

## COMMENTARY to Kwon et al. on p. 241

**Diet in Acne: Further Evidence for the Role of Nutrient Signalling in Acne Pathogenesis**

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**Recent evidence underlines the role of Western diet in the pathogenesis of acne. Acne is absent in populations consuming Palaeolithic diets with low glycaemic load and no consumption of milk or dairy products. Two randomized controlled studies, one of which is presented in this issue of *Acta Dermato-Venereologica*, have provided evidence for the beneficial therapeutic effects of low glycaemic load diets in acne. Epidemiological evidence confirms that milk consumption has an acne-promoting or acne-aggravating effect. Recent progress in understanding the nutrient-sensitive kinase mammalian target of rapamycin complex 1 (mTORC1) allows a new view of nutrient signalling in acne by both high glycaemic load and increased insulin-, IGF-1-, and leucine signalling due to milk protein consumption. Acne should be regarded as an mTORC1-driven disease of civilization, like obesity, type 2 diabetes and cancer induced by Western diet. Early dietary counselling of teenage acne patients is thus a great opportunity for dermatology, which will not only help to improve acne but may reduce the long-term adverse effects of Western diet on more serious mTORC1-driven diseases of civilization. *Key words: acne; diet; glycaemic load; milk; mTORC1.***

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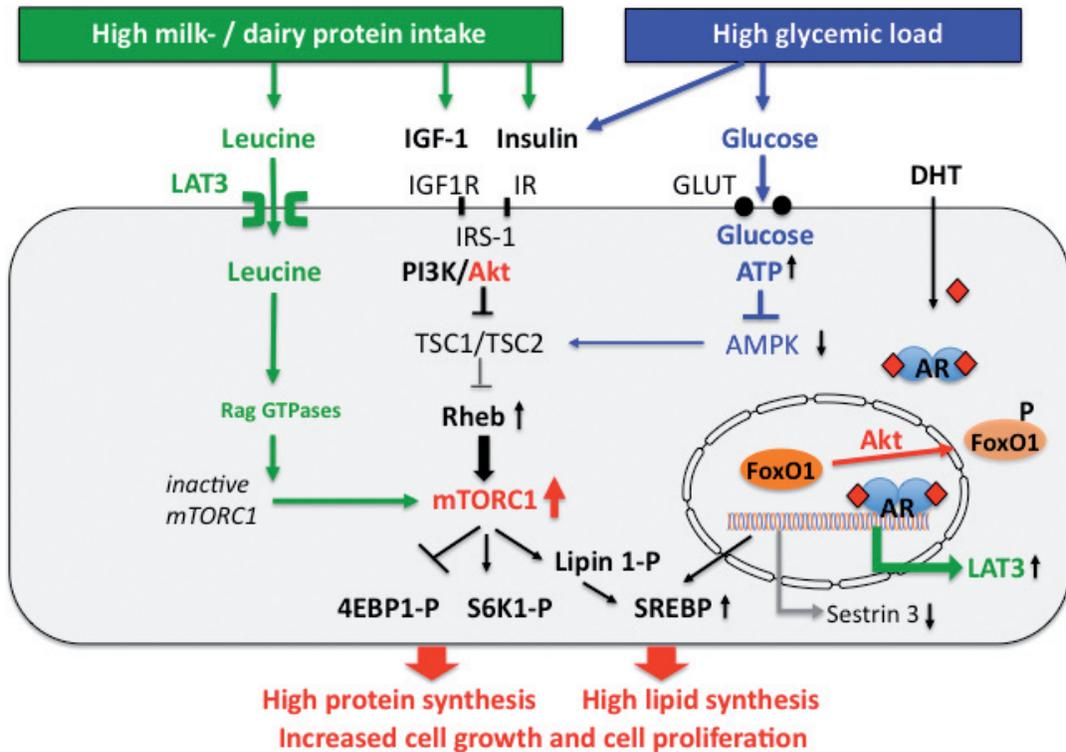
The influence of diet on the induction and aggravation of acne has been a matter of intense debate over the last few years. The pioneering observation by Cordain et al. (1), who demonstrated that acne is a disease of Western civilization and is absent in populations consuming Palaeolithic diets without refined sugars, grains, milk and dairy products, resulted in a paradigm change. The randomized, controlled Australian study by Smith et al. (2) provided the first clinical evidence for the beneficial therapeutic effects of a low glycaemic load diet on the clinical course and intensity of acne and sebum production. The randomized controlled South Korean trial of Kwon and co-workers in this issue of *Acta Dermato-Venereologica* (3) confirmed that glycaemic load plays

