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# FoxO1 – the key for the pathogenesis and therapy of acne?

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## Summary
Five main factors play a pivotal role in the pathogenesis of acne: androgen dependence, follicular retention hyperkeratosis, increased sebaceous lipogenesis, increased colonization with *P. acnes*, and inflammatory events. This paper offers a solution for the pathogenesis of acne and explains all major pathogenic factors at the genomic level by a relative deficiency of the nuclear transcription factor FoxO1. Nuclear FoxO1 suppresses androgen receptor, other important nuclear receptors and key genes of cell proliferation, lipid biosynthesis and inflammatory cytokines. Elevated growth factors during puberty and persistent growth factor signals due to Western life style stimulate the export of FoxO1 out of the nucleus into the cytoplasm via activation of the phosphoinositide-3-kinase (PI3K)/Akt pathway. By this mechanism, genes and nuclear receptors involved in acne are derepressed leading to increased androgen receptor-mediated signal transduction, increased cell proliferation of androgen-dependent cells, induction of sebaceous lipogenesis and upregulation of Toll-like-receptor-2-dependent inflammatory cytokines. All known acne-inducing factors exert their action by reduction of nuclear FoxO1 levels. In contrast, retinoids, antibiotics and dietary intervention will increase the nuclear content of FoxO1, thereby normalizing increased transcription of genes involved in acne. Various receptor-mediated growth factor signals are integrated at the level of PI3K/Akt activation which finally results in nuclear FoxO1 deficiency.

## Keywords
acne – FoxO1 – sebogenesis – comedogenesis – retinoids – acne therapy

### Introduction
It is the purpose of this paper to demonstrate that the nuclear transcription factor FoxO1, a member of the class O subfamily of forkhead box (FoxO) transcription factors, regulates the activity of most important target genes involved in the pathogenesis of acne, i. e., androgen receptor (AR) transactivation, follicular keratinocyte hyperproliferation, sebaceous lipogenesis and follicular inflammation. FoxO1 is proposed to be the key to understand the influence and link between genetic and environmental factors in acne. Upregulation of nuclear FoxO1 by retinoids might explain the beneficial effects of increased nuclear FoxO1 in the treatment of acne.

### FoxO-transcription factors
Forkhead box O (FoxO) transcription factors FoxO1, FoxO3a, FoxO4 and FoxO6 are emerging as an important family of regulatory proteins that modulate the expression of important genes involved in cell cycle control, DNA damage repair, apoptosis, oxidative stress, cell differentiation, glucose metabolism and other cellular functions (Figure 1) [1].
The potent functions of FoxO proteins are tightly controled by complex signaling pathways under physiological conditions [2]. Central to the regulation of FoxO transcription factors is a shuttling system, which confines FoxO factors to either the nucleus or the cytosol (Figure 2).
Shuttling of FoxO1 requires protein phosphorylation of nuclear FoxO1 by

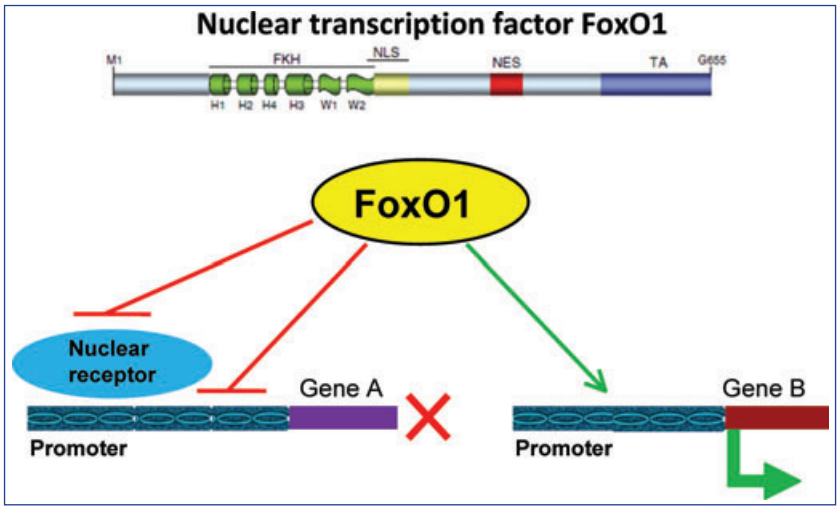


**Figure 1:** Regulatory functions of nuclear transcription factor FoxO1. FoxO1 directly inhibits nuclear receptors like PPARγ or LXR. FoxO1 activates or represses the promoter of target genes.

