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## Sebaceous-immunobiology is orchestrated by sebum lipids

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### ABSTRACT

The major role of sebaceous glands in mammals is to produce sebum, which coats the epidermis and the hair providing waterproofing, thermoregulation and photoprotection. However, as the need for these functions decreased along the evolutionary changes in humans, a relevant question has been raised: are sebaceous glands and sebum the remnants of our mammalian heritage or do they have overtaken a far more complex role in human skin biology? Trying to provide answers to this question, this review introduces the evolving field of sebaceous immunobiology and puts into the focus the pathways that sebum lipids use to influence the immune milieu of the skin. By introducing possible modifiers of sebaceous lipogenesis and discussing the – human-specific – alterations in composition and amount of sebum, the attribute of sebum as a sensitive tool, which is capable of translating multiple signalling pathways into the dermal micro environment is presented. Further their interaction with macrophages and keratinocytes involves sebum lipid fractions into disease pathogenesis, which could lead – on the other side – to the development of novel sebum-based therapeutic strategies.

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### Lipid composition of human sebum



Sebocytes undergo a maturation process followed by a cell type specific cell death. This procedure results in the holocrine secretion of a composite substance called sebum.<sup>1,2</sup> Sebum is primarily composed of cell debris and nonpolar (neutral) lipids, namely triglycerides, wax esters, squalene, cholesterol and free fatty acids.<sup>3,4</sup> Notably the sebum composition is species-specific, human sebum is dominantly made up of triglycerides and fatty acids adding up to 57.5% of total lipids, followed by wax esters (26%), squalene (12%) and cholesterol (4.5%).<sup>5</sup>

While some sebum lipid fractions are unique products of the human sebaceous gland, others are also synthesized elsewhere in the body. Such example for the latter is squalene, an unsaturated hydrocarbon, which is a precursor of cholesterol. While in other tissues squalene is rapidly converted to cholesterol, in human sebocytes squalene is highly accumulated in the produced sebum. Due to its prominent lubricant

and penetration efficiency squalene is capable of neutralizing the formation of UV irradiation-induced reactive oxygen species in the skin.<sup>6,7</sup> On the other hand, peroxidated squalene along with unsaturated free fatty acids (FFA), has been reported to be comedogenic and therefore responsible for pathological skin conditions.<sup>8,9</sup>

Linoleic (18:2,  $\Delta$ 9,12), an  $\omega$ 6 polyunsaturated compound, and  $\alpha$ -linolenic acid (18:3,  $\Delta$ 9,12,15), an  $\omega$ 3 polyunsaturated compound, are essential fatty acids.<sup>10</sup> Ge et al. identified stearyl-CoA  $\Delta$ -6 desaturase as the major fatty acid desaturase in human sebaceous glands, which induces rapid oxidation and degradation of linoleic acid and its derivatives in sebaceous gland cells.<sup>11</sup>

Due to the rapid degradation of linoleic acid in the sebaceous cells, stearyl-CoA  $\Delta$ -6 desaturase is able to convert palmitic acid (C16:0) into sapienic acid (C16:1 $\Delta$ 6).<sup>3</sup> Sapienic acid is a unique sebaceous

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monounsaturated fatty acid with a single double bond at the sixth position.<sup>12,13</sup> The elongation and further desaturation of sapienic acid yields another unique sebaceous gland fatty acid, sebaleic acid (18:2Δ5, 8).<sup>3</sup> Sapienic acid exerts strong antibacterial and antifungal activities.<sup>14</sup> Remarkably, dietary palmitic acid directly activates Toll-like receptor (TLR)-2 in mouse monocytes<sup>15</sup> and activates both the NLRP3 inflammasome and mTORC1<sup>16,17</sup>, however, it provides direct antibacterial activities against *Propionibacterium acnes* (*P. acnes*) and enhances the skin innate antibacterial defence by inducing the expression of human  $\beta$ -defensin-2 (hBD2) in human sebocytes and mouse skin.<sup>18</sup>

