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Reviewer

Linking diet to acne metabolomics, inflammation, and comedogenesis: an update

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Abstract: Acne vulgaris, an epidemic inflammatory skin disease of adolescence, is closely related to Western diet. Three major food classes that promote acne are: 1) hyperglycemic carbohydrates, 2) milk and dairy products, 3) saturated fats including trans-fats and deficient ω-3 polyunsaturated fatty acids (PUFAs). Diet-induced insulin/insulin-like growth factor (IGF-1)-signaling is superimposed on elevated IGF-1 levels during puberty, thereby unmasking the impact of aberrant nutrigenomics on sebaceous gland homeostasis. Western diet provides abundant branched-chain amino acids (BCAAs), glutamine, and palmitic acid. Insulin and IGF-1 suppress the activity of the metabolic transcription factor forkhead box O1 (FoxO1). Insulin, IGF-1, BCAAs, glutamine, and palmitate activate the nutrient-sensitive kinase mechanistic target of rapamycin complex 1 (mTORC1), the key regulator of anabolism and lipogenesis. FoxO1 is a negative coregulator of androgen receptor, peroxisome proliferator-activated receptor-γ (PPARγ), liver X receptor-α, and sterol response element binding protein-1c (SREBP-1c), crucial transcription factors of sebaceous lipogenesis. mTORC1 stimulates the expression of PPARγ and SREBP-1c, promoting sebum production. SREBP-1c upregulates stearoyl-CoA- and Δ6-desaturase, enhancing the proportion of monounsaturated fatty acids in sebum triglycerides. Diet-mediated aberrations in sebum quantity (hyperseborrhea) and composition (dyssseborrhea) promote Propionibacterium acnes overgrowth and biofilm formation with overexpression of the virulence factor triglyceride lipase increasing follicular levels of free palmitate and oleate. Free palmitate functions as a “danger signal,” stimulating toll-like receptor-2-mediated inflammasome activation with interleukin-1β release, Th17 differentiation, and interleukin-17-mediated keratinocyte proliferation. Oleate stimulates P. acnes adhesion, keratinocyte proliferation, and comedogenesis via interleukin-1β release. Thus, diet-induced metabolomic alterations promote the visible sebofollicular inflammasomopathy acne vulgaris. Nutrition therapy of acne has to increase FoxO1 and to attenuate mTORC1/SREBP-1c signaling. Patients should balance total calorie uptake and restrict refined carbohydrates, milk, dairy protein supplements, saturated fats, and trans-fats. A paleolithic-like diet enriched in vegetables and fish is recommended. Plant-derived mTORC1 inhibitors and ω-3-PUFAs are promising dietary supplements supporting nutrition therapy of acne vulgaris.

Keywords: acne, comedogenesis, diet, inflammasome, metabolomics, quorum sensing

Introduction

Based on accumulating indirect translational and in vitro evidence, this review presents an update of the dietary impact on acne metabolomics, follicular inflammation, and comedogenesis. The first part links Western diet to disturbed sebaceous lipogenesis promoted by systemic aberrations of endocrine signaling. To understand the role of nutrigenomics in the pathogenesis of acne, two central players will be highlighted: the role...
of the metabolic transcription factor forkhead box O1A (FoxO1), and the nutrient-sensitive kinase mechanistic target of rapamycin complex 1 (mTORC1). The second part explains the molecular link between disturbed sebocellular metabolomics and inflammation. The reader will understand that Western diet is the major factor overstimulating sebum production, Propionibacterium acnes overgrowth, and biofilm formation. Biofilm-transformed P. acnes produce abundant exogenous lipase, a virulence factor that increases local levels of free palmitic acid, a recently recognized danger signal activating the NLRP3 inflammasome. Abundance of sebum-derived free palmitate together with P. acnes-derived danger-associated molecular patterns (DAMPs) stimulates innate immunity, inflammasome activation, and interleukin-1β (IL-1β)-signaling. IL-1β finally orchestrates follicular and perifollicular inflammation with Th17 cell differentiation and IL-17-mediated local keratinocyte hyperproliferation.

IGF-1: central player of acne

Most textbooks of dermatology still define acne as an androgen-dependent skin disease. There is no doubt that androgen excess promotes acne and seborrhea, whereas acne does not develop under conditions of androgen receptor (AR) loss of function leading to androgen insensitivity. These facts clearly point to the involvement of AR-dependent signaling in the pathogenesis of acne. Yet there is still an unsolved contradiction: it is well established that androgen serum levels increase during puberty and stay at high levels for decades, whereas acne physiologically fades spontaneously after puberty. After the climax of puberty, serum levels of insulin-like growth factor 1 (IGF-1), the major growth hormone of puberty, decrease continuously. Deplewski and Rosenfield pointed out that not serum androgens but serum IGF-1 levels correlate with the clinical manifestation of acne. Evidence will be presented that not androgens but IGF-1 plays the primary role in acne pathogenesis. IGF-1 signaling is the central endocrine pathway of puberty and sexual maturation, and is the converging point of nutrient signaling in acne.

Which facts do prove this change of paradigms? There is a human experiment of nature supporting the primary role of IGF-1 signaling in acne pathogenesis, the Laron syndrome. Short-statured individuals with Laron syndrome exhibit a congenital IGF-1 deficiency due to growth hormone receptor (GHR) mutations. Notably, Laron patients, who are not treated with recombinant IGF-1, never develop acne or other common diseases of Western civilization. However, high-dose IGF-1 administration induces acne and hyperandrogenism in these GHR-deficient patients. The occurrence of hyperandrogenism in IGF-1-treated Laron patients already implies that IGF-1 enhances AR-dependent signal transduction.

IGF-1 inhibits FoxO1 signaling at multiple regulatory layers

IGF-1 promotes cell growth and cell proliferation by activating the IGF-1 receptor (IGF1R), resulting in upregulation of the phosphoinositide-3-kinase (PI3K)–protein kinase B (AKT) signaling cascade. Pioneering autoradiographic studies of Plewig et al showed that acne is a hyperproliferative disease of the sebaceous follicle. In acne, increased cell proliferation has been demonstrated in keratinocytes of the acroinfundibulum and ductus seboglandarius, and sebocytes of the sebaceous gland. Thus, the question arose as to how IGF-1 increases local proliferation of acroinfundibular keratinocytes, epithelial cells of the ductus seboglandarius, and sebocytes. To understand the stimulatory effects of IGF-1 on sebocellular androgen signaling, it is of critical importance to become familiar with the major regulatory mechanisms that enhance AR transcriptional activity.

