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Cosmetic Regulation of Sebaceous Gland Activity

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Summary

There is over one hundred thousands of sebaceous glands in humans. They are uneven distributed all over the skin. Sebaceous glands belongs to holocrine type glands. Their activity is regulated by both internal and external factors and active substances. To the endogenous factors belongs hormones mostly androgens and progestagens. Estrogens play the minor role inhibiting the sebum secretion. Other hormones like propiomelanocortin and somatotropin have some activity but are not very important for the sebaceous glands secretion. The development of those glands is strongly determined on the presence of several cytokines like IL-1, TGF-β, EGF and IGF-1. Also the PPAR (α,β and γ) receptors are engaged in the sebum composition and releasing control.
Among the exogenous substances on the top of list are retinoids, particularly 13-cis retinoic acid which inhibits the activity and size of sebaceous glands even by 90%. Of importance are also compounds inhibiting 5-α-reductase like organic acids zinc salts, zinc oxide, azelaic acid and vitamins of the B group the proven activity have pyridoxal phosphate (vitamin B6) .
Indirect action provide also some skin microrganisms producing many substances which stimulate sebaceous gland and antioxidants inhibiting sebum trasformations.

Riassunto

Il corpo umano è ricoperto in modo irregolare da migliaia di ghiandole sebacee che, distribuite nelle diverse zone cutanee, svolgono l'attività secretoria regolata da fattori endogeni ed esogeni. Tra i fattori endogeni, i più importanti sono gli ormoni androgeni e progestinici, mentre gli estrogeni svolgono un ruolo secondario di inibizione della secrezione del sebo. Altri ormoni quali la propiomelanocortina e la somatotropina, pur svolgendo una certa attività, non hanno un ruolo determinante per la secrezione sebacea.
Lo sviluppo delle ghiandole sebacee è fortemente influenzato dalla presenza di molte citochine quali:

IL-1, TGF-Beta, EGF e IGF-1. Anche i recettori PPAR (alfa, beta e gamma, sono coinvolti nella composizione e nella secrezione del sebo.
Tra le sostanze esogene il primo posto è rappresentato dai retinoidi, in modo particolare dall'acido 13-cis retinoico che inibisce al 90% sia l'attività che le dimensioni delle ghiandole sebacee. Rivestono una certa importanza anche i composti che inibiscono l'attività della 5-alfa reduttasi quali i sali di zinco, l'ossido di zinco, l'acido azelaico e le vitamine del gruppo B, soprattutto il piridossal fosfato (vit B6).
Una azione indiretta è svolta anche da alcuni microorganismi che producono molecole che stimolano la produzione delle ghiandole sebacee, o antiossidanti che ne inibiscono la trasformazione in sostanze maleodoranti.

The sebaceous gland

The sebaceous glands are simple or compound clustered structures (acini), which develop embryologically in the upper part of a hair follicle. Their development starts in the third month of a human fetal life. There are two cell types in sebaceous glands – the lipid producing sebocytes and keratinocytes – the duct builders. Their holocrine lipid secretion is released into a common duct with an orifice to the hair follicle, placed at the funnel level 200 - 500μm under the skin surface (1), (2), (3). The sebaceous glands, well developed in the embryonic period, produce vernix caseosa, which plays an essential role in protecting the skin and the organization of the epidermal barrier of the neonate. Among others, along with sebum, onto the surface of the skin photoprotective, inhibiting oxidation processes and anti-irritant substances are secreted. A significant role is also played by one of the main components of sebum - sapienic acid (C16:1, n6) with antimicrobial properties, like antimicrobial peptides whose secretion is induced by the presence of bacteria, (3), (4). After birth the activity of sebaceous glands diminishes and maintains at the lowest level up to period of pubescence. The enlargement of the sebaceous glands is one of the first changes occurring during puberty. All of the above changes are hormonally controlled (1).

The physiology of the sebaceous glands

In man there is about 100000 sebaceous glands distributed all over the skin. The largest number is located on the scalp, and the T-zone (forehead, nose, chin) and the front and back of the gutter sweat torso. These areas are prone to oily skin. One follicle is usually surrounded by 3-5 glands, having one common wire lead-out. On the scalp follicles and glands are large. The size of the gland influences, inter alia, the amount of sebum produced and secreted to the skin surface (1), (5).

