# Evidence for Acne-Promoting Effects of Milk and Other Insulinotropic Dairy Products

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## Abstract

Acne vulgaris, the most common skin disease of western civilization, has evolved to an epidemic affecting more than 85% of adolescents. Acne can be regarded as an indicator disease of exaggerated insulinotropic western nutrition. Especially milk and whey protein-based products contribute to elevations of postprandial insulin and basal insulin-like growth factor-I (IGF-I) plasma levels. It is the evolutional principle of mammalian milk to promote growth and support anabolic conditions for the neonate during the nursing period. Whey proteins are most potent inducers of glucose-dependent insulinotropic polypeptide secreted by enteroendocrine K cells which in concert with hydrolyzed whey protein-derived essential amino acids stimulate insulin secretion of pancreatic β-cells. Increased insulin/IGF-I signaling activates the phosphoinositide-3 kinase/Akt pathway, thereby reducing the nuclear content of the transcription factor FoxO1, the key nutrigenomic regulator of acne target genes. Nuclear FoxO1 deficiency has been linked to all major factors of acne pathogenesis, i.e. androgen receptor transactivation, comedogenesis, increased sebaceous lipogenesis, and follicular inflammation. The elimination of the whey protein-based insulinotropic mechanisms of milk will be the most important future challenge for nutrition research. Both, restriction of milk consumption or generation of less insulinotropic milk will have an enormous impact on the prevention of epidemic western diseases like obesity, diabetes mellitus, cancer, neurodegenerative diseases and acne.

Acne vulgaris, the most common dermatological disease, has evolved to an epidemic in western countries, affecting more than 85% of adolescents and often persisting into adulthood [1]. Adults in the US within the age range of 20–29 years, exhibit acne prevalence rates of 50.9% in women and

42.5% in men, respectively [2]. In contrast, acne is absent in non-western-ized populations such as the Inuit, Okinawa islanders, Ache hunter-gather-ers and Kitavan islanders [3] which do not consume milk and dairy products and ingest less carbohydrates with high glycemic index (GI) [3]. Thus, epi-demiological observations clearly point to nutritional factors in the etiology of acne.

Until 2005, cross-sectional, case-control, cohort, and clinical intervention studies designed to address the relationship between diet and acne failed to incorporate adequate controls, objective measures, and appropriate statis-tical analyses. However, well-designed prospective studies published since 2005 provided evidence that components of western diets, particularly milk and dairy products and diets enriched in carbohydrates with high GI and gly-cemic load (GL) are associated with acne [4]. It has been recognized that acne pathogenesis is closely related to the consumption of insulinemic foods providing increased growth factor signaling of insulin and insulin-like growth factor-I (IGF-I) [5, 6]. Insulinotropic food, especially refined sugars and grains, potatoes, milk and dairy products are ubiquitous elements in western diet and comprise nearly 50% of the per capita energy intake [7].

## Epidemiological Evidence for the Relation between Milk Consumption and Acne

Retrospective evaluation of the data of the Nurses Health Study II of 47,355 women who completed questionnaires on their high school diet and physician-diagnosed severe teenage acne showed a positive association with acne for intake of total milk and skim milk [8]. Prospective cohort studies in the US (Growing Up Today Study) in 4,273 teenage boys and 6,094 teenage girls confirmed a correlation between milk consumption and acne [9, 10]. In the study of boys, the strongest association has been found between intake of skim milk and acne [10] which already points to the acne-promoting activity of the protein fraction of milk.

Increased insulin/IGF-I signaling plays a most important role in acne pathogenesis [5, 6]. A correlation between increased facial sebum secretion and IGF-I serum levels has been reported in acne patients [11], whereas isot-retinoin treatment, the most effective sebum suppressive anti-acne agent, decreased IGF-I serum levels [12].