The AR is a nuclear transcription factor that stimulates the expression of genes that promote androgen-dependent growth and proliferation. AR activation requires two major stimuli: 1) binding of its hormone ligand (androgen), and 2) derepression of its inhibitory nuclear coregulator FoxO1. Ligand-mediated activation of AR depends on androgen binding affinity. Highest AR binding affinity exhibits dihydrotestosterone (DHT), which is ten times higher compared with testosterone. IGF-1 is a potent inducer of gonadal testosterone and adrenal dehydroepiandrosterone (DHEA) synthesis and promotes the intracutaneous conversion of testosterone to DHT by enhancing 5α-reductase activity. Thus, IGF-1 increases the total amount of gonadal and adrenal androgen synthesis and enhances androgen bioactivity by increasing the cutaneous availability of DHT, the most powerful physiological androgen. Conversely, the androgens induce IGF-1 in the hair follicle. Thus, IGF-1 stimulates AR signal transduction by upregulating the amount and affinity of AR-activating ligands.

Most dermatologists are not aware of the second most important IGF-1-dependent mechanism that increases AR signaling that involves the metabolic transcription factor FoxO1. In the nucleus, FoxO1 functions as an AR cosuppressor. Nuclear FoxO1 levels are negatively regulated by insulin and IGF-1. Both sister hormones activate the PI3K–AKT pathway. Activated AKT phosphorylates FoxO1 in the nucleus, which is the critical step promoting its translocation into the cytoplasm.
FoxO1 suppresses AR transactivation by binding to the transcription activation unit (TAU5) located in the AR N-terminal domain (NTD). The TAU5 motif is most important for androgen-independent activation of the AR, is controlled by insulin/IGF-1-mediated activation of AKT, and is thus connected to the nutrient status.

Taken together, AR activation requires two different IGF-1-dependent pathways: 1) enhanced ligand potentiation and ligand binding to the AR ligand binding domain and 2) activation of AR transactivation by the nuclear extrusion of the AR suppressor FoxO1 from the NTD. Notably, the NTD contains a polyglutamine-enriched region encoded by CAG trinucleotide repeats. Expansion of these CAG repeats in the AR reduces AR activation, whereas AR polymorphisms featuring shorter CAG repeats are associated with androgenetic alopecia, hirsutism, and acne. Individuals featuring AR polymorphisms with shorter CAG repeats in comparison with individuals with normal CAG repeat length apparently exhibit easier AR hyperactivation by insulin/IGF-1 signaling. These insights also explain increased AR signaling in states of hyperinsulinemia and insulin resistance and conditions with increased IGF-1 serum levels such as puberty and nutrient signaling of Western diet. Individuals with shorter CAG repeats may thus exhibit stronger androgenic reactions by dietary exposure to a high glycemic load diet and milk consumption, which both enhance insulin/IGF-1 signaling.

My hypothesis of aberrant IGF-1/FoxO1 signaling in the pathogenesis of acne has recently been confirmed experimentally in SZ95 sebocyte cultures. Prolonged IGF-1 exposure of SZ95 sebocytes induced nuclear translocation of FoxO1 into sebocyte’s cytoplasm. Thus, the transcriptional coordinator of metabolism FoxO1 links insulin/IGF-1 signaling to transcriptional activation of AR-dependent target genes. Notably, the highest nuclear FoxO1 activity is observed during starvation, whereas nutrient excess leads to reduced nuclear levels of FoxO1.

Serum levels of DHEA, the major adrenal androgen that increases during adrenarche, correlate with the onset of acne vulgaris. Notably, DHEA induces ERK1/2-mediated phosphorylation and translocation of FoxO1. Thus, increased adrenal DHEA signaling, which begins prior to puberty, already suppresses FoxO1 activity, increasing AR transactivation. DHEA-induced inactivation of FoxO1 may also explain neonatal hyperseborrhoea and acne due to excessive fetal DHEA production, a physiological mechanism ensuring the generation of the vernix caseosa, which is important for birth.

Nuclear FoxO1, which is upregulated by isotretinoin treatment, controls endocrine signaling of the hypothalamus, pituitary, liver, adrenal, and sebaceous gland. FoxO1 was recently reported to be an inhibitor of follicle stimulating hormone and luteinizing hormone production. Notably, luteinizing hormone/human chorionic gonadotropin triggers androgen synthesis in theca-interstitial cells of the ovary by activating mTORC1 signaling. Insulin and IGF-1 act as negative regulators of FoxO1 activity and enhance gonadotropin expression. Increased insulin/IGF-1 signaling of Western diet thus promotes the synthesis of pituitary gonadotropins, which are pivotal stimuli for gonadal steroidogenesis.

FoxO1 is a negative regulator of GHR, which plays the key role in hepatic IGF-1 synthesis. Thus, insulin signaling via repression of hepatic FoxO1 stimulates hepatic IGF-1 synthesis, demonstrating an interactive hepatic network of metabolic and growth factor signaling. Inactivation of hepatic FoxO1 by insulin signaling is required to adapt nutrient homeostasis and endocrine growth regulation. Notably, isotretinoin, the most powerful antiacne drug, reduced serum concentrations of gonadotropins, adrenocorticotrophic hormone, and IGF-1. This can be well explained by isotretinoin-mediated upregulation of nuclear FoxO1 activity at various regulatory levels of the somatotropic axis.

Acne correlates with increased sebum production. GH, insulin, and IGF-1 increase sebaceous gland growth, differentiation, and sebaceous lipogenesis. Vora et al observed a linear correlation between serum IGF-1 concentrations and facial sebum excretion rates of male acne patients. Remarkably, increased serum IGF-1 levels have been measured in women with postadolescent acne. Recently, an association between IGF-1 gene polymorphism and acne has been reported. Patients who observed an aggravation of their acne by food intake exhibited higher IGF-1 serum levels (mean =543.9 ng/mL) compared with those who observed no acne aggravation by food intake (mean IGF-1 =391.3 ng/mL).