The sebaceous gland belongs to holocrine glands, composed of rapidly dividing flat peripheral cells. As the cells approach the central part of the gland, they lose the ability to divide and undergo disintegration. The time of transition of a descendant cell, already proliferating, to the phase of a mature cell, i.e. the differentiation period, lasts for over a week. After 8 days a sebocyte turns into sebum. The pressure exerted by the liquid accumulated in a vesicle leads to the final phase of a natural apoptosis. As is easy to calculate, sebocyte's turnover time is approximately 3 weeks. The vesicle bursts and the secretion gets into the duct lumen. Then, sebum is released onto the surface of the epidermis (1).

The cells in an outer layer of the acinus, which rests on an external membrane, are the reproductive cells. The synthesis of lipids takes place in a smooth endoplasmatic reticulum. Next they are packed to Golgi apparatus, forming the drops of fat inside the cell. After differentiation, the nucleus of sebocyte diminishes and disappears. The remaining cellular structures are also eradicated. Finally the mature sebocyte explodes releasing its entire content to the gland duct. The liquid mixture of lipids floats through the sebaceous duct consisting of multilayered cuticle up to the funnel and hair channel, reaching skin surface (1), (2).

The sebum biosynthesis

The most visible function of sebaceous glands is sebum secretion. The humans are born with a certain number of sebaceous glands, which reveal different activity and efficiency in various stages of life. The sebaceous glands fully develop by the 6 month of life. The intensification of sebum secretion takes place few hours after birth and reaches maximal values during the first

week and gradually slows down. It rises again at the age of 9 years, together with an increased activity of adrenal glands and lasts up to the age of 17 throughout the whole period of pubescence. (6), (7).

Chemically sebum is a mixture of the few hydrophobic groups of compounds with the prevailing glycerides. The sebum includes mono-, di- and triglycerides (depending on age: about 45-50%), conditioning the viscosity of sebum, waxes (20-25%), free fatty acids (about 16%, including 10% of unsaturated linoleic acid), ensuring adequate sebum liquidity, squalene (approximately 10-12%), cholesterol esters (3.5-4%), free cholesterol (about 1-1.5%), other sterols (1-2%). Daily secretion standard is about 1-2g (8), (9), (10).

The hydrolysis of human sebum delivers a mixture of numerous fatty acids with branched chains. The predominant forms are iso and anteiso isomers (with a methyl substituent group at the third from the end or penultimate carbon atom in chain), although also acids with branched chains and substituent methyl groups in different positions are present, as well as the acids with two or three methyl substituents. Almost half of the fatty acids of human sebum consist of the monounsaturated acids with double bond in n-6 position. The model of n-6 unsaturation seems to be characteristic for a human. For the other analyzed mammalian species, which were investigated n-9 unsaturated chains are characteristic(1).

The analyses proved that the composition of sebum fatty acids changes with age. The sebaceous fatty acids differ during fetal period and before pubescence from the fatty acids of the adults. The differences include length of chains, proportion of monounsaturated fatty acids n-6 to n-9 and with a number of various branchings. The sebum of children before puberty is different from the one of the adults with a larger amount of cholesterol, its esters and a smaller amount of wax esters. The holocrine nature of sebum secretion reveals a mechanism, which may cause the changes of sebum composition without any changes during synthesis of sebaceous lipids. Because it takes sebocyte disintegration to release sebum, the product incorporates the synthesized lipids as well as the ones from the structure of sebocyte cell membranes. The lipids from both sources have different composition. The synthesized endogenous sebaceous lipids contain mainly squalene, wax esters and n-6 unstaturated fatty acids, while the exogenous lipids from the sebocyte cell membranes abound in cholesterol, n-9 fatty acids and linoleic acid. During the pubescence period, the amount of endogenous sebaceous lipids increases in sebum, while the exogenous types proportionally diminish (1).

The endogenous control of the sebaceous gland

The development and function of sebaceous gland is regulated by the number of factors such as transcription factors, hormones, hormone nuclear receptors, retinoids, ILGF and cytokines. The hormones significantly influencing the activity of sebaceous gland are the androgens, estrogens, growth factor, corticoliberin, insulin and glicocorticoids. They mostly stimulate secretion of sebaceous lipids, while the retinoids, cytokines and hormone nuclear receptors seem to be the promising inhibitors of sebum synthesis (2), (11).