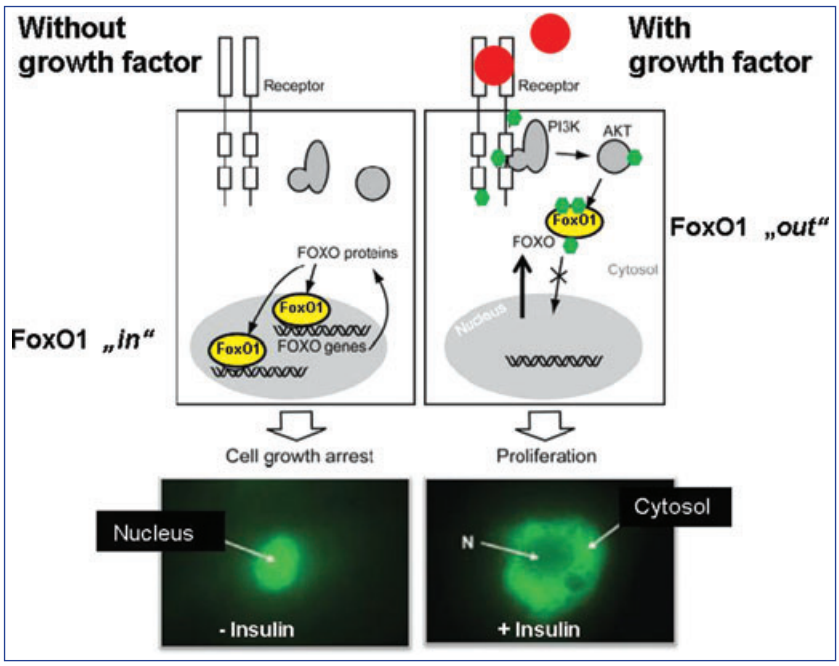


**Figure 2:** Growth factors activate the PI3K/Akt pathway. Activated Akt phosphorylates (green hexagons) nuclear FoxO1 which is exported from the nucleus into the cytosol and degraded. Growth factor signaling provides a switching mechanism for FoxO1 shuttling between the nucleus and cytoplasm. PI3K = phosphoinositide-3 kinase; Akt = Akt kinase.

activated phosphoinositide-3-kinase (PI3K) and Akt kinase. Activated Akt translocates into the nucleus for FoxO phosphorylation. Phosphorylated FoxO1 leaves the nucleus, thereby changing gene regulation. Dysregulation of FoxO1 and its nuclear export by insulin, insulin-like growth factor-1 (IGF-1) or other growth factor-mediated activation of PI3K/Akt affects the transcriptional activity of key target genes and nuclear receptors involved in acne pathogenesis.

It will be shown that upregulation of nuclear FoxO1 concentration is the underlying mechanism of retinoid treatment, retinoid-induced downregulation of AR transactivation as well as retinoid-induced hypertriglyceridemia.

## FoxO1 and androgen dependence of acne

The role of androgens in *acne vulgaris* and the beneficial effect of anti-androgen treatment of female acne patients are well established. Androgen-mediated signal transduction plays an essential role for the stimulation of the size of sebocytes and sebum production as well as keratinocyte proliferation in the *ductus seboglandularis* and the *infundibulum.* Androgen-signal transduction is mediated by nuclear ARs which are localized in the basal layer of sebaceous glands, keratinocytes and perifollicular fibroblasts. Androgens induce the expression of *sterol regulatory element binding proteins* (SREBPs), the most important transcription factors of lipogenesis [3]. Androgen-insensitive subjects who lack functional ARs do not produce sebum and do not develop acne [4]. Increased AR protein levels have been determined in skin of acne patients [5]. Thus, sufficient evidence supports the view that the AR system plays a key role in the pathogenesis of acne.

### *FoxO1 and androgen receptor*

AR is a modular protein organized into functional domains, consisting of an N-terminal transcription activation domain (TAD), a DNA-binding domain, a small hinge region and a C-terminal ligand-binding domain for androgens [6, 7] (Figure 3). Testosterone and its more potent metabolite, 5α-dihydrotestosterone (DHT), bind AR and activate the expression of androgen-responsive target genes at the transcriptional level. The TAD mediates the majority of AR transcriptional activity and provides the most active co-regulator interaction surface [8, 9].