In 2,109 European women, a positive correlation between dairy consump-tion und IGF-I serum levels has been observed [13]. A recent systematic meta-analysis confirmed the relationship between milk consumption and IGF-I serum levels [14]. Most convincingly, the multicenter study group of the European Prospective Investigation into Cancer and Nutrition has presented data for a significant correlation between milk protein consumption and IGF-I serum levels in 4,731 male and female participants [15].

## Combinations of Milk and Carbohydrates Potentiate Insulinotropic Effects

It has been demonstrated in a randomized, investigator-masked, controlled trial that a low GL diet resulted in clinical improvement of acne and reduced sebum secretion [16]. A great part of processed food products of western diet are combinations of milk, milk protein, carbohydrates and sugar. A typical western breakfast of adolescents consists of milk and cornflakes, a combination of insulinotropic milk protein and hyperglycemic carbohydrates. The addition of an ordinary amount of 200 ml milk to a meal with a low GI increased the insulin response by 300% to a level typically seen from a meal with a very high GI like white bread [17]. A lot of food products of industrialized countries are combinations of milk and carbohydrates and sugar like chocolate and ice cream. A most critical development is the abuse of highly insulinotropic whey protein concentrates – provided in 5-kg buckets – in the body building and fitness environment [18]. The daily intake of 40 to 80 g of concentrated whey protein is a usual procedure during muscle training periods. As 1 liter of milk contains approximately 6.6 g whey proteins, the whey abuse corresponds to a daily milk intake between 6 l and 12 l. Moreover, insulinotropic whey protein concentrates are often combined with synthetic growth hormone (GH), insulin, IGF-I as well as androgens, which all potentiate growth factor signaling [18].

## Milk Consumption Elevates Postprandial Insulinemia, GH and IGF-I Plasma Levels

After a month of drinking 710 ml of UHT vitamin D-fortified whole milk daily, Mongolian children, prior not used to milk consumption, had a higher mean plasma level of IGF-I, higher IGF-I/IGFBP-3, and 75th percentile of GH levels [19]. The mean plasma IGF-I levels were significantly raised in the children after 4 weeks of milk consumption by 23.4% from mean pretreatment values of $290.93 \pm 93.98$ to $358.34 \pm 125.62$ ng/ml [19].

Fermented and nonfermented milk products give rise to hyperinsulinemic responses far exceeding what could be expected from their low GIs. Despite a low GI of 15–30, milk products exhibit 3- to 6-fold higher insulinemic indices (IIs) of 90–98 [20]. A large and similar dissociation of the GI and II exists for both whole milk (GI: $42 \pm 5$; II: $148 \pm 14$) and skim milk (GI: $37 \pm 9$; II: $140 \pm 13$) [21]. It has already been suggested that some factor within the protein fraction of milk is responsible for milk's insulinotropic effect [21]. Skim milk has been identified as a potent insulin secretagogue in type 2 diabetic patients [20]. Except for cheese with an II of 45, milk and all dairy products including yoghurt, ice cream, cottage cheese, and fermented milk products have potent insulinotropic properties [22]. In a 1-week intervention study of

24 prepubertal 8-year-old boys, the effect of daily intake of 53 g of either lean meat or skim milk (1.5 l per day) was studied with regard to insulin and IGF-I responses. In the skim milk group, insulin significantly increased by 105% (from 22 to 45 pM) and IGF-I significantly increased by 19% (from 209 to 249 ng/ml) [23]. Remarkably, there was no significant increase in either insulin or IGF-I in the meat group [23].