The factors regulating development of sebaceous glands still long for detailed investigation. The important mediators of gland development are the epidermal growth factor (EGF), homeotic HOX genes and sonic hedgehog genes (SHH), which when inhibited, cause sebocyte growth disorders.

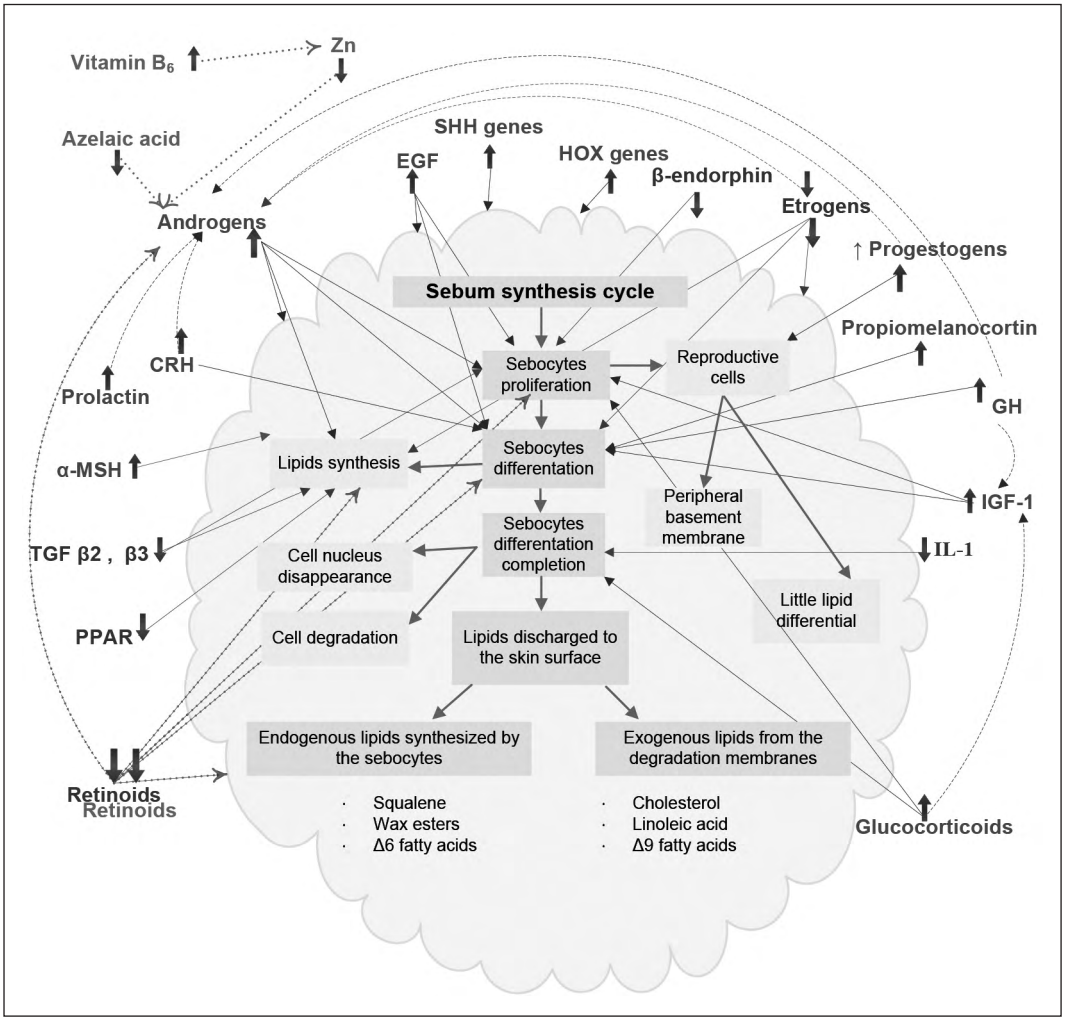

Fig. 1 *Development and control the sebaceous gland. Somatotropin (GH); Corticotropin-releasing hormone (CRH); Insulin-like growth factor-1 (IGF-1); Epidermal growth factor (EGF); Transforming growth factor (TGF); Interleukin-1 (IL-1); Peroxisome proliferator activated receptors (PPAR); α-melanocyte-stimulating hormone (α-MSH).*

The androgens

The ability of sebaceous gland to respond to androgens is determined in fetal period. The growth of sebaceous glands and their differentiation requires the influence of androgens and a few other biological factors (2).