FoxO1 is a transcription factor sensing metabolic changes and is an important metabolically regulated AR corepressor. FoxO1 binds to the TAD of AR where it disrupts p160 coactivator binding and suppresses N-terminal/C-terminal-interaction of AR, which is most important for AR transcriptional activity [10]. By this mechanism, FoxO1 reduces the expression of AR target genes. The level of AR transcriptional activity by endocrine and nutritional factors is regulated by FoxO1 phosphorylation. The AR repressive function of FoxO1 is attenuated by increased growth factor (insulin/IGF-1) signaling with activation of the PI3K/Akt cascade [11, 12]. Activated Akt kinase translocates into the nucleus and phosphorylates nuclear FoxO1, which is extruded from the nucleus into the cytosol, where FoxO1 is sequestered by the cytoplasmic 14-3-3 proteins,

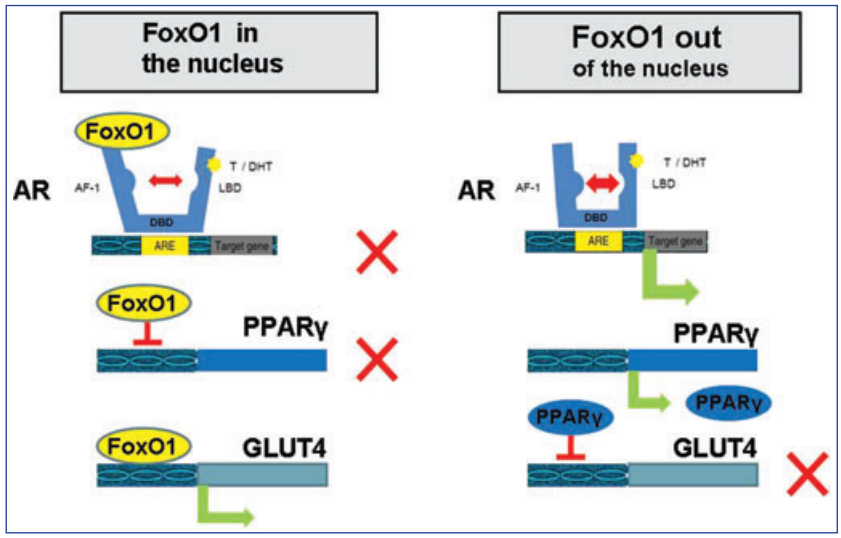


**Figure 3:** FoxO1 is a corepressor of the transactivation domain of androgen receptor. FoxO1 suppresses the promoter of PPARγ and activates the promoter of glucose transporter protein-4 (GLUT4). AR = androgen receptor; AF-1 = activation factor 1; PPARγ = peroxisome proliferator-activated receptor-γ; T = testosterone; DHT = dihydrotestosterone; DBD = DNA binding domain; LBD = ligand binding domain; ARE = androgen receptor response element.

ubiquitinylated and send to proteasomal degradation [2]. Not only androgen binding but the availability and action of coactivators and corepressors like FoxO1 dictate the final transcriptional response of the AR regulatory system in specific cells. The expression of several growth factors like IGF-1 and regulatory proteins of cell cycle control and lipogenesis are dependent on androgen signal transduction [13]. Thus, nuclear FoxO1 extrusion and upregualtion of AR transcriptional activity will augment the expression of a substantial set of AR-responsive target genes resulting in further increase in growth factor signaling. Thus, FoxO1-mediated regulation of AR modifies the gene expression of AR-expressing tissues like the sebaceous and prostate gland.

## FoxO1 and sebaceous lipogenesis

*Peroxisome proliferator-activated receptors*

In vitro experiments with human sebocytes have shown that testosterone affects cell proliferation in a dose-dependent manner [14, 15] but not lipid synthesis [16, 17]. This unexpected observation led to the assumption that cofactors may be required for complete induction of the full lipogenic program of sebocytes [18]. Another type of nuclear receptors, the *peroxisome proliferator-activated receptors* (PPARs) and their ligands were confirmed to be the important coregulators for sebaceous lipogenesis [16–19]. Three subtypes of PPARs, PPARα, PPARδ, and PPARγ are expressed in follicular keratinocytes and sebocytes and are involved in the regulation of lipogenesis and cell differentiation [20]. Specific agonists of each PPAR isoform stimulate sebocyte differentiation [20]. Fatty acids of *n-3-* and *n-6* origin and their cyclooxigenase and 5-lipoxigenase products play an important role as natural PPAR ligands that modulate PPAR function [21]. PPARδ ligand *linoleic acid* is a most effective agonist in stimulation of lipid formation in sebocytes and keratinocytes [20]. Inhibition of the formation of the PPARα agonist *leukotriene B4* [22, 23] is the rationale for the sebum suppressive treatment of moderate acne with the 5-lipoxygenase inhibitor Zileuton [24, 25]. However, the most important PPAR in the regulation of lipid metabolism is PPARγ, whose natural ligand is *prostaglandin J2*. PPARγ is essential for sebaceous gland development and function [20]. Increased release of *substance P* might mediate stress-induced effects on the pilosebaceous follicle and upregulates PPARγ protein expression and RNA amplification in cultured sebocytes [26]. Furthermore, PPARγ plays a significant role in mediating insulin sensitivity, glucose and lipid homeostasis [27–29]. PPARγ is present in rat preputial sebocytes and cultured sebocytes [16, 30–32] and like the other PPAR subtypes increases human sebum production [33]. Isotretinoin (*13-cis* retinoic acid) significantly decreased lipogenesis in SEB-1 sebocytes, whereas the PPARγ agonist rosiglitazone increased lipogenesis. This is the reason why patients treated with thiazolidinediones or fibrates had significant increases in sebum production.