Similarly to sapienic acid, oleic acid (18:1Δ9), a major  $\omega$ 9 monounsaturated fatty acid of sebum triglycerides, exerts the strongest antibacterial and anti-inflammatory properties among sebaceous fatty acids and strongly enhances the innate antibacterial defence of the skin.<sup>18,19</sup>

### Sebum lipids in the dermis

The key question, whether sebum lipids could also contribute to the dermal lipid content has been unanswered for more than 70 years.<sup>20</sup> Butcher has proven that sebaceous lipids, such as stearic (C18:0), oleic and linoleic acids can penetrate through the follicle and, moreover, accumulate around the sebaceous gland in high concentrations.<sup>21,22</sup> Extending these studies, we measured the transepidermal penetration of *ex vivo* topically applied lipids (linoleic, stearic, oleic, palmitic acids and squalene) into the dermis using skin grafts from hair and sebaceous gland poor regions with Raman spectroscopy. We convincingly showed that each of the tested lipids could readily penetrate through the epidermis into the dermis.<sup>22</sup>

Moreover, lipid staining with Oil Red further confirmed prominent differences in the lipid content of sebaceous gland-rich vs sebaceous gland-poor skin samples.<sup>23</sup> Visualizing the diffuse accumulation throughout the upper part of the dermis in the sebaceous gland-rich skin further supports the concept that sebum lipids should be accounted to have a role not only in the vicinity of the sebaceous glands but also in the homeostasis of the entire dermis. This suggests a far more complex physiological role of sebum and sebaceous glands, than that considered until recently, and lay ground for further studies to also investigate their effects on various cell types.

### Sebum alterations in various skin diseases

Variations in the composition and amount of sebum in different skin diseases have been detected, which are suggested to not be simply disease markers but may also play a significant role in disease pathogenesis.

#### Acne

In the recent years numerous studies have showed, that in addition to an elevated sebum production, acne patients have a markedly altered sebum composition.<sup>24,25</sup> An altered ratio between saturated and unsaturated fatty acids has been identified, and particularly, an increase in the C16:0/C16:1 nutrition lipid ratio has been shown to improve acne, accompanied by diminishing levels of linoleic acid content.<sup>24,26</sup> These data imply that desaturation of fatty acids may drive towards acne development.

Another interesting aspect of the detected changes is the accumulation of lipid peroxides, specifically squalene peroxide, which activates the Peroxisome Proliferator Activated Receptors (PPARs), stimulate keratinocyte proliferation and lipoxygenase (LOX) activity, overall increasing the expression and secretion of proinflammatory cytokines in acne.<sup>27-29</sup>

Furthermore, studies also detected decreased level of vitamin E in acne subjects, which also leads to inflammation and underlines a general importance of lipid peroxidation in the development of acne.<sup>3</sup>

#### Seborrheic dermatitis

In relation to seborrheic dermatitis, studies suggest that the lipases and phosphatases produced by *Malassezia* hydrolyse sebaceous lipids, resulting in decreased triglycerides and a corresponding increase in FFA, which may cause irritation.<sup>30</sup> Therefore, individual sensitivity to the irritating FFA determines the consequent inflammatory response and may define susceptibility for seborrheic dermatitis.<sup>31</sup>

#### Rosacea

Despite the occurrence of rosacea in the sebaceous gland-rich areas of the body, the amount of sebum excretion does interestingly not show alterations in rosacea patients compared to healthy controls. However, there are changes in the overall relative composition of sebum.<sup>32,33</sup> Affected individuals

exhibit elevated levels of myristic acid (C14:0) and reduced levels of saturated long chain fatty acids.<sup>33</sup> These lipids have a role in maintaining the skin barrier integrity, therefore it is reasonable to assume that the altered sebaceous fatty acid profile is an important contributor to skin barrier dysfunction leading to rosacea.<sup>33</sup>