The androgens influence the sebaceous glands through mitosis and lipogenesis stimulation. The human sebaceous glands seem to respond to testosterone and other androgens. Both dehydroepiandrosterone (DHEA) and androstenedione stimulate sebum secretion in the areas retarded by estrogens. However such effects were not observed in case of androsterone. The most effective androgens are those with 17β-hydroxy

group, like testosterone, 5α-dihydrotestosterone (DHT), 5α-androstane-3β,17β-diol. Androgene-sensitive skin areas like sweat glands, hair follicles and sebaceous glands, metabolise androgens in accordance with characteristic pathways. Although the skin is unable to synthesize androgens *de novo* from cholesterol, it incorporates all the indispensable enzymes to transform prohormones DHEA and androstenediones into testosterone and the strongest androgen - dihydrotestosterone (DHT). The metabolic pathway, illustrating formation of active androgens from dehydroepiandrosterone sulfate (DHEAS) is shown in the Figure.4 (1), (6), (12), (8).

The activity of the enzymes participating in metabolic pathway in skin is different depending on the body area. In the non-seborrheic areas prevails the oxidizing action of 17β-dihydrogenase (17β-HSD) (the transformation of estrogens and testosterone into less active precursors). Meanwhile in sebaceous glands in the acnegenic regions, like face skin and scalp the activity of 5α-reductase (5α-R) is 2-4 times larger than 17β-dihydrogenase. The isozyme of the first type of 5α-reductase participates in transformation of testosterone into dihydrotestosterone (DHT), the strongest among androgens stimulator of sebum secretion. (13), (12), (2).

The estrogens

The estrogens undoubtfully influence the human sebaceous glands, by inhibiting their activity. On the contrary to the androgens, which stimulate mitogenesis and sebogenesis, the estrogens influence only sebum secretion and don't participate in the cells proliferation. It is an interesting problem whether the estrogens react circumferentially or locally as inhibitors of secretion of endogenous androgens. It seems less likely because the inhibiting reaction is observed also in the presence of supplementary testosterone. On the other hand it was demonstrated in the foreskin glands of mice and rats, that estradiol inhibits a metabolism of testosterone, which proves that estrogens can directly influence androgens performance. There are numerous studies on the circumferential and local inhibiting action of androgens in relation to the differentiation of sebaceous lipids (2), (1).

The progestagens

We can observe a profound impact of progesterone on the amount of produced sebum. Theoretically, progesterone should reduce seborrhea as it inhibits the activity of 5-alpha –reductase, which regulates the amount of dihydrotestosterone (DHT), thus lowering oil secretion. Unfortunatelly, it is not that simple (6), (14).

The amount of produced sebum is not affected by the mere presence of progesterone, but in fact, its ratio to estrogens. If the progesterone concentration is higher than that of estrogens, and the amount of progesterone in the body is higher than the amount of estrogens, a rapid sebum production occurs. The adverse effect of progesterone activity is attributed to the inhibition of the beneficial effects of estrogen activity.

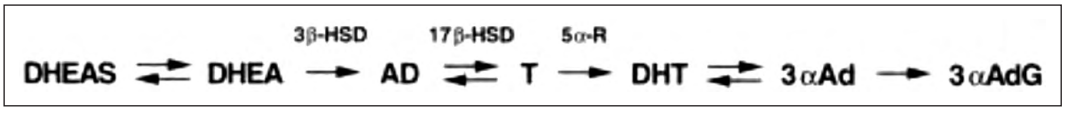

Fig. 2 *A schematic representation of androgen metabolism in the skin. The enzymes 3β-hydroxysteroid dehydrogenase (HSD), 17β-HSD, and 5 -reductase (5 -R). Dehydroepiandrosterone-sulfate (DHEAS); dehydroepiandrosterone (DHEA); androstenedione (AD); testosterone (T); 3 -androstanediol (3 Ad); 3 -androstanediol glucuronide (3 AdG)[6].*

In females, the quantitative ratio of these hormones is strictly dependent upon the luteinizing hormone, called lutropin (LH), needed for the proper course of the menstrual cycle. The peak concentration of this hormone is observed in the last days of the follicular phase of the menstrual cycle. Lutropin is responsible for the luteinizing of the corpus luteum, i.e., for the transformation of the granulosa cells of the ruptured ovarian follicle (the follicle surrounding the oocyte) into lutein cells (producing progesterone). The level of these hormones is strictly connected with the phases of the menstrual cycle and with the woman's current physiological condition. As is known, the progesterone level also rises in pregnant women, because the hormone is responsible for supporting gestation, and, adequately, in the second part of the menstrual cycle it prepares the body for embryo implantation; that is, in the period of increased sebum production (11), (13), (7).