## Whey Proteins: The Major Inducers of Postprandial Hyperinsulinemia

The major protein fraction of cow's milk is casein (80%), and the remaining 20% are whey proteins. Both, whey and casein contain specific proteins and peptides that have growth-stimulating effects. The effect of whey and casein fractions of milk on fasting concentrations of insulin and IGF-I has been examined in 57 8-year-old boys who received over 7 days either whey protein or casein fractions with protein amounts of whey or casein similar to the content of 1.5 l skim milk. In the whey group, fasting insulin increased by 21%, with no change in IGF-I. In the casein group, serum IGF-I increased by 15%, whereas there was no change in fasting insulin [24]. The insulin response to a whey meal has been reported to be higher than that of a milk meal. This differential response suggests that the insulinotropic component of milk resides predominantly within the whey fraction of soluble milk proteins, whereas casein has a stronger IGF-I stimulating effect than whey [24]. It has been shown that specific whey proteins or their enzymatically cleaved peptides function as secretagogues for the release of the intestinal incretin glucose-dependent insulinotropic polypeptide (GIP) [25]. GIP is a 42-amino acid hormone that is produced by enteroendocrine K cells and released into the circulation in response to nutrient stimulation [26] (fig. 1).

## A Possible Role of Bovine Betacellulin in Acne Pathogenesis

The bovine whey protein fraction contains several active growth factors, in particular high concentrations of betacellulin (BTC) [27], a ligand of epidermal growth factor receptor (EGFR). Remarkably, EGFR faces the gut contents rather than the bloodstream pointing to a special biological function of luminal EGFR expression. In rat duodenum, EGFR has been located at the luminal apical surface of enterocytes in the brush border [28], whereas in humans EGFR was detected at the basolateral membrane of enterocytes [29]. It has been hypothesized by Cordain [30] that milk-derived BTC is taken up and internalized by luminal EGFRs and released by a transcellular EGFR route into the lymphatic circulation and blood plasma, where BTC stimulates EGFR expressed on keratinocytes and sebocytes. The human and bovine BTC
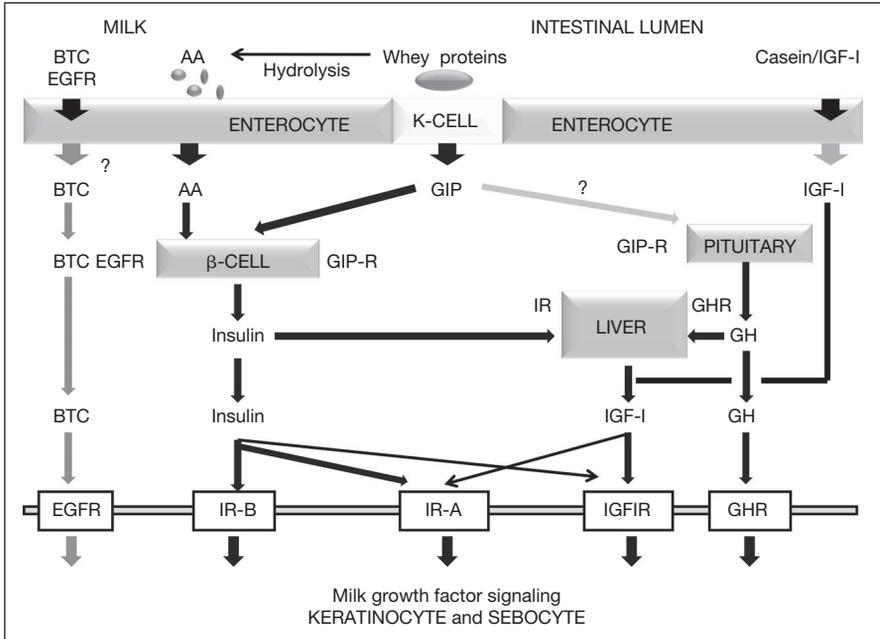
**Fig. 1.** Impact of milk protein consumption on enteroinsular-pilosebaceous signaling network. AA = Essential amino acids; IR = insulin receptor.

precursors share 88% sequence identity and it is generally expected that BTC is absorbed through the small intestine. Of great importance is the mitogenic effect of BTC on β-cell stimulation and insulin secretion. BTC plays an important role in β-cell mass regulation and growth. BTC binding to EGFR results in the activation of the phosphoinositide-3 kinase (PI3K)/Akt pathway leading to reduced nuclear levels of FoxO1 [31]. Thus, milk-derived bovine BTC may directly stimulate sebocyte and keratinocyte proliferation via binding to EGFRs and may induce an indirect stimulation of the cells of the pilosebaceous unit by BTC-induced upregulation of insulin secretion (fig. 1).