### Psoriasis

Psoriatic lesions are usually characterized by various degrees of sebaceous gland atrophy, however there has been no correlation found between sebaceous gland size and either total Psoriasis Area Severity Index (PASI) or with the degree of erythema and inflammatory infiltration.<sup>34</sup> Despite having sebaceous gland atrophy, the total amount of sebum production in psoriatic skin is not significantly changed.<sup>35</sup> However, an increase in the levels of phospholipids, triacylglycerols, and cholesterol were found in the epidermis of psoriatic patients, which correlated with the severity of psoriasis.<sup>36–38</sup>

### Atopic Dermatitis (AD)

Although AD is mainly characterized by the dysfunctional synthesis of ceramides in keratinocytes<sup>39</sup>, AD patients seem to exert a severely reduced sebum production, which should contribute to diminished skin hydration. However, and despite the fact that the proportion of sebaceous lipids in the casual lipids is decreased and epidermal lipids (e.g. cholesterol) are increased, the total casual lipid amount is barely changed (own unpublished data). Therefore, a link between an altered sebaceous gland function and skin barrier dysfunction seem to contribute to the development of the disease, although the exact mechanisms have not been elucidated.<sup>40,41</sup>

### Immune functions of sebum lipids

Although, sebocytes are able to alter their sebum production in response to different inflammatory stimuli<sup>42–45</sup>, research has mostly focused so far on identifying a possible role of the co-produced proteins. Studies of the last two decades delivered important data; sebocytes have been shown to exert inflammatory properties with the production of antimicrobial peptides, cytokines and chemokines<sup>24</sup>, in which the activation of TLR-2 and -4, shown to also be expressed

in sebocytes, play a crucial role.<sup>46–48</sup> Furthermore, sebocytes have also been identified as sources of various adipokines, such as adiponectin, interleukin (IL)-6, leptin, serpin E1, resistin and visfatin, within the skin, highlighting that sebaceous glands could represent a link between inflammation and lipid metabolism similarly to adipocytes.<sup>42,49</sup> However, it is still unknown how sebum lipids could contribute to the inflammatory milieu of the skin, despite previous findings that free fatty acids may exert pro-inflammatory effects.<sup>50</sup>

### Modulation of the microbiome

Sebaceous glands secrete acids that form the acid mantle, a fine, slightly acidic (between pH 4.5 and pH 6.0) film on the surface of the skin that provides a barrier against pathogens, such as bacteria and viruses that might penetrate the skin and are primarily of alkaline nature.<sup>51</sup> Moreover, sebaceous lipids make an important contribution in maintaining the integrity of the skin barrier along with lipids of epidermal origin<sup>2,52</sup> thus contributing to the body's first line of defence.<sup>53</sup>

The healthy human skin is populated with a characteristic microbiome.<sup>54</sup> Interestingly, its diversity was found to be associated with the differences in the quantitative levels of sebum and hydration even between various parts of the face.<sup>55</sup> One of the most studied colonizing member is *P. acnes*, an anaerobic bacterium, which is capable of metabolizing sebaceous triglycerides into FFA on the surface of the skin via its lipases and peroxidases.<sup>56,57</sup> This bacterial lipase activity not only leads to an increased presence of FFA on the surface of the skin, but also to an altered sebum composition.<sup>58</sup> Squalene in particular has been proposed as the precursor of highly toxic proinflammatory mediators, produced by bacterial lipoperoxidase activity.<sup>59</sup> These changes lead to hyperkeratinisation and chronic inflammation, which further increases the pathological microbial colonization of the skin, thus sustaining acne formation.

Sebum may also act as a delivery system for antioxidants and antimicrobial peptides. Such molecules with antimicrobial properties are cathelicidin, psoriasin, dermcidin and human hBD-2.<sup>60–62</sup> As previously described, Nakatsuji et al. found that linoleic, palmitic and oleic acid, typically found in human sebum

enhanced the hBD-2 expression and antimicrobial activity of human sebocytes against *P. acnes*.<sup>18</sup>

Other studies have showed that lauric and sapienic acid as well as long-chain bases (sphingosine, dihydrosphingosine and 6-hydroxysphingosine) have broad-acting antimicrobial properties.<sup>63</sup> These antimicrobials act as part of the innate immune system of the skin, and are generated through the action of ceramidases from the stratum corneum.<sup>63</sup>