The prolactin

It is produced in large amounts during the pregnancy and stimulates sebaceous glands. During hiperlactemia it participates in development of hirsutism and seborrhea in women (11), (13).

The corticoliberin (CRH) – corticotropin releasing hormone

The Pro-CRH transformed into CRH seems similar regardless its location (whether circumferential or locally present – including skin structures). The particular neuropeptides, hormones, cytokines function as signal transmitters in communication between the three cooperating systems the pituitary gland - hypothalamus – adrenal glands. Reacting to stress, the skin can also produce similar mediators. The research shows that human sebocytes have the expression of functional receptors, for a hormone releasing corticotropin (CRH), melanotropines (α-melanocyte-stimulating hormone; α-MSH), β-endorfins, vasoactive intensinal polypeptide (VIP), neuropeptide Y and calcitonin gene-related peptide (CGRP). After establishing ligands bonds, the receptors initiate secretion of inflammatory cytokines, proliferation, differentiation, lipogenesis and androgens metabolism in sebocytes (5), (15).

The CRH is active in human sebocytes and may for them an autocrine hormone with homeostasis of differentiation activity, it directly causes even double increase of lipid synthesis, without stimulation of proliferating cells and growth of expression of mRNA hydroxysteroid 3β-dehydrogenase (the enzyme, which converts dihydroepiandrosterone to testosterone in human sebocytes). These observations confirm participation of CRH in clinical development of acne, skin aging, excessive cornification and other skin disorders related to the changes of secretion of sebaceous lipids (5), (15).

The propiomelanocortin (POMC)

The propiomelanocortin (POMC) is released by the pituitary gland and functions as a precursor hormone for the substances influencing activity of sebaceous gland, like adrenocorticotropin (ACDH), melanocyte-stimulating hormone (α-MSH) and β-endorfin. The melanocortins, especially ACTH and MSH are important mediators of stress reaction of classical HPA line (hypothalamus-pituitary gland-adrenal gland). It was discovered that these both hormones are also produced by skin keratinocytes, melanocytes and cultured sebocytes. The melanocortins cause various biological effects by bonding and activating their receptors on a plasmatic membrane (16).

The POMC peptides stimulate differentiation of sebocytes.