IGF-1 plays a pivotal role in sebaceous lipogenesis. Downstream of IGF-1/Pi3K/AKT signaling respond four key lipogenic transcription factors: the AR, peroxisome proliferator-activated receptor-γ (PPARγ), liver X receptor-α (LXRα), and sterol response element binding protein-1c (SREBP-1c), which are all negatively regulated by FoxO1 (Figure 1). IGF-1 stimulated SREBP-1 expression and induced lipogenesis in SEB-1 seocytes via activation of the Pi3K/AKT pathway. Mirdamadi et al confirmed that IGF-1 suppresses nuclear FoxO1 in SZ95 sebocytes associated with increased lipogenesis. Under conditions of nutrient excess and high-insulin/IGF-1 signaling, downregulated nuclear FoxO1 thus derepresses all master transcription factors of sebaceous lipogenesis such...
as AR, PPARγ, LXRα, and SREBP-1c. In fact, Kwon et al.\textsuperscript{78} observed decreased SREBP-1 expression in facial acne skin after 4 weeks of a low glycemic load diet. Notably, acne-free Kitavan islanders,\textsuperscript{79} who are still exposed to a paleolithic diet (less-hyperglycemic carbohydrates, no milk and dairy products, but plenty of fish intake), exhibit low basal insulin serum levels that are only half of those of Europeans living under conditions of Western neolithic diet.\textsuperscript{80} Incubation of epithelial cells with IGF-1-deficient serum of Laron patients exhibited increased nuclear FoxO1 activity and decreased expression of TOR.\textsuperscript{14} Notably, excessive meat intake is another characteristic feature of Western diet. Recent epidemiological evidence underlines that low protein intake is associated with a major reduction in serum IGF-1 in the middle-aged population.\textsuperscript{81}

**FoxO1 interacts with TGFβ- and β-catenin signaling**

McNair et al.\textsuperscript{82} demonstrated that transforming growth factor-β (TGFβ) signaling is necessary and sufficient for maintaining sebocytes in an undifferentiated state. TGFβ receptor type 2 (TGFRII)–SMAD2 signaling decreased the expression of genes required for sebaceous lipogenesis and sebocyte differentiation such as Δ6-desaturase and PPARγ, thereby decreasing sebaceous lipid accumulation. A recent genome-wide association study identified three novel susceptibility loci of the TGFβ pathway for severe acne vulgaris, namely, transforming growth factor β2 (TGFβ2), Ovo, Drosophila homologue-like 1 (OVOL1), and follistatin (FST).\textsuperscript{83} The authors noted a significant reduction in TGFβ2 and OVOL1 transcript levels in lesional compared with non-lesional skin of acne patients.\textsuperscript{83} Canonical TGFβ signaling starts after binding of TGFβ to TGFRII, which recruits and activates TGFRI. TGFRI phosphorylates the receptor-bound transcription factors SMAD2 and SMAD3, which later associate with SMAD4. The activated SMAD2/3/4 complex translocates into the nucleus and executes its transcriptional functions.\textsuperscript{84} Importantly, activated SMAD proteins associate with FoxO1, FoxO3, and FoxO4. In human keratinocytes, FoxO–SMAD synexpression plays
a crucial role in the induction of the cyclin-dependent kinase inhibitors p15 and p21. Genes that require FoxO–SMAD synexpression in response to TGFβ coordinate cell cycle control via p15 and p21 and adaptive cell signaling responses such as OVOL1. Increased expression of p21 has been detected in sebocytes treated with isotretinoin, the most potent antiacne drug that obviously functions as a FoxO1 inducer. Thus, it is conceivable that isotretinoin enhances SMAD–FoxO1-mediated expression of p21. Western diet with exaggerated insulin/IGF-1 signaling thus affects SMAD–FoxO1-regulated synexpression of important cell cycle checkpoints of keratinocytes and sebocytes. Furthermore, conditional deletion of TGFβ signaling resulted in PI3K/AKT activation, the major FoxO1-controlled pathway promoting sebaceous lipogenesis.

FoxO1 interacts with Wingless (Wnt)/β-catenin signaling, which blocks differentiation toward the sebocyte phenotype, since inhibition of Wnt target genes promotes sebocyte development. β-catenin reduces c-Myc-stimulated sebocyte differentiation. Notably, β-catenin strongly binds FoxO1 and FoxO3a. This interaction enhances FoxO’s transcriptional activity.

**FoxOs are negative regulators of the nutrient-sensitive kinase mTORC1**

FoxO1 and FoxO3 are negative regulators of the nutrient-sensitive kinase mTORC1. mTORC1 has recently been recognized to play a major role in diet-induced acne. FoxO1 activates the transcription of the eukaryotic initiation factor 4 binding protein-1 (4EBP-1), which is a major downstream substrate of mTORC1 and functions as a potent translational inhibitor and growth suppressor. Insulin and IGF-1 activate mTORC1, the cell’s master regulator orchestrating insulin and IGF-1 signaling, nutrient, glucose, energy, and amino acid availability. Insulin, IGF-1, and amino acids are required for full activation of mTORC1 signaling. The essential branched-chain amino acid (BCAA) leucine plays a primary role in mTORC1 activation. Glutamine, an abundant amino acid constituent of milk proteins, has recently also been demonstrated to have a supportive role in mTORC1 activation. Leucine and glutamine stimulate mTORC1 by rag GTPase-dependent and independent mechanisms. In contrast to other amino acids, leucine promotes mTORC1 signaling also independent of lysosomal translocation of mTOR.

mTORC1 regulates anabolism, nutrient-dependent cell cycle progression, and activates lipogenesis by inducing the expression and activation of SREBP-1c and PPARγ. Insulin/IGF-1-mediated activation of AKT results in mTORC1 activation. Importantly, mTORC1 phosphorylates and inactivates the negative SREBP-1 regulator lipin and promotes gene expression of SREBP-1c. mTORC1 via activation of the kinase S6K1 promotes SREBP-1c cleavage into its transcriptionally active form. Thus, several converging mTORC1-dependent pathways enhance the activation of the lipogenic transcription factor SREBP-1c.