### Immunoregulatory effect on macrophages

To address how sebum lipids and their possible inflammatory role could be placed into the setting of skin (patho)physiology at a cellular level, the interaction between sebum component lipids and macrophages has been investigated in a current study. The sebum lipids linoleic and oleic acid were detected to be potent inducers of the so-called alternative macrophage activation, which is the characteristic activation pathway for macrophages involved in tissue homeostasis and repair functions.<sup>64</sup> Furthermore, these lipids also enhanced the ability of macrophages to phagocytose different particles as well as *P. acnes* bacteria.<sup>23</sup> Importantly, fatty acids exhibited a differential effect on the inflammatory response of *P. acnes*-activated macrophages.<sup>23</sup> These results shed light on how sebum composition plays a key role in regulating immune responses against bacteria, such as *P. acnes*, proving that sebum lipids not only can regulate macrophage function, but also integrate into disease-specific settings, such as acne.<sup>25</sup> These results undoubtedly set the basis for further considerations on how macrophages and most likely other cell types of the skin could be possible targets for the altered sebum production not just in acne but also in other dermatological diseases.

### Interaction with keratinocytes

Keratinocytes have a significant lipid production and metabolism pivotal in the formation of the epidermal lipid barrier, which made sebum lipids to be overlooked for long time in understanding epidermal integrity and functions. To find a possible link between sebum lipids and keratinocytes, the observed prominent differences in the keratinocyte expression of thymic stromal lymphopoietin (TSLP), one of the major epimunomes (epithelial cell-derived molecules that can instruct immune cells), between

sebaceous gland-rich and -poor skin have been addressed. When keratinocytes were cultured in the presence of sebocyte supernatant, which contained all sebocyte-derived lipids<sup>65</sup>, the expression of TSLP mRNA increased. Searching for the lipid(s) behind the induction, we found linoleic acid to increase TSLP mRNA levels in a dose-dependent manner.<sup>66</sup> These data put forward the possibility that lipids not only of epidermal but also of sebaceous origin could contribute to a sensitive homeostasis that highly influences skin barrier functionality.

### Signalling pathways affecting sebum lipid composition

Sebaceous lipogenesis is controlled by a network of processes. One of the major factors in humans are the hormonal changes taking place at puberty.<sup>67</sup> Sebaceous glands not only respond to androgens, but are also capable of producing them. A prominent androgen is 5 $\alpha$ -dihydrotestosterone (5 $\alpha$ -DHT), as sebocytes are able to convert testosterone to 5 $\alpha$ -DHT with the enzyme 5 $\alpha$ -reductase type I<sup>68</sup>. Both testosterone and 5 $\alpha$ -DHT increase sebaceous proliferation, however, they do not affect lipid synthesis.<sup>68,69</sup>

Studies revealed that for the androgenic influence co-factors are also required, like members of the nuclear receptor family, which by directly binding to specific DNA sequences can regulate the expression of their target genes upon activation with their ligands.<sup>70</sup> PPARs with all three isoforms namely PPAR- $\alpha$ , - $\delta$ , - $\gamma$ 1 and - $\gamma$ 2 which are all expressed in sebocytes<sup>47</sup>, are the prime members<sup>71</sup> with varying effects on sebocyte proliferation and lipogenesis.<sup>72</sup> Previous studies showed that linoleic and arachidonic acid activation of PPAR- $\delta$  and PPAR- $\gamma$  has led to an increased intracellular lipid content of sebocytes, while PPAR- $\alpha$  agonists blocked lipogenesis via inhibiting the leukotriene pathway. Furthermore, PPAR- $\alpha$  seems to be related to  $\beta$ -oxidation of fatty acids and lipid catabolism.<sup>73</sup> Interestingly, *P. acnes* and its soluble factors may also participate in the augmentation of sebaceous lipogenesis by increasing the production of the 15-deoxy- $\Delta$ 12,14-prostaglandin J2 (15d-PGJ2), an endogenous activator of PPAR $\gamma$ .<sup>74</sup>