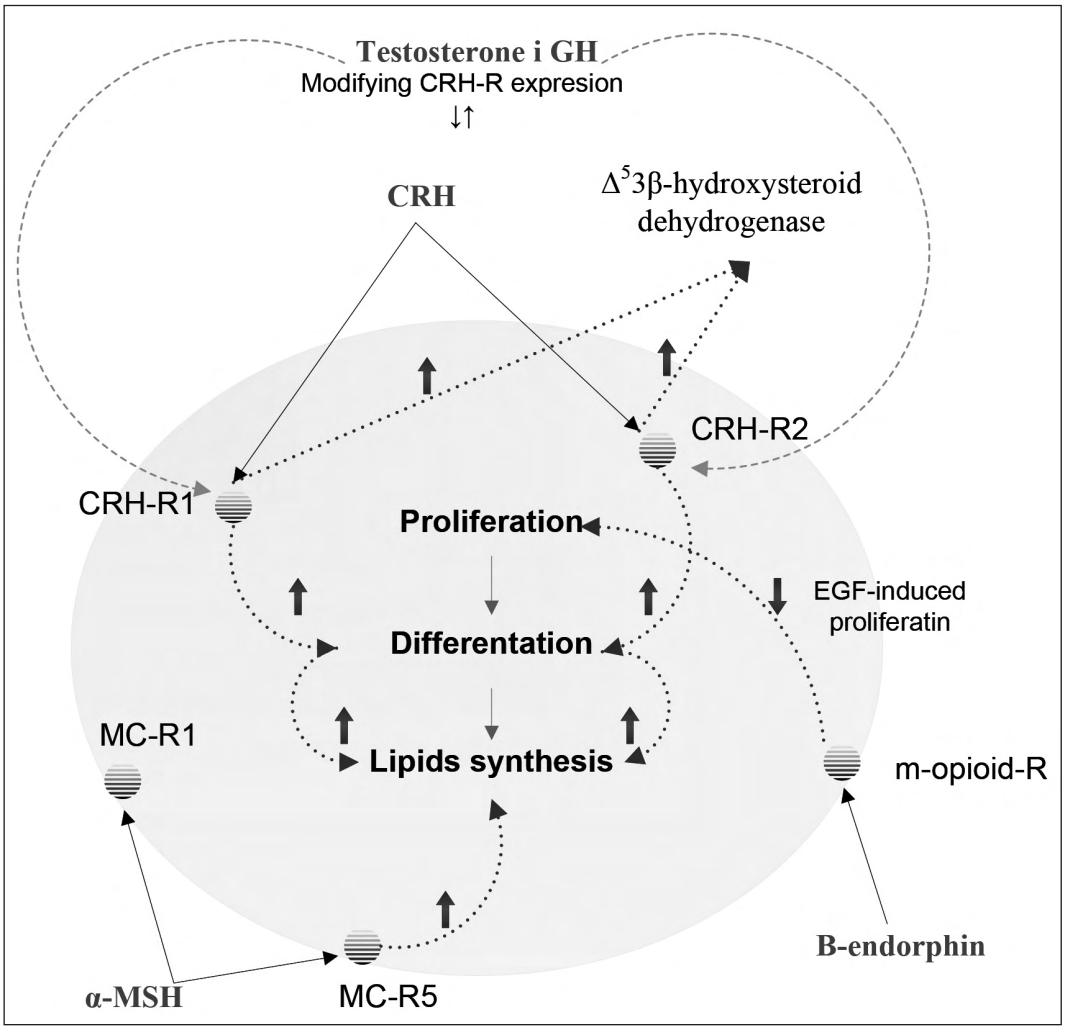

Fig. 3 *Functioning of sebocyte. Corticotrophin receptors (CRH-R1, CRH-R2); Melanocortin receptors (MC-R1, MC-R5); opioid receptor (m-opioid-R); corticotropin-releasing hormone (CRH); α-melanocyte-stimulating hormone (α-MSH); growth hormone (GH);*

The secretion of human sebaceous lipids may increase as a result of α-MSH hormone influence on melanocortine receptor MC5-R. This hormone influences also squalene synthesis, which is an important sebum ingredient. The increased squalene production and induction of MC5-R takes place only during sebocytes differentiation, which suggests an active role of MC5-R in sebum synthesis (16).

The β-endorfin is a paracrine neuropeptide for human sebocytes, which inhibits their proliferation, caused by the epidermal growth factor (EGF), when bounded with opioid receptor(5).

The somatotropin (GH)

The strong expression of a growth hormone (GH) is visible on human skin. This hormone is engages in the development of sebaceous gland. It stimulates differentiation of sebocytes and increases the influence of a 5α- dihydrotestosterone on the synthesis of sebaceous lipids and induces IGF. The GH doesn't stimulate DNA synthesis in sebocytes (2), (13), (5).

The insulin-like growth factor-1 (IGF-1),

The main activity of IGF-1 (Insulin-like growth factor-1) is directed to stimulate sebocyte proliferation, while additionally it plays an important role in their differentiation.

The epidermal growth factor (EGF),

The EGF (Epidermal growth factor) strongly determines development of sebaceous glands and additionally regulates sebocytes differentiation (2).

The transforming growth factor (TGF)

The TGF β_3 and β_2 but no β_1, (transforming growth factor) reduce cell proliferation and lipogenesis in the human sebaceous glands.

The interleukin-1 (IL-1)

The interleukin-1 (IL-1) is an important cytokine in skin, where it plays a role of mediator in inflammatory reactions. It occurs in sebaceous glands and their ducts. The increased expression of IL-1 reflects in blackheads in the skin. IL-1 also retards sebocytes differentiation, but don't influence their proliferation(2).

The glycocorticosteroids

They perform stimulating activity on the proliferation and differentiation of sebocytes and increase the performance of IGF-1 on the sebaceous cells(13).