Thus, an accumulated body of evidence points to the most critical role of the whey protein/whey growth factor signaling network in the elevation of postprandial insulin plasma levels. The concomitant increase in the more slowly reacting basal IGF-I plasma levels after prolonged consumption of milk and dairy protein can be explained by increased insulin-mediated hepatic IGF-I synthesis as well as intestinal IGF-I absorption from the casein fraction. Thus, overactivation of the whey protein/BTC enteroinsular axis by consumption of whey proteins and BTC results in overstimulated GIP and most likely EGFR signaling which both contribute to milk-induced hyperinsulinemia and increased IGF-I plasma levels. Elevated insulin/IGF-I signaling has been
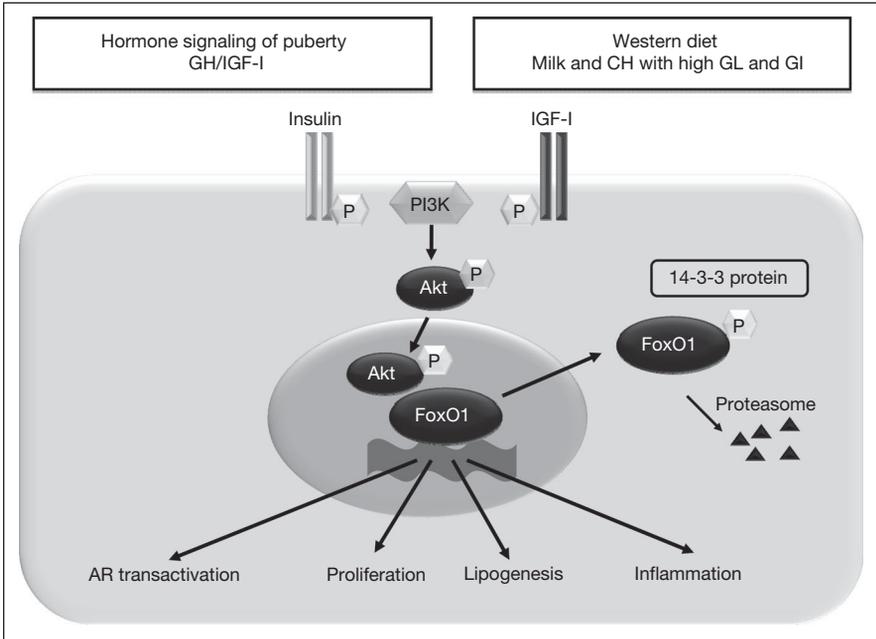
**Fig. 2.** Overstimulating effect of milk-derived growth factor signaling on PI3K/Akt/FoxO1 pathway. Milk protein-derived growth factor signaling is superimposed on physiological growth hormone-mediated PI3K/Akt signaling of puberty overstimulating nuclear export of FoxO1. Nuclear FoxO1 deficiency results in AR transactivation, increased follicular proliferation (comedogenesis), increased sebaceous lipogenesis and follicular inflammation. CH = Carbohydrate.

related to nutrigenomic dysregulation of the metabolic sensor and transcription factor FoxO1 which controls important target genes and nuclear receptors involved in acne pathogenesis [5, 6] (fig. 2).