The Liver X Receptor (LXR) receptors which have a well-defined role in cellular cholesterol homeostasis and lipid metabolism<sup>75,76</sup>, also belong to the nuclear receptors. Using LXR ligands such as 22R-hydroxycholesterol



an increase in the expression of key fatty acid synthetases as well as sterol regulatory element-binding protein-1 (SREBP-1) was observed, followed by the accumulation of lipid droplets, a hallmark of sebaceous lipogenesis.<sup>77,78</sup>

Retinoids also direct control sebaceous gland proliferation and lipogenesis.<sup>79,80</sup> Both retinoic acid receptors (RAR- $\alpha$  and - $\gamma$ ) and retinoid X receptors (RXR- $\alpha$ , - $\beta$ , - $\gamma$ ) are expressed in human sebocytes and their ligands all-trans retinoic acid (atRA) and 9-cis-retinoic acid (9cRA) inhibit sebocyte differentiation and lipid synthesis.<sup>80</sup>

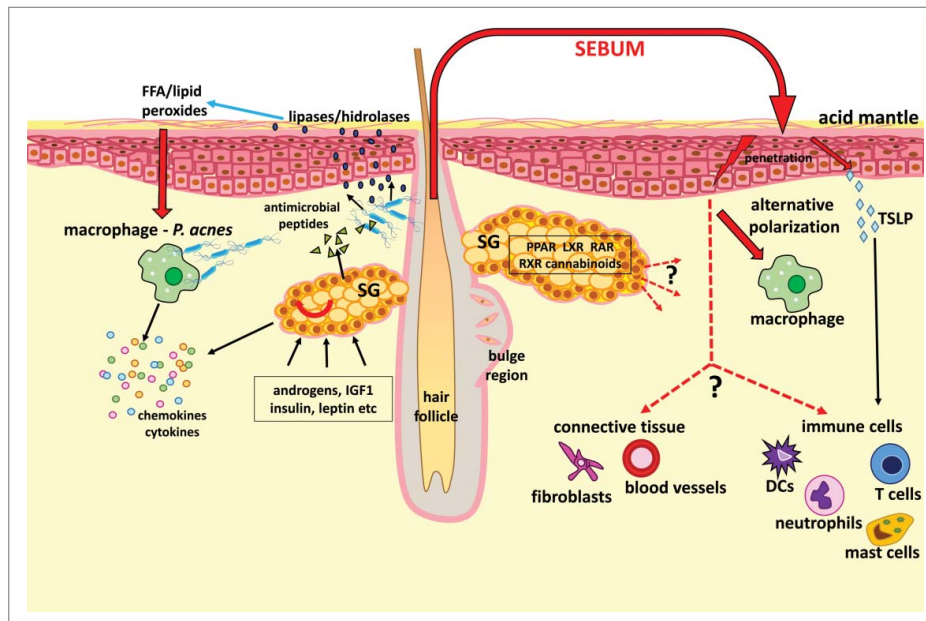
Although often disregarded, the role of diet should also be taken into account in order to understand sebaceous lipogenesis. A widely accepted mechanism is that a diet rich in carbohydrates increases the activity of the insulin-like growth factor 1 (IGF-1) pathways.<sup>81-83</sup> The presence of the IGF-1 receptor in sebocytes has been described and was shown to activate the PI3K/ Akt/ FoxO1 pathway thus providing evidence that FoxO1 may be a key factor in the regulation of growth-factor stimulatory effects on sebaceous lipogenesis and inflammation in response to elevated IGF-1 and insulin levels.<sup>84</sup> Moreover, we have demonstrated that leptin “the satiety hormone”, besides inducing the expression of

inflammatory cytokines such as IL-6 and IL-8 in sebocytes also affects lipogenesis by increasing triglyceride levels, thus increasing the ratio of monounsaturated fatty acids or polyunsaturated fatty acids to saturated fatty acids and by decreasing the levels of vitamin E, which altogether are also the characteristics for acne patients' sebum.<sup>24,25,44</sup>