The peroxisome proliferator activated receptors (PPAR)

The transcriptive factors (PPAR peroxisome proliferator- activated receptor) belong to the superfamily of hormone nuclear receptors, which contains also steroid receptors, thyroid hormones receptors, vitamin D receptors and retinoic acid receptors. These receptors are engaged into control of gene coding proteins, responsible for lipids metabolism and are activated i.e. by physiological concentrations of fatty acids as well as by the medicines diminishing the excess lipids in blood. In human sebocytes there is an noticeable expression of PPAR-α, PPAR-β and PPAR-γ.
The activators of PPAR-α and PPAR-γ regulate differentiation of sebocytes, slowing down sebaceous lipogenesis and reducing synthesis of specific sebaceous lipids: squalane and triglicerides, while the activators of PPAR-β influence lipids formation in sebocytes and keratinocytes (2), (11).

The retinoids

Of all the retinoids the strongest action on the sebaceous gland has an 13-cis-retinoic acid (isotretinoin). It inhibits the activity of sebaceous glands and reduces their size even by 90%. Sebaceous glands undergo involution, with resulting limited lipid production. Isotretinoin has bacteriostatic properties, inhibiting the development of *Propionibacterium acnes*. It stabilizes the natural flora on the surface of the skin. It normalizes the keratinisation process due to the inhibition of the proliferation of sebocytes, and it

probably restores the proper process of cell differentiation. This substance considerably dries out the skin, contributing to its fine texture. It reveals teratogenic properties. It may lead to fetus deformation. It reduces telomerase activity, which promotes the death of epidermal cells, and it reveals pro-apoptotic activity. Thanks to this, pathologically changed epidermal cells die rapidly, whereas new and healthy ones take their place. Isotretinoin inhibits seborrhea and its long-term efficacy is estimated at 70-85%. Isotretinoin also acts as an inhibitor of 3-alpha-hydrosteroids oxidation by retinol dehydrogenase, leading to the diminished amount of androstendione and dihydrotestosterone. Additionally, retinoic acid induces a rapid and short-term expression of the transforming growth factor (TGF). Isotretinoin is present in such preparations as Isotrexin for topical use, as well as Izotek and Roaccutane for oral application. It cannot be used in cosmetic preparations (17).

The exogenous inhibitors of activity of sebaceous glands

Many exogenous factors may stimulate action of the endogenous substances, which in case of sebaceous glands leads to the increased seborrhea. Moreover, the increased amount of lipids on skin, causes growth of skin bacteria. The larger number of microorganisms may cause irritations, that finally intensify seborrhea (7).

The most accurate method of improving skin condition and appearance in case of excess sebum secretion, should be topical application of formulas containing substances inhibiting activity of sebaceous glands.

One of the potential reduction possibilities of sebaceous glands activity is diminishing concentration of DHT in hair follicle area and sebaceous gland by inhibition of 5-α-reductase (7). The substances approved for use in cosmetics and performing in the described way are the zinc salts (mainly organic acids salts, glutaminic and pirolidonecarboxilic acids), pirydoxine (B_6 vitamin) and azelaic acid. The zinc performance on reduction of sebum secretion concerns both inhibition of action of 5-α-reductase and also inhibiting microbial lipases, disintegrating sebum triglicerides to the free fatty acids. Zinc in large concentrations may completely reduce activity of 5-α-reductase (7), (16), (18).

In case of azelaic acid the diminishing performance on 5-α-reductase is already observed in its small concentrations (0,2mol/L), while at 3mol/L almost complete reduction of enzyme activity is achieved(19). Additionally, azelaic acid like zinc, decreases number of the skin bacteria and the number of free fatty acids remaining from the disintegration of lipid compounds(20), (21).

The mechanism of action of B_6 vitamin is slightly different, for it doesn't inhibit directly 5-α-reductase. However it boosts up zinc performance as inhibitor of 5-α-reductase, doesn't influence activity of azelaic acid(19). Because of the large sensitivity, the B_6 vitamin is incorporated into cosmetics in a form of biological extracts i.e. yeast (7).

The different sebostatic mechanism present retinoids when applied topically. The compounds of retinoids like retinal, approved for cosmetics, or all-trans-retinoic acid used in dermatological preparations don't directly influence sebum secretion. Some indirect action may occur after conversion into isotretinoin in skin. Because of the fact that biochemical processes in skin will lead not only to the 13-cis-retinoic acid, but also other compounds, its activity will be much weaker that isotretinoin action (7).