## Evidence for a Milk-Entero-Pituitary Axis?

The pathophysiology of acne appears to be closely linked to the enteroinsular axis. GIP is rapidly released from K cells by nutrient stimulation with glucose and whey protein. GIP is an important incretin which stimulates insulin secretion of pancreatic β-cells. GIP itself exerts growth-promoting and anabolic effects on various other organ systems like adipose tissue by binding to GIP receptors (GIP-Rs). Most intriguingly, GIP-Rs have been found in the pituitary [32], where GIP may activate GH secretion as observed in acromegalic patients [33]. GIP-stimulated GH release from the pituitary may be a fundamental signaling mechanism of whey proteins during the nursing period

(fig. 1). In fact, Mongolian children not used to milk consumption exhibited markedly higher GH levels after 1 month of drinking milk [19]. Thus, whey-induced GIP stimulation not only activates pancreatic insulin secretion, but most likely stimulates the secretion of pituitary GH which is the strongest inducer of hepatic IGF-I synthesis. Moreover, GH has been shown in dogs to enhance the insulin secretory response to GIP.

## Existence of a Milk-Pituitary-Adrenal-Sebocyte Axis?

GIP enhances pituitary ACTH release and is involved in the regulation of the hypothalamus-pituitary-adrenal axis [34]. ACTH is a ligand of melanocortin-5 receptor [35] which is upregulated in differentiated sebocytes stimulating lipogenesis [36]. GIP-Rs are also present in the zona fasciculata reticularis of normal adrenals and are particularly abundant in some types of adrenocortical adenomas and adrenal hyperplasia. This interaction may be of importance in acne pathogenesis, as increasing DHEAS plasma levels are associated with hormonal changes of prepuberty and the development of acne comedonica. Furthermore, in the sebaceous follicle, DHEAS is converted in an intracrine manner to testosterone and the more potent dihydrotestosterone. The activity of the converting enzyme, 5-$\alpha$-reductase, is IGF-I dependent.

## Nutrigenomic Effects of Milk on FoxO1 Signaling in Acne Pathogenesis

Sebocytes and follicular keratinocytes express androgen receptor (AR), EGFR, FGFR2, insulin receptor, IGF-I receptor (IGFIR) and GHR. The IGF-I/IGFIR-mediated activation of the PI3K/Akt pathway has been shown to play a crucial role in upregulation of sterol response element binding protein-1 expression associated with increased sebaceous lipogenesis [37].

Five main factors play a pivotal role in the pathogenesis of acne: androgen dependence, follicular retention hyperkeratosis, increased sebum production, increased colonization with *Propionibacterium acnes*, and inflammatory follicular events (fig. 2). Puberty is a period of transient insulin resistance with increased GH secretion and elevated hepatic IGF-I synthesis. Milk consumption mimics the endocrine signaling of puberty and increases GH and IGF-I plasma levels [19]. In this regard, physiological GH/insulin/IGF-I signaling of puberty is superimposed by nonphysiological GH/insulin/IGF-I signaling due to milk consumption, the potent growth factor signaling network of bovine milk.

The resulting net effect of elevated growth factor signaling during puberty and persistent growth factor signals of western diet due to increased dairy consumption finally overstimulate the export of nuclear FoxO1 into the cytoplasm via overactivation of the PI3K/Akt pathway [38]. In the absence of growth fac-

tors, nuclear FoxO1 suppresses nuclear receptors (AR, PPARγ) and key genes and transcription factors of cell proliferation (cyclin D2), matrix modulation (matrix metalloproteinases), lipid biosynthesis (sterol response element binding protein-1) and inflammatory signaling (NFκB) [5]. With increased growth factor signaling, however, genes and nuclear receptors involved in acne are de-repressed, leading to increased AR-mediated signal transduction [39], increased cell proliferation of androgen-dependent cells, induction of sebaceous lipogenesis [37], upregulation of Toll-like-receptor-2-dependent inflammatory cytokines and decreased synthesis of antimicrobial peptides.

In contrast, retinoids, antibiotics and dietary intervention may increase the nuclear content of FoxO1 [5], thereby normalizing increased transcription of acne target genes upregulated by increased diet-mediated growth factor signaling. Various receptor-mediated growth factor signals and especially whey proteins and carbohydrates induce elevations of the insulin/IGF-I signal transduction pathways, which are finally integrated at the level of PI3K/Akt activation resulting in a nuclear FoxO1 deficiency, the underlying nutrigenomic mechanism in the pathogenesis of acne [5].