At last, neuropeptides are also known as factors that enhance sebaceous lipogenesis. Corticotropin-releasing hormone is expressed in human sebocytes and augments the synthesis of sebaceous lipids *in vitro*.<sup>85,79</sup> Moreover, adrenocorticotrophic hormone and  $\alpha$ -melanocyte-stimulating hormone have been shown to increase squalene synthesis in primary human sebocytes.<sup>86</sup> Human sebocytes also express melanocortin 5 receptor (MC5R), which is involved in sebocyte differentiation and lipogenesis.<sup>87,88</sup>

### Therapeutic perspectives in modulating sebum composition

The observations of altered sebum composition made so far in various skin diseases puts forward the question of possible therapeutical solutions through



**Figure 1.** Sebum lipids orchestrate sebaceous-immunobiology. Sebum production and composition is regulated by intrinsic (i.e. PPAR, LXR, RAR, RXR, endocannabinoids) and extrinsic (i.e. androgens, IGF1, insulin, leptin) factors. Sebum lipids (marked with red arrows) contribute to the lipid barrier of the skin and penetrate through the epidermis to the dermis, however a direct diffusion from the sebaceous glands has been proposed as well. Sebum fraction lipids also have a role in modulating both keratinocyte as well as macrophage functions by altering their gene and protein expression levels, which may be important in maintaining the physiological dermal immune milieu. In the defence response against pathogens, sebum lipids have multiple functions: exert antimicrobial effects, induce the cytokine expression of sebocytes and keratinocytes as well as modulate the macrophage – *P. acnes* interaction, which may have a central role not just in the pathogenesis of acne but also in other diseases. Further identification of how sebum lipids could alter the functions of other cell types is also a promising field for research with pathological and therapeutic relevance.

modulation of sebum composition.<sup>25</sup> New compounds might be utilized as topical treatments in acne, such as long-chain polyunsaturated fatty acids, which could target *P. acnes* and treat infections, e.g. with *Staphylococcus aureus*, due to their antimicrobial and anti-inflammatory properties, thus providing an alternative for antibiotics in acne treatment.<sup>89</sup> Palmitic acid, oleic acid, and lauric acid have been already proposed as alternatives to antibiotic therapy in acne vulgaris.<sup>18,19,89,90</sup>

Controlling lipid production not only can be beneficial for acne patients, where the overproduction of sebum and its compositional imbalance represents the main problem. Severe skin dryness as observed in AD patients might be remedied by manipulation of sebum production towards a normal composition via the stimulation of androgen or PPAR receptors, which could potentially repair the defective skin barrier.<sup>91</sup> Furthermore, the activation of LXR by synthetic ligands may have therapeutic relevance, which could also augment lipid production along with exerting anti-inflammatory effects.<sup>91</sup>

Novel compounds such as endocannabinoids may also provide solutions to various sebaceous gland-related diseases. Recently Bíró et al. provided evidence that sebocytes express cannabinoid receptor-2, more interestingly arachidonoyl ethanolamide/anandamide, 2-arachidonoyl glycerol are also present in sebocytes and can induce lipid production and apoptosis.<sup>42</sup> Endocannabinoids generally up-regulate the expression of genes involved in lipid synthesis, such as PPAR transcription factors, thus cannabinoid receptor-2 antagonists or agonists may be utilized in the management of sebaceous gland disorders.<sup>42,92</sup>

## Conclusion

With the improvement of sebaceous gland research more and more receptors, transcriptional factors, chemokines and cytokines have been recognized in sebocytes both *in vitro* and *in vivo*, leading to a better understanding and positioning of sebaceous gland biology in the context of immune mediated pathways. However, only in recent years did our focus shift to the most prominent feature of sebaceous glands: sebum production. Sebaceous gland lipids have been shown to exhibit pro-and anti-inflammatory properties, attributed with antimicrobial qualities and most recently they have been

demonstrated to exert a modulating role on immune cells (Fig. 1). Further research is required, both in understanding sebocyte function and lipodomics, to provide useful data for therapeutic advances in sebaceous gland-related skin diseases. Therefore, placing (sebum) lipids in the centre of research provides a vast and intriguing field for further studies to come.

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