**SREBP-1c promotes sebum fatty acid desaturation**

It is of critical importance to consider that SREBP-1c is a key regulator of stearoyl-CoA desaturase and Δ6-desaturase gene expression. Insulin stimulates the expression of Δ6-desaturase, Stearyl-CoA desaturase catalyzes the conversion of stearic acid (18:0) to oleic acid (18:1), a major fatty acid of sebum triglycerides. Δ6-Desaturase and Δ5-desaturase are key enzymes for the synthesis of highly unsaturated fatty acids such as arachidonic acid, which is the precursor of proinflammatory eicosanoids such as leukotriene B4 (LTB4) and prostaglandin E2 (PGE2) involved in inflammatory responses of sebaceous glands. Sebocyte Δ6-desaturase converts palmitic acid (16:0) to sapienic acid (16:1), which functions as a natural antimicrobial agent involved in epidermal host defenses. Thus, sebocyte SREBP-1c activity not only controls the total amount of synthesized sebum triglycerides but, via SREBP-1c-mediated gene expression of Δ6-desaturase and stearoyl-CoA desaturase, increases sebum triglyceride levels of monounsaturated fatty acids. In fact, an association between the synthesis of total sebum triglycerides with increased triglyceride levels of sapienic acid (16:1) and decreased stearic acid (18:0) – due to its conversion to oleic acid (18:1) – has been observed (Figure 1).

FoxO1 is critically involved in the regulation of SREBP-1c activity via GHR-mediated hepatic IGF-1 synthesis, FoxO1-regulated expression of IGF binding protein 1, FoxO1-mediated suppression of LXRs, and FoxO1-regulated expression of SREBP-1c. FoxO-mediated inhibition of mTORC1 also controls mTORC1-dependent SREBP-1c expression and its final nuclear activation.

**Western diet drives acne metabolomics**

High-acne prevalence rates of over 90% during adolescence, and increasing persistence of acne into the second and third decades of life in around 64% and 43% of
individuals respectively, clearly point to the predominance of environmental and epigenetic factors.\textsuperscript{124, 125} Populations exposed to paleolithic dietary conditions (low glycemic load, no milk and dairy consumption) such as the Kitavan islanders of Papua New Guinea, the Ache hunters in Paraguay, the Inuit, and adolescents of rural areas of Brazil are examples of acne-free populations. An increase in acne prevalence has been reported for Inuits, Okinawa islanders, and Chinese after transition from their traditional diets to Westernized nutrition. Accumulating epidemiological, clinical, and translational evidence underlines the impact of nutritional factors in the pathogenesis of common acne vulgaris. Especially nutrients that increase insulin/IGF-1 signaling and thus reduce nuclear FoxO1 levels but enhance mTORC1 have been identified as the most critical inducers of epidemic acne. According to Burris et al.,\textsuperscript{126} acne severity in a cohort of New York young adults was associated with: 1) increased intake of sugar (high glycemic load), 2) number of milk servings per day, and 3) amount of saturated fat and trans-fatty acid (TFA) intake. The nutrigenomic impact of these aceneicogenic food classes will now be discussed in more detail.

**Hyperglycemic carbohydrates**

There is a general consensus that a high intake of refined carbohydrates plays a pivotal role in acne pathogenesis.\textsuperscript{127} The effect of high glycemic load diets on the induction and aggravation of acne has been confirmed by several placebo-and case-controlled studies.\textsuperscript{126, 128–132} A low glycemic load diet increased IGF binding protein 1 (IGFBP1) and IGFBP3, whereas a high glycemic load diet decreased sex hormone binding globulin (SHBG).\textsuperscript{133} Thus, the amount of hyperglycemic carbohydrates modulates the bioactivity of free serum IGF-1 and free serum androgens. Importantly, Kwon et al.\textsuperscript{178} observed a decrease of sebaceous gland size and reduced SREBP-1 expression in facial acne skin after 10 weeks of a low glycemic load diet. This metabolic reaction pattern is explained by attenuated AKT–mTORC1 signaling due to carbohydrate reduction with attenuated insulin signaling. Resulting increases of nuclear FoxO1 and decreased mTORC1 activity are in accordance with reduced cutaneous expression of SREBP-1. Decreased cutaneous SREBP-1 expression should not only reduce total sebum production but should also decrease the rate of sebum triglyceride fatty acid desaturation. In fact, a low glycemic load diet increased the ratio of saturated to monounsaturated fatty acids in skin surface triglycerides.\textsuperscript{133} In contrast, increased sebum outflow was associated with an increase in the proportion of monounsaturated fatty acids, thus reflecting SREBP-1-driven total lipogenesis as well as increased SREBP-1c-dependent stimulation of desaturase activity (Figure 1). Thus, a high glycemic load changes the composition of sebum fatty acids, a most critical proinflammatory and comedogenic mechanism that will be discussed later.

There is recent evidence that diet also modifies the expression of microRNAs that play an important role in posttranscriptional regulation of metabolism.\textsuperscript{134} High glucose concentration upregulates microRNA-21 in macrophages.\textsuperscript{135} MicroRNA-21 is a central regulator of cell proliferation and inflammation.\textsuperscript{136} MicroRNA-21 promotes macrophage polarization toward proinflammatory M1 macrophages secreting IL-1β, and stimulates Th17 cell differentiation.\textsuperscript{137, 138}

**Milk**

In 1885, Bulkley\textsuperscript{139} reported on acne-aggravating effects of milk consumption in his extensive dietary studies involving 1,500 patients with acne. Harvard epidemiologists Adebamowo et al.\textsuperscript{140–142} provided the first epidemiological evidence for the association between milk consumption and acne by evaluating data of the retrospective Nurses’ Health Study II and the prospective Growing-up Today Study. Further controlled clinical studies corroborated the milk–acne connection.\textsuperscript{51, 129, 143} A recent semantic connectivity map approach of 563 subjects showed that moderate-to-severe adolescent acne was closely associated with high consumption of milk, in particular, skim milk, cheese/yogurt, sweets/cakes, chocolate, and a low consumption of fish, and limited intake of fruits/vegetables,\textsuperscript{144} which is the opposite food pattern of paleolithic nutrition.