### Acne-Cancer Relationship

There is now considerable evidence that insulin/IGF-I signal transduction networks play an important role in neoplasia [40]. Acne is often associated with disorders of increased growth factor signaling and insulin resistance, like polycystic ovary syndrome, acromegaly and Apert syndrome with a gain of function mutation of fibroblast growth factor receptor-2 [6]. All these diseases are associated with an increased incidence of cancer. Polycystic ovary syndrome is associated with an increased risk for endometrial cancer and diabetes mellitus. Patients with acromegaly have an increased prevalence of colorectal cancer, breast cancer and prostatic malignancies. Severe acne in males has been associated with an increased risk of prostate carcinoma [41]. Intriguingly, a recent meta-analysis confirmed that a high intake of dairy products is related to an increased risk of prostate cancer [42]. It is conceivable that elevated insulin/IGF-I signal transduction may stimulate proliferation of androgen-dependent cells of the prostate by FoxO1-mediated upregulation of AR transactivation and subsequent androgen-dependent growth factor signaling [39].

In the field of oncology, recent efforts are undertaken to reduce increased insulin/IGF-I signaling by the administration of insulin-sensitizing agents like metformin or IGFIR and EGFR antagonists [40, 43]. However, all these pharmacological efforts affect the 'too late' efferent site of western nutrition and lifestyle. It would be more prudent to control the afferent, causative mechanisms of acne and cancer promotion associated with increased growth factor signaling of insulinotropic western diet.

**Table 1.** Proposed impact of milk-induced GIP/insulin/IGF-I oversignaling in the pathogenesis of acne and other chronic western diseases [44]

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| Prenatal | Increased insulin-IGF-I signaling in the thymus | Disturbed T cell maturation, impaired T cell apoptosis | Allergy, atopy, autoimmune diseases |
| | Increased placental growth and maternal glucose transport | Fetal overgrowth, increased birthweight | Fetal macrosomia, disposition for obesity |
| Postnatal | Increased GIP, insulin and IGF-I plasma levels | Disturbed neonatal programming of the somatotropic IGF-I axis | Increased linear growth, increased risk for cancer, obesity, diabetes and arterial hypertension |
| Adolescence | Overstimulation of physiological growth factor signaling of puberty, nuclear FoxO1 deficiency | Promotion of acne, increased androgen signaling, increased sebogenesis, comedogenesis | Epidemic acne, persistence of acne in adulthood |
| | | GIP-induced adipocyte differentiation and lipogenesis | Early onset of childhood obesity |
| Adulthood | Overstimulation of pancreatic β-cells | Early onset of replicative β-cell senescence | Diabetes mellitus type 2 |
| | Overstimulation of endothelial and smooth muscle cells and increased lipogenesis | Promotion of atheroma formation | Coronary heart disease, stroke |
| | Overstimulation of the insulin/IGF-I signaling network | Stimulation of the oncogenic PI3K/Akt pathway | Cancer promotion |
| | Insulin/IGF-I over-stimulation of neuronal cells | Imbalance between protein synthesis and degradation, 'diabetes of the brain' | Early onset of neurodegenerative diseases |

### Conclusion

Acne, an epidemic skin disease in countries with western nutrition, is promoted by increased consumption of insulinotropic food, especially milk, dairy products as well as high loads of carbohydrates with high GI. Acne can be regarded as the visible metabolic syndrome of skin displaying the daily adverse effects of exaggerated insulinotropic nutrition. Therefore, acne is a useful clinical and epidemiological indicator of optimized healthy human nutrition.

