygotic twins, the sebum secretion rate was homogeneous between monozygotic twins.<sup>39</sup> Differences in the iso-even fatty acids proportion were very small in identical twins, whereas inter-pairs differences were comparable to the non-twin population, suggesting that the synthesis of branched fatty acids is under genetic control.<sup>40</sup>

## Conclusion

Human sebum is a complex and specific mixture of lipids. Its uniqueness, when compared with the sebum of other mammals, could be attributable to the different functions it has to accomplish among species. Currently, the ultimate role of human sebum is not completely understood and the metabolic pathways regulating its composition and secretion rate are far from completely understood. In particular, the pathways leading to the formation of lipids, which are typically sebaceous, such as branched fatty acids and fatty acids with unshared unsaturation positions, remain to be elucidated. New insights regarding modifications in the amount, composition and arrangement of fatty acids assembled in complex lipids of sebum could improve our knowledge on the function of sebum and on the role of alteration of sebum organization in the pathogenesis of acne

and of different sebaceous gland disorders. Moreover, understanding the factors and mechanisms that regulate sebum production is needed in order to identify new targets that could be addressed to achieve a selective modulation of lipid biosynthesis as a novel therapeutic strategy to correct lipid dysregulations in acne and other disorders of the pilosebaceous unit.

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