Milk is a very special functional food designed by evolution to promote anabolism and growth of newborn mammals. To understand milk’s impact on acne, it is important to realize that milk promotes anabolic mTORC1 signaling.\textsuperscript{145} To fulfill its growth-promoting function, this secretory product of mammary glands transfers a hardware consisting of amino acids that promote insulin/IGF-1/mTORC1 signaling, and a software delivering exosomal microRNAs, including microRNA-21 that enhances AKT–mTORC1 signal transduction (Figure 1).\textsuperscript{145}

Daily consumption of 710 mL ultra-heat-treated (UHT) milk in prepubertal Mongolian children not used to milk consumption over 4 weeks substantially increased serum GH and IGF-1 levels.\textsuperscript{146} Notably, IGF-1 serum levels increased by 23% from pretreatment concentrations. These data clearly show that milk consumption switches the somatotropic axis. It is important to realize that it is not the IGF-1 content of cow’s milk that exaggerates serum IGF-1 levels of the milk.
consumer, but the milk-driven hepatic production of IGF-1 by the transfer of amino acids that promotes IGF-1 synthesis in the liver of the milk recipient. Notably, the major whey protein α-lactalbumin has the highest tryptophan content among all other protein food sources. Tryptophan availability is of critical importance for hepatic IGF-1 synthesis. Milk’s essential BCAAs (leucine, isoleucine, and valine) induce pancreatic insulin secretion and explain the high insulinemic index of whole milk and skim milk.

Thus, milk intake enhances insulin/IGF-1 signaling. Furthermore, milk proteins transfer high amounts of the insulinotropic amino acid leucine, which promotes mTORC1 activation. Whey proteins contain the highest amount of leucine (14%) compared with all other animal proteins such as beef (8%). In comparison with beef protein (4.74 g glutamine/100 g), milk protein (8.09 g glutamine/100 g) contains about twice as much glutamine. Glutamine not only promotes cellular leucine uptake, but is the precursor of the glutaminolysis pathway that is critically involved in mTORC1 activation. Remarkably, the glutaminolysis pathway plays a special role in sebaceous lipogenesis and sebocyte proliferation. In freshly isolated human chest sebaceous glands, glutamine deprivation reduced cell proliferation and lipogenesis by 41% and 37%, respectively. These data indicate that milk is the ideal fuel for FoxO1/mTORC1/SREBP-1c-regulated sebaceous gland hyperplasia and sebaceous lipogenesis. Increased IGF-1 production by milk protein intake is thus superimposed on exaggerated IGF-1 signaling of puberty, which explains the earlier onset of puberty and the persistence of acne in the third decade of life in milk-consuming populations.

Analogously to androgen abuse in the bodybuilding environment, excessive milk protein intake has to be considered as a form of doping. It is of critical concern that milk protein (whey and casein) abuse in the fitness and bodybuilding scenario is associated with the onset and aggravation of acne.

The recent prediction of Melnik et al that milk transfers a gene-regulatory metabolically active software consisting of exosomal bioactive microRNAs has recently been confirmed experimentally for cow’s milk. Binding of microRNAs through partial sequence homology to the 3′-untranslated region of target mRNAs causes translational block or degradation of target mRNAs. MicroRNAs, enclosed by membranous microvesicles (exosomes), allow intercellular transfer of microRNAs over long distances. Milk is apparently the exosomal signaling system of mammals that allows maternal–neonatal communication.

It is of critical concern that the 245 microRNAs of pasteurized cow’s milk are absorbed by humans in biologically meaningful amounts, reach the systemic circulation, and affect the expression of more than the estimated 11,000 genes of the human milk consumer. In fact, it has been shown that exosomal milk-derived microRNAs are taken up by human cells and modify gene expression. Intriguingly, bovine microRNA-21, a predominant microRNA constituent of cow’s milk, is identical to human microRNA-21. MicroRNA-21 inhibits mRNA expression of phosphatase and tensin homologue (PTEN). PTEN is a dual protein/lipid phosphatase. Its main substrate, phosphatidyl-inositol 3,4,5, triphosphate, is the product of PI3K. MicroRNA-21-mediated suppression of PTEN mRNA thus promotes PI3K/AKT signaling, which downregulates nuclear FoxO1. Furthermore, there is recent evidence that microRNA-21 directly targets FoxO1 mRNA. Another recently identified target of microRNA-21 is IGFBP3, which reduces the bioavailability of IGF-1. The recent observation that exosomal microRNA-21 downregulates the expression of TGFβR2 is of critical importance for acne-prone individuals with a genetic weakness of TGFβ signaling. Thus, milk-derived microRNA-21 inhibits FoxO1- as well as TGFβ-signaling at various layers of posttranscriptional regulation.

Danby emphasized that 75%–90% of marketed commercial milk and milk products in the US are derived from pregnant cows. The milk of these animals contains DHT precursors. During pregnancy, the bovine adrenal gland produces substantial amounts of DHEA, which can be converted to androstenedione via the enzyme 3β-hydroxysteroid dehydrogenase. Androstenedione levels increase in cow’s plasma and milk during pregnancy. Raw milk of pregnant versus nonpregnant cows contains 3.4 times more androstenedione (mean = 36.7 versus 10.9 ng/dL), 1.2 times more DHEA (mean = 10.5 versus 8.7 ng/dL), and 1.3 times more testosterone (mean = 10.3 versus 8.0 ng/dL), respectively. Activation of estrogen receptor beta and AR by the DHEA metabolites androst-5-ene-3,17-dione, androst-5-ene-3β,17β-diol, DHT, and 5α-androstane-3β,17β-diol increased microRNA-21 transcription in HepG2 human hepatoma cells, increasing cell proliferation. Thus, both milk-derived exosomal microRNA-21 and milk androgen precursor-mediated expression of microRNA-21 may enhance PI3K–AKT-signaling, decreasing FoxO1’s nuclear activity. Intriguingly, there has recently been interest in the role of microRNAs as natural ligands of toll-like receptors (TLRs). MicroRNA-21 and microRNA-29a, both components of cow’s milk, can directly bind to TLR8 stimulation activates the inflammasome and upregulates IL-1β secretion.
Saturated and trans-fats

Recently, Yasuda et al. provided evidence that the major saturated fatty acid palmitate activates mTORC1 and enhances its lysosomal translocation, whereas the ω3-fatty acid eicosapentaenoic acid (EPA), a major fatty acid of fish oil, inhibited mTORC1 activation. It is thus conceivable that sebum-derived free palmitate may activate cell proliferation of acroinfundibular keratinocytes by palmitate-driven mTORC1 signaling, thereby promoting comedogenesis. Notably, palmitate is a major fatty acid, constituting 32% of milk triglycerides. Burris et al. and Jung et al. observed an aggravation of acne with increased intake of saturated fat, whereas a higher intake of fish, a nutrient source enriched in ω3-fatty acids, exhibited an acne-protective effect.}