Nuclear FoxO1 deficiency induced by increased insulin/IGF-I signaling upregulates all major mechanisms of acne pathogenesis [5]. Whey proteins are most important essential signaling proteins promoting increased insulin/IGF-I signaling for growth and survival of mammalian neonates. By million years of evolution, this signaling system of mammalian milk is exclusively and physiologically provided to the newborn only during the nursing period. The chronic 'abuse' of this mammalian postnatal signaling system by widespread cow milk and dairy consumption in humans of industrialized societies has been proposed to be the major cause of the acne epidemic and the more serious chronic western diseases [44].

There are two solutions to this problem: the restriction of milk protein consumption or the elimination of the insulinotropic effectors of milk. The attenuation of the whey protein- and whey growth factor-based insulinotropic signaling mechanisms of milk will be the most important future challenge for an interdisciplinary cooperation between medicine, molecular biology, nutrition research and milk processing biotechnology. The goal will be to reduce the II of milk to a level corresponding only to its carbohydrate moiety. The generation of less insulinotropic milk and milk products with an II below 45 will have an enormous impact on the prevention of epidemic western diseases like obesity, diabetes mellitus, cancer, neurodegenerative diseases and acne (table 1) [44].

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## Discussion

*Dr. Hernell:* Do you intend to do a blinded study? You could use encapsulated whey protein powder to see whether there is an effect on acne or not. I think that would be useful. The second question is, how organ specific is the effect on lipogenesis? Do you see it also in other organs? With high IGF-I level, do you for instance see a change in plasma lipoproteins with increased VLDL secretion by the liver?

*Dr. Melnik:* The sebaceous gland is not the only target exhibiting stimulated lipogenesis by increased IGF-I signaling. The differentiation of preadipocytes to adipocytes is also IGF-I dependent [1]. It is well known that insulin and IGF-I regulate hepatic VLDL synthesis via nuclear extrusion of the transcription factor FoxO1. However, in the liver VLDL synthesis and secretion are downregulated by insulin and IGF-I signaling. Intriguingly, milk consumption, especially whey protein has been shown to stimulate the secretion of the intestinal incretin glucose-dependent insulinotropic polypeptide (GIP), which has strong adipogenic effects in adipocytes that express the GIP receptor. It will be important to intensify studies focusing on whey protein-mediated GIP responses [2]. Formula-fed infants gain weight more easily than breastfed infants. Whey-based formula-fed infants exhibited high postprandial serum levels of GIP and insulin. Especially hydrolyzed α-lactalbumin provokes a strong GIP response with increased postprandial GIP serum concentrations [3, 4]. The transcription factor FoxO1 plays a crucial role in adipogenesis and is regulated by insulin and IGF-I [5, 6]. Insulin and IGF-I-mediated regulation of the transcription factor FoxO1 plays also an important role in insulin secretion of pancreatic β-cells [7–9]. Thus, the insulinotropic effect of milk with increased insulin and IGF-I signal transduction modifies the transcription factor FoxO1 in various cell systems, the sebocyte, the adipocyte

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and the pancreatic β-cell, explaining the observed insulinotropic, lipogenic and adipogenic effects of milk consumption.

*Dr. Rock:* As you move into the cancer arena here, I have to add a cautionary note and comment on a few things. Although IGF-I is certainly involved in the whole signaling and cell proliferation and differentiation regulation, it's really only a player, and in fact I would argue that emerging evidence suggests that it's simply eating a calorically dense diet that has the effect rather than milk per se. The primary problem is insulin resistance, probably triggered by an inflammatory response in relation to obesity and excess caloric intake. Inflammatory markers trigger the insulin resistance, and hyperinsulinemia has this effect of stimulating the synthesis of IGF-I. And then the other part that I don't see on your graphics is the effect of insulin on synthesis of sex hormone-binding globulin, so although you mention androgens as being a dated idea, I would argue that the reproductive hormones are a part of this pathway too, so it's reductive to focus only on IGF-I.