a substantial role in the pathogenesis and treatment of acne. Subjects within the low glycaemic group demonstrated significant clinical improvement in the number of both non-inflammatory and inflammatory acne lesions. Remarkably, Kwon et al. (3) now provide the first histopathological and immunohistochemical evidence that a low glycaemic load diet reduced the size of sebaceous glands, decreased inflammation, and diminished the expression of pro-inflammatory interleukin-8 and sterol regulatory element binding protein-1 (SREBP-1), the key transcription factor of lipid biosynthesis.

**HIGH GLYCAEMIC LOAD AND MILK ACTIVATE THE NUTRIENT-SENSITIVE KINASE mTORC1**

Experimental evidence has been provided for the important role of insulin/insulin-like growth factor-1 (IGF-1) signalling in SREBP-1-mediated sebaceous lipogenesis (4, 5). Although the impact of hyperglycaemic carbohydrates on enhanced insulin-/IGF-1 signalling in acne has been robustly supported by the studies of Smith et al. (2) and Kwon et al. (3), until recently only a weak association has been accepted for the role of milk and dairy products in acne pathogenesis (6). There is, however, substantial epidemiological and biochemical evidence supporting the effects of milk and dairy products as enhancers of insulin-/IGF-1 signalling and acne aggravation (7–12). In fact, milk signalling potentiates the signalling effects of hyperglycaemic carbohydrates (13) (Fig. 1).

We have to ask whether there is a unifying link connecting the nutrient signalling pathways induced by hyperglycaemic carbohydrates with those of milk consumption. We will answer this question only when we change our perception of milk and dairy as simple food. We have to appreciate that milk is a species-specific endocrine signalling system that activates a central signalling node in cellular metabolism for stimulation of growth and cell proliferation: the nutrient-sensitive kinase mammalian target of rapamycin complex 1 (mTORC1) (14). Both puberty-induced growth and milk-induced neonatal growth are driven by the same insulin/IGF-1 signal transduction pathways, which finally upregulate mTORC1 signalling. In all mammalian species, mTORC1 integrates nutrient signals, such as glucose (ATP/energy status of the cell), essential amino



*Fig. 1.* Nutrient-mediated signalling pathways in acne. High glycaemic load increases cellular adenosine triphosphate (ATP) levels, which suppress AMPK. Low AMPK activity impairs the inhibitory effect of TSC2, thus promoting the activation of Rheb, the final activator of mTORC1. High insulin/IGF-1-signals activate Akt (protein kinase B), thereby reducing the inhibitory function of TSC1/TSC2 towards Rheb, thus leading to activation of mTORC1. Milk activates insulin/IGF-1 signalling towards Rheb and furthermore activates mTORC1 by increased availability of leucine. Activated Akt phosphorylates FoxO1, which is expelled from the nucleus, thereby augmenting androgen receptor (AR) signalling. LAT3 is expressed in an AR-dependent manner and activates intracellular leucine-uptake for further mTORC1 activation. Akt-mediated nuclear extrusion of FoxO1 decreases the expression of Sestrin 3, an important activator of AMPK. mTORC1 is activated by high glycaemic load diets and increased milk/dairy protein consumption. Hyperactivated mTORC1 promotes protein (via 4EBP-1, S6K1) and lipid synthesis (via SREBP-1). Abbreviations: IGF-1: insulin-like growth factor-1; IGF1R: IGF-1 receptor; IR: insulin receptor; IRS-1: insulin receptor substrate-1; PI3K: phosphoinositol-3 kinase; Akt: Akt kinase; AMPK: AMP-activated kinase; TSC1: hamartin; TSC2: tuberin; Rheb: ras homolog enriched in brain; mTORC1: mammalian target of rapamycin complex 1; 4EBP1: 4E-binding protein; S6K1: S6 kinase 1; LAT3: L-type amino acid transporter-3; GLUT: glucose transporter; SREBP: sterol regulatory binding protein; DHT: dihydrotestosterone; AR: androgen receptor; FoxO1: forkhead box class O transcription factor 1.

acids (predominantly leucine availability) and growth factor signals (insulin, IGF-1, fibroblast growth factors (FGFs)) (14) (Fig. 1). The endocrinological changes in milk signalling are thus comparable to the endocrinology of puberty. Both periods of growth, the milk-driven period of neonatal growth and growth hormone-driven puberty are associated with elevations in IGF-1, insulin and insulin resistance.