Industrially produced TFAs, which structurally resemble palmitate, are major components of fast food and have been found to aggravate acne. Their mTORC1-activating effect is predictable, but has not yet been studied. These partially hydrogenated fats have displaced natural solid fats and liquid oils in many areas, the most notable ones being in fast food, snack food, fried food, and baked goods that have all been associated with diet-induced acne. In a comparative study of the TFA content of Swedish bakery products in 2007, 3 of 41 products had TFA levels above 2% of total fatty acids. However, TFA intakes of Canadian children aged 5–6 years have decreased since 2004 to a 95% intake of 1.28% of energy. TFA intake during pregnancy and lactation of rats increased the expression of TNF receptor-associated factor 6 (TRAF6) in the rat offspring. Remarkably, TRAF6 mediates IL-1 signaling. Toll/IL-1 receptor (TIR) domain-containing adaptor protein (TIRAP) is involved in bridging MyD88 to the receptor complex for TLR2 and TLR4 signaling in response to bacterial infection. Verstak et al. characterized a novel role for TIRAP in facilitating the direct recruitment of TRAF6 to the plasma membrane, which is necessary for TLR2- and TLR4-induced transactivation of NF-κB and induction of subsequent proinflammatory responses. Thus, Western diet-derived TFA intake via TRAF6-mediated stimulation of proinflammatory TLR2/TLR4 signaling may contribute to nutrient-mediated inflammatory responses of pilosebaceous follicles.

Western diet promotes NLRP3 inflammasome activation

It has long been known that “sebum is the oil of the acne flame.” P. acnes strain 266, which belongs to the IA (I-la/ST18) phyotype, is associated with moderate to severe acne and possesses particular virulence potential. The gehA gene (PPA2105) encoding the secreted triacylglycerol lipase is a virulence factor that is upregulated in P. acnes strain 266 during exponential growth phases. Recently, P. acnes biofilm formation has been confirmed in sebaceous follicles of acne patients. Bacteria undergo behavioral and transcriptional changes based on the surrounding bacterial population, a process called quorum sensing (QS). QS inhibitors appear to play an important role in the inhibition of biofilm formation. Biofilm formation substantially increases P. acnes virulence associated with enhanced expression of exogenous P. acnes triglyceride lipase that increases sebum concentrations of free palmitate and oleate (Figure 1). Zouboulis et al. recently emphasized that not only the total amount of sebum but, predominantly, alterations of sebum lipid composition are main players in the induction of inflammatory acne. Notably, free oleic acid generated by SREBP-1c-dependent stearoyl desaturase and subsequent triacylglycerol lipase-mediated hydrolysis increases P. acnes adherence and growth. Thus, P. acnes lipase may aid colonization and biofilm formation within the pilosebaceous follicle, by promoting oleate-dependent cell adherence.

Innate immunity is activated in acne. Incubation of human keratinocytes with P. acnes fractions induced the expression of TLR2 and TLR4. Positive TLR2 expression in epidermis, pilosebaceous units, and dermal inflammatory infiltrates has been demonstrated immunohistochemically in acne-involved skin. Notably, excess saturated fatty acids appear to function as danger signals (DAMPs), which activate TLR2/TLR4-driven inflammatory signaling. Snodgrass et al. recently demonstrated that human monocyte TLR2 activation and inflammasome-mediated secretion of IL-1β are modulated by dietary fatty acids. Remarkably, palmitic acid directly activates TLR2 by inducing heterodimerization with TLR1, whereas docosahexaenoic acid (DHA), a major ω3-fatty acid of fish oil, inhibited TLR2/TLR1 dimerization. TLR2/TLR1 dimerization is thus a most critical palmitate-dependent regulatory mechanism in inflammasome activation resulting in subsequent IL-1β secretion. This molecular mechanism apparently links enhanced levels of free sebum palmitate to TLR2-driven inflammasome activation of the pilosebaceous follicle in acne. There is recent evidence that inflammatory TLR2–NF-κB signaling in macrophages is well enhanced by palmitate. Sebum free saturated fatty acids apparently promote a TLR-mediated danger response of the sebaceous
follicle associated with upregulated β-defensin-2 expression of human sebocytes.\textsuperscript{207} Palmitate has been recognized as a crucial stimulator of the NLRP3 inflammasome and plays an important role in lipotoxic inflammasome activation of macrophages.\textsuperscript{208,209} In human monocyte/macrophages, both palmitate and stearate triggered IL-1β secretion in a caspase-1/ASC/NLRP3-dependent pathway.\textsuperscript{210} In chondrocytes as well, palmitate synergized with IL-1β in stimulating proinflammatory cellular responses.\textsuperscript{211} Thus, excessive production and release of sebum-derived free palmitic acid appears to be a lipotoxic danger signal of the sebaceous follicle that drives inflammation.

The NLRP3 inflammasome is regarded as a sensor of metabolic danger signals activated by lysosomal rupture, potassium efflux, and reactive oxygen species production.\textsuperscript{212} Kistowska et al\textsuperscript{213} demonstrated that lysosomal rupture is required for IL-1β secretion in response to \textit{P. acnes}. Notably, palmitate is known to destabilize lysosomes, leading to NLRP3 inflammasome activation.\textsuperscript{208} Thus, excess saturated fatty acids stimulate and augment a danger response via TLR2 activation and lysosomal destabilization finally processed by the NLRP3 inflammasome that mediates IL-1β signaling (Figure 1).\textsuperscript{208,214} In addition to palmitate, \textit{P. acnes} itself triggers NLRP3 inflammasome activation of monocyte–macrophages and human sebocytes, increasing IL-1β secretion.\textsuperscript{213,215,216}

**IL-1β release stimulates the Th17 response**

IL-1β activates IL-17A positive T cells (Th17 cells) and CD83 dendritic cells in acne lesions, resulting in the activation of Th17-related cytokines.\textsuperscript{217} In addition to IL-17A, both Th1 and Th17 effector cytokines, transcription factors, and chemokine receptors are strongly upregulated in acne lesions.\textsuperscript{218} IL-17A and IL-17F are key cytokines for the recruitment and activation of neutrophils and can target keratinocytes, endothelial cells, monocytes, and fibroblasts to produce proinflammatory mediators such as IL-6, TNFα, IL-1β, PGE2, nitric oxide, matrix metalloproteinases, and various chemokines.\textsuperscript{219} IL-17-related antimicrobial peptide and CXCL chemokine production with neutrophil attraction in acne lesions are thus important factors triggering the inflammatory infiltrate. There is substantial support for the hypothesis of Lwin et al,\textsuperscript{195} who suggest that \textit{P. acnes} sends no signals or only “safety signals” when present in controlled quantities under commensal conditions, but becomes pathogenic and sends “danger signals” via QS in the form of excessive free fatty acid production, which stimulates TLR2 and TLR4 as the bacterial population and its virulence increases (Figure 1).