*Dr. Melnik:* I agree, increased IGF-I is only one important player of the cancer-promoting effect of milk. There is also evidence that milk consumption induces basal serum insulin levels as well as insulin resistance [10]. Insulin and IGF-I via modulation of the nuclear content of FoxO1 also have an impact on androgen metabolism. FoxO1 is a nuclear corepressor of the androgen receptor. Thus, increased insulin and IGF-I signaling results in increased androgen receptor transactivation [11]. Milk-driven insulinotropic signaling via insulin/IGF-I-mediated nuclear exclusion of FoxO1 may stimulate androgen-mediated cancerogenesis in the prostate, a possible link confirmed by epidemiological evidence [12]. There is more experimental evidence for the cancer-promoting effect of milk consumption in anthracene-induced mammary cancers in rats fed a cow's milk diet in comparison with rats without cow's milk in their diet [13]. Milk-fed rats doubled their increase in tumor volume and tumor mass. With regard to insulin/IGF-I/FoxO1 signaling, it is remarkable that the anthracene-induced tumor system is phosphoinositol-3 kinase (PI3K)/Akt dependent. A further milk-mediated upregulation of PI3K/Akt stimulation may explain the observed milk-stimulated tumor progression in anthracene-induced mammary tumors in rats [14].

*Dr. Martin:* Thank you very much for a very nice talk. The signaling information was very convincing. How do you tie all that in with systematic reviews showing that increased milk intake is associated with a reduced risk of colorectal cancer, breast cancer, cardiovascular disease, diabetes and stroke, such that overall, in absolute numbers, milk seems to have an overall survival advantage [15]?

*Dr. Melnik:* Epidemiological studies of the past concerning milk and dairy consumption and their relation to chronic Western diseases gave conflicting results most likely because they did not differentiate between strong insulinotropic and less insulinotropic milk products. Studies which mixed dairy products with variable insulinemic index are thus not suitable to present a clear picture of the situation.

*Dr. De Beer:* You mentioned that in your clinical practice you advise your patients to reduce the milk intake and go on a low glycemic index diet. My question to you is, if we consider that acne is a multifactorial disease, how big is the role that milk or a low glycemic index diet might play, and if you then divide the two, which one is the most important, the milk or the low glycemic index diet?

*Dr. Melnik:* Both milk and insulinotropic milk products and hyperglycemic carbohydrates play a role in the induction or aggravation of acne [16–18]. At present, studies comparing the effects of diets with milk vs. high glycemic carbohydrates or combinations of both on the course and activity of acne are missing. It has to be expected that the combination of milk with high glycemic carbohydrates will provoke the strongest effect on acne because it has been shown that the addition of milk to a meal with a low glycemic index significantly increases postprandial insulin response [19].

*Dr. Saldanha:* Concerning the drug isotretinoin, do you know studies correlating the use of this drug and the final height of adolescents? I mean are we treating acne and getting shorter adults?

*Dr. Melnik:* Yes, it is possible with high isotretinoin doses like those given to patients with ichthyosis and other generalized disorders of keratinization. It has recently been demonstrated that isotretinoin treatment of acne patients lowered serum IGF-I levels and growth hormone [20]. Growth hormone/IGF-I signaling of puberty is superimposed by insulinotropic signaling of western diet. I could recently provide indirect evidence for isotretinoin-mediated increase in nuclear FoxO1 [21].

*Dr. Jongpiputvanich:* You suggested that acne is more related to IGF-I than androgen level. I wonder what would happen if we conducted a randomized-controlled trial in elderly persons and included one group with a high amount of milk intake and another with no milk intake.

*Dr. Melnik:* Indeed, milk consumption raises serum IGF-I levels and via IGF-I-mediated extrusion of FoxO1 from the nucleus increases androgen receptor transactivation. IGF-I also increases the free androgen index by downregulating sex hormone-binding globulin. IGF-I also stimulates 5-α-reductase activity and adrenal DHEAS and gonadal androgen synthesis. Thus, IGF-I has a strong influence on androgen-mediated signal transduction [22, 23].

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