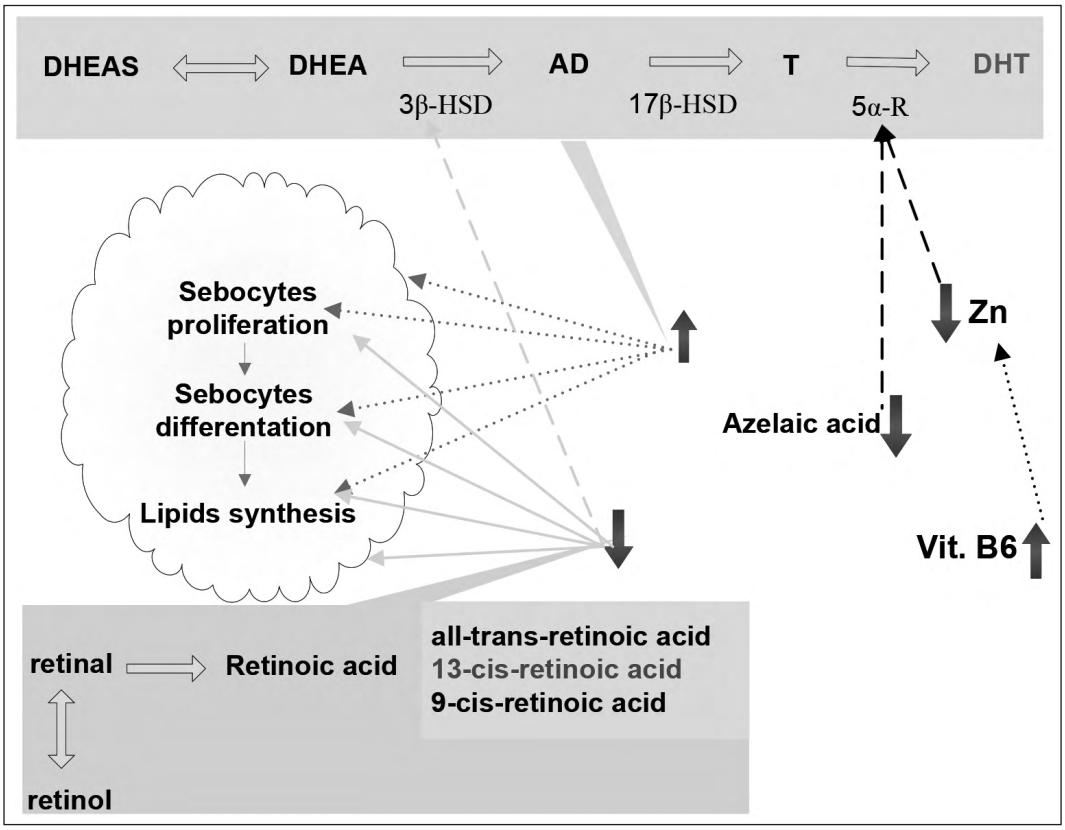

Fig. 4 *Sebaceous gland activity inhibition...*

Role of micro-organisms in stimulating sebaceous glands

Natural bacterial flora contains *Propionibacterium acnes*, a Gram-positive bacterium, which may turn into a parasite in the case of immune system deficiency and bacterial overgrowth. It also contains *Corynebacterium acnes, Brevibacterium acnes, Staphylococcus epidermidis*, physiologically producing exfoliatin, which stimulates exfoliation of the epidermis. In pathological cases the toxin leads to excessive epidermal exfoliation. Additionally, the flora contains a yeast species, *Malassezia furfur (Pirytrosporum ovale)* (10), (7). Its role is not known, though. However, it has been observed that the amount of yeast diminishes due to the antifungal treatment, resulting in the improved clinical results (sebaceous gland activity diminishes), and vice versa – in the periods of increased oil production the amount of yeast increases. *Malassezia's* metabolism changes sebum content. Certain substances are transformed into compounds that irritate the skin (22), (23).

Antioxidant role in the inhibition of sebaceous gland activity

Sebum content changes not only due to Malassezia furfur activity, but also during the

process of oxidation. In order to prevent this, a number of antioxidants are used. Antioxidants, such as vitamin E, coenzyme Q10, β-carotene and ascorbic acid belong, among others, to such substances. Their objective is to neutralize free radicals. These substances protect fats found in sebum against oxidation.

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