**Sebum free fatty acids promote comedogenesis**

Abnormal follicular keratinization is important for comedo formation in acne. Diet-induced changes in sebum quantity and composition may not only induce the inflammation of acne but may also drive the process of comedogenesis. Increased release of the danger signal “free palmitate” activates TLR2/IL-1β signaling of dendritic cells that promote Th17 cell differentiation with increased secretion of IL-17A.\textsuperscript{220} In fact, increased local levels of IL-1β and IL-17A have been detected in lesional acne skin (Figure 1).\textsuperscript{217} IL-17 is a key cytokine that stimulates keratinocyte proliferation via IL-6/STAT3 signaling.\textsuperscript{221} IL-17 contributes to keratinocyte hyperproliferation and attenuates keratinocyte differentiation.\textsuperscript{222} Thus, IL-17 disturbs follicular keratinocyte homeostasis in acne, a comparable mechanism driving keratinocyte hyperproliferation in psoriasis.\textsuperscript{223}

Choi et al\textsuperscript{224} reported that oleic acid applied on the inner surface of the ear of New Zealand White rabbits induced comedones. Permeability barrier disruption in oleic-acid-applied follicular keratinocytes may disrupt the keratinocyte intracellular calcium gradient, leading to keratinocyte proliferation and follicular hyperkeratosis.\textsuperscript{224} In fact, application of oleic acid and palmitoleic acid induced scaly skin, abnormal keratinization, and epidermal hyperplasia.\textsuperscript{225}

Furthermore, application of unsaturated fatty acids increased the intracellular calcium concentration of the keratinocytes. Notably, intracellular calcium increase of keratinocytes stimulated by exposure to free oleic acid increased the production of IL-1α (Figure 1),\textsuperscript{226} which has been implicated in comedogenesis.\textsuperscript{227–231}

Taken together, there is compelling evidence that the nutrigenomic changes promoted by Western diet increase the local availability of sebum free palmitic and oleic acid, driving IL-1β- and IL-1α-mediated comedogenesis. Both cytokines not only play an important role in early- and late-inflammatory responses in acne,\textsuperscript{232} but apparently represent key mediators of comedo formation.

**Nutrition therapy of acne**

In 2005, Cordain\textsuperscript{233,234} emphasized the beneficial effects of a paleolithic diet (no hyperglycemic carbohydrates, no milk and dairy products) for the treatment of acne. Today, his dietary recommendations can be interpreted on the basis of nutrigenomic disturbances induced by Western diet.
mTORC1 activity is also attenuated by plant-derived natural compounds such as the major green tea polyphenol epigallocatechin-3-gallate (EGCG) and the stilbenol resveratrol. EGCG suppressed IGF-1-induced lipogenesis, reduced the activation of AKT and mTOR, and attenuated the expression of IL-1, IL-6, and IL-8 in SZ95 sebocytes. EGCG is a dual PI3K/mTOR inhibitor, and it enhances nuclear FoxO1 and attenuates mTORC1 signaling, explaining the improvement of acne by topical EGCG treatment. EGCG has been shown to inhibit SREBP-1 in SEB-1 sebocytes, and improved acne in an 8-week randomized clinical trial with EGCG. EGCG-mediated activation of AMP-activated kinase is another inhibitory mechanism attenuating mTORC1–SREBP-1 signaling, which explains EGCG-mediated suppression of sebaceous lipogenesis.

These data are in accordance with reduced sebum production of healthy volunteers topically treated with a 3% green tea emulsion. Notably, a preliminary case study reported improvement of acne with daily oral intake of 1 g EPA and 200 mg EGCG (Table 2).

Resveratrol, the polyphenolic flavonoid from grapes and red wine, downregulates PI3K/AKT/mTORC1 signaling. Furthermore, it inhibits the growth of P. acnes, directly inhibits PI3K, upregulates FoxO1, and downregulates PPARγ mRNA expression. Importantly, resveratrol inhibited SZ95 sebocyte growth through inactivation of the PI3K/AKT pathway. Resveratrol via stimulation of

Table 1 Acneigenic food components of Western diet

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>Metabolic and nutrigenomic effects</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemic carbohydrates</td>
<td>Postprandial hyperinsulinemia</td>
<td>Sugar</td>
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<td></td>
<td>Insulin-mediated hepatic IGF-1 synthesis</td>
<td>Sweets</td>
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<tr>
<td></td>
<td>Reduction of IGFBP3</td>
<td>Soft drinks</td>
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<tr>
<td></td>
<td>Increased bioavailability of free circulating IGF-1</td>
<td>Pizza</td>
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<tr>
<td></td>
<td>Reduction of SHBG</td>
<td>Pasta</td>
</tr>
<tr>
<td></td>
<td>Increased bioavailability of free circulating testosterone</td>
<td>Wheat bread</td>
</tr>
<tr>
<td></td>
<td>Reduced nuclear activity of FoxO1</td>
<td>Wheat rolls</td>
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<tr>
<td></td>
<td>Increased expression of sebocyte SREBP-1c</td>
<td>Cornflakes</td>
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<tr>
<td></td>
<td>Activation of mTORC1</td>
<td></td>
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<tr>
<td></td>
<td>Glucose-mediated microRNA-21 expression</td>
<td></td>
</tr>
<tr>
<td>Milk and dairy products</td>
<td>Postprandial hyperinsulinemia</td>
<td>Whole and skim milk</td>
</tr>
<tr>
<td></td>
<td>Increased levels of circulating IGF-1</td>
<td>Pasteurized fresh milk</td>
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<tr>
<td></td>
<td>Leucine-mediated activation of mTORC1</td>
<td>Yogurt</td>
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<td></td>
<td>Glutamine-mediated activation of mTORC1</td>
<td>Ice cream</td>
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<td></td>
<td>Palmitate-mediated activation of mTORC1</td>
<td>Whey and casein supplements</td>
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<tr>
<td></td>
<td>Milk-microRNA-21-mediated proliferation and inflammation</td>
<td>Cheese</td>
</tr>
<tr>
<td>Saturated fats</td>
<td>Palmitate-mediated activation of mTORC1</td>
<td>Butter</td>
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<tr>
<td>Trans-fats</td>
<td>Palmitate-driven inflammasone activation</td>
<td>Cream</td>
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<td></td>
<td>Possible mTORC1 activation</td>
<td>Fast food</td>
</tr>
<tr>
<td></td>
<td>Proinflammatory signaling</td>
<td>French fries</td>
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</tbody>
</table>