#### CROSS-TALK BETWEEN ANDROGEN-, FOXO1- AND mTORC1 SIGNALLING

Remarkably, insulin/IGF-1 signalling via activation of phosphoinositol-3 kinase and Akt kinase control the nuclear localization of the nutrient-sensitive transcription factor FoxO1, which has been implicated to play a major role in acne pathogenesis (15). The androgen receptor (AR) co-suppressor FoxO1 regulates AR transcriptional activity (16, 17). High insulin/IGF-1 signalling results in Akt-mediated nuclear extrusion

of FoxO1 and activation of AR-mediated gene expression (16, 17). Intriguingly, AR signalling increases the expression of the L-type amino acid transporter LAT3 (18), which increases intracellular leucine levels, a most critical step for mTORC1 activation by amino acids (18, 19). An important downstream target of mTORC1 is the kinase S6K1, which induces insulin resistance in adipose tissue, liver and skeletal muscle by inhibiting insulin signalling via phosphorylation of insulin receptor substrate-1 (IRS-1) (20). The fact that most acne-associated syndromes, such as polycystic ovary syndrome, are associated with insulin resistance points to increased mTORC1-S6K1 signalling in acne (21). Although there are no randomized controlled clinical studies investigating the impact of milk and dairy products on sebaceous gland signal transduction, epidemiological data and recent biochemical concepts strongly support the acne-promoting effect of milk consumption. Milk consumption has been demonstrated to induce hyperinsulinaemia, insulin resistance, and raise serum IGF-1 levels in children and adults (8, 9, 22).

## mTORC1-SREBP-1 PATHWAY

Intriguingly, the key lipogenic transcription factor SREBP-1 has recently been identified as an important downstream target of mTORC1 (23, 24). Attenuation of mTORC1 hyperactivity by a low glycaemic load diet may thus suppress the expression and activity of SREBP-1, a possible mechanism compatible with the findings of Kwon et al. (3). The intake of abundant hyperglycaemic carbohydrates and high consumption of milk and dairy protein predominantly during puberty, a period of high insulin/IGF-1 signalling, may over-activate mTORC1, which enhances sebocyte growth and proliferation and SREBP-1-mediated sebaceous lipogenesis. A lipid-enriched sebaceous gland microenvironment may than promote excessive proliferation of *Propionibacterium acnes* with resultant inflammatory reactions of the pilosebaceous follicle. A low influx of glucose due to restriction of hyperglycaemic carbohydrates thus reduces insulin/IGF-1 signalling and increases cellular AMPK levels, which finally attenuate mTORC1- and SREBP-1-activity.

## HYPERACTIVATED mTORC1 AND OTHER DISEASES OF CIVILIZATION

The importance of the insulin/IGF-1 signalling axis towards mTORC1 becomes obvious in untreated short-stature individuals with Laron syndrome, who exhibit congenital insulin/IGF-1 deficiency and do not develop acne (25). Intriguingly, untreated patients with Laron syndrome are protected from common diseases of civilization, such as acne, type 2 diabetes and cancer (25, 26). In contrast, increased mTORC1 signalling has been associated with obesity, type 2 diabetes and cancer (27, 28). Dairy protein consumption in adults as well as daily milk consumption during adolescence has been related to higher risk of prostate cancer (29, 30). Moreover, the addition of commercial milk or purified casein to an AR-sensitive prostate cancer cell line significantly enhanced cancer cell growth (31). These findings shed new light on the role of milk signalling during adolescence and may explain the observed association of severe acne and increased risk of prostate cancer later in life by a common mode of signal transmission (32).

## CONCLUSION

We are only beginning to understand crucial nutrient-derived signalling pathways that are integrated and further processed by mTORC1. The high glycaemic load pathway to mTORC1 in acne appears to be established, but the nutrient signalling of high milk/dairy protein consumption awaits further experimental confirmation. Acne appears to be an early clinical indicator

of hyperactivated mTORC1 signalling, paving the way to other more serious late-onset mTORC1-driven Western diseases of civilization, such as obesity, type 2 diabetes and cancer. Dermatologists have the opportunity to observe and elaborate nutrient-driven skin pathology of Western diets, and should provide early dietary counselling for teenage acne patients at the beginning of their lifelong exposure to Western diets.

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