Abbreviations: IGF-1, insulin-like growth factor 1; IGFBP3, IGF binding protein 3; SHBG, sex hormone binding globulin; FoxO1, forkhead box O1; SREBP-1c, sterol response element binding protein 1c; mTORC1, mechanistic target of rapamycin complex 1.
Table 2 Paleolithic-type diet for the nutrition therapy of acne

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>Metabolic effects</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrates with low glycemic index</td>
<td>Reduced insulin signaling</td>
<td>Salads</td>
</tr>
<tr>
<td>o-3-fatty acids (docosahexaenoic acid and eicosapentaenoic acid)</td>
<td>Reduction of free IGF-1</td>
<td>Vegetables</td>
</tr>
<tr>
<td>Plant products and spices enriched in natural mTORC1 inhibitors and FoxO1 enhancers</td>
<td>Increase of nuclear FoxO1</td>
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FoxO1 signaling apparently inhibits SREBP-1c. In fact, topical treatment of facial acne vulgaris in 20 patients with a resveratrol-containing gel (0.01% wt/vol) significantly reduced the number of microcomedones, papules, and pustules compared with vehicle control. Furthermore, resveratrol eradicated P. acnes biofilm formation (Table 2).

**Conclusion**

Food is a conditioning environment that shapes the activity of the human genome. Acne is obviously the visible outcome of imbalanced nutrigenomics induced by Western diet, the maximized form of neolithic nutrition, that exaggerates insulin/IGF-1 signaling. Suppression of FoxO1 by Western diet increases the activity of most important transcription factors involved in sebaceous lipogenesis (Figure 1). Upregulated SREBP-1c not only enhances total sebum production but modifies sebum triglyceride fatty acid composition by generating a proinflammatory and comedogenic fatty acid pattern. These metabolic changes are of critical importance for P. acnes overgrowth and biofilm formation and subsequent P. acnes-driven inflammation. Oleic acid promotes P. acnes adherence, which favors biofilm formation with QS that enhances P. acnes virulence by increasing the synthesis of exogenous lipase that releases free palmitic and oleic acid. Free palmitic acid functions as a danger signal that stimulates TLR2-mediated activation of the NLRP3 inflammasome providing proinflammatory IL-1β. IL-1β with subsequent Th17 activation and IL-17 signaling promotes comedogenesis and inflammation.

There is good reason to assume that genetic predispositions to acne increase the acneigenic responsiveness to Western diet. Individuals with persistent insulin resistance, hyperinsulinemia, and hyperandrogenism, such as women with polycystic ovary syndrome (PCOS), will exhibit increased responsiveness to the acneigenic signals of Western diet. Notably, PCOS responds favorably to metformin, a recently characterized mTORC1 inhibitor. Exaggerated mTORC1–S6K1 signaling links acne to increased BMI and insulin resistance.

Androgen abuse has synergistic acneigenic effects with Western diet-driven nutrient signaling, because androgens activate mTORC2 that activates AKT and thus reduces nuclear levels of FoxO1.

Nutrient signaling induced by Western diet synergizes with IGF-1 polymorphism associated with increased serum IGF-1 levels, fibroblast growth factor receptor-2 (FGFR2) gain-of-function mutation (Apert syndrome) with increased activation of AKT, CAG repeat polymorphism with enhanced AR transcriptional activity, P450 polymorphisms with accelerated retinoic acid catabolism decreasing nuclear levels of FoxO1, disturbed TFGβ signaling impairing FoxO–SMAD-dependent gene expression, IL-1α polymorphism with increased IL-1α signaling, and finally, the IL-1β-producing PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) syndrome.

Epidemic acne vulgaris is an mTORC1-driven systemic disease of Western civilization such as obesity, diabetes, and cancer. Acne patients should control their total calorie uptake and restrict sugar and refined carbohydrates, milk, whey, and casein protein supplements, saturated fats, and trans-fats. Acne patients should avoid pasteurized fresh milk intake that transfers bioactive microRNA-21, a most critical microRNA that downregulates FoxO1 and promotes inflammation.

The ideal “antiacne diet” will be a paleolithic-like nutrition with accentuated intake of vegetables and fruits with low glycemic index and sea fish enriched in anti-inflammatory o3-fatty acids. Beneficial and acne-preventive nutrients should contain plant-derived natural mTORC1 inhibitors such as green tea (EGCG), resveratrol, curcumin, genistein, and silymarin (Table 2). Western diet obviously induces an IGF-1/mTORC1-driven pilosebaceous inflammasomopathy of adolescence, unmasking a visible metabolic danger signal, which should alert the medical community. Comparable NLRP3-driven reaction patterns have been realized as major pathogenic factors of serious
diseases of civilization. The advice of Kapahi et al. “with TOR less is more” apparently applies for the treatment and prevention of the most common diet-induced inflammatory skin disease. Future acne research should determine in vivo mTOR expression and mTORC1-dependent phosphorylation states of S6K1 and 4E-binding protein 1 in acne skin, which could explain the disturbed diet-induced metabolomics in acne skin and their corrections by dietary intervention such as the decreased expression of SREBP and IL-8 in lesional skin of acne patients during a low glycemic load diet.

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