PPARγ like AR is transrepressed by FoxO1. FoxO1 directly binds and represses the PPARγ2 promoter as well as PPARγ function [34, 35] (Figure 3). Growth factor signaling reduces nuclear FoxO1 concentrations via activation of Akt, thereby augmenting PPARγ activity required for terminal differentiation of sebocytes. Insulin and other growth factors like IGF-1 induce FoxO1 phosphorylation and its nuclear exportation, which prevents FoxO1-PPARγ interaction and rescues transrepression of genes involved in lipogenesis [36]. In fact, serum levels of IGF-1 correlate with facial sebum excretion [37]. PPARγ heterodimerizes with the retinoid X receptor (RXR) and binds to PPAR response elements in promoters of target genes. One mechanism by which FoxO1 antagonizes PPARγ activity is through disruption of DNA binding as FoxO1 inhibits the DNA binding activity of the PPARγ/RXRα heterodimeric complex [35]. PPARγ/RXRα heterodimers have recently been detected in sebocytes [38]. Thus, growth factor signaling inhibits the transrepressive effect of FoxO1 on AR and PPARγ/RXRα, resulting in terminal differentiation of sebocytes with augmented lipogenesis.

*Liver X receptors*

*Liver X receptors* (LXRs) are further members of the nuclear receptor superfamily which play a critical role in cholesterol homeostasis and lipid metabolism [39]. Expression of LXRα and LXRβ has been detected in SZ95 sebocytes [40]. LXR ligands enhance the expression of LXRα and stimulate lipid synthesis [40, 41]. LXRs directly control the expression of SREBP1 [39, 42–45]. A LXRE motif is present in the PPARγ promoter, on which LXRα/RXRα heterodimer is bound and activated by a LXR ligand [46]. In the SZ95 sebocyte cell line activation of LXRα induced lipid synthesis that was accompanied with the induction of SREBP1 and PPARs

[15, 41, 47]. In SEB-1 sebocytes, IGF-1 induced SREBP1 expression and increased lipogenesis via activation of the PI3K/Akt signaling pathway [48, 49].
FoxO1 plays an important role in the regulation of the SREBP1c promoter activity. From studies of SREBP1c gene expression in skeletal muscle it is known that SREBP1c expression is regulated by a heterodimer of LXRα and RXRα. In the fasting state, RXRγ is markedly decreased and restored by refeeding [50]. RXRγ or RXRα, together with LXRα activate the SREBP1c promoter [50]. The expression of FoxO1 negatively correlated with SREBP1c expression. Overexpression of FoxO1 decreased gene expression of RXRγ and SREBP1c and suppressed LXRα/RXRα-mediated SREBP1c promoter activity [50]. Thus, nuclear FoxO1 has a fundamental impact on the regulation and expression of SREBP1c, the key transcription factor of multiple lipogenic target genes. Growth factor-mediated derepression of RXRγ and LXRα/RXRα heterodimers of the SREBP1c promoter finally stimulate the expression of SREPB1c and concomitant lipogenesis.

**FoxO1 and comedogenesis**

The formation of a microcomedo, the first microscopic change in the evolution of acne, results from increased proliferation and retention of infundibular keratinocytes, which has convincingly been demonstrated based on increased labeling of the comedonal wall with tritiated thymidine [51]. Hyperproliferation of keratinocytes and hypercornification of the follicular wall could be experimentally induced by interleukin-1α (IL-1α) and blocked by the addition of IL-1 receptor antagonist [52]. These observations underline the importance of IL-1α in comedogenesis.
The recruitment of PI3K to activated receptor complexes is a common feature of signal transduction of tyrosine kinase receptors. However, not only tyrosine kinase receptors but also G protein-coupled receptors (GPCRs) like IL-1 receptor are also able to activate the PI3K/Akt pathway [53–55]. It is conceivable that IL-1α-induced PI3K/Akt signaling is associated with acne in IL-1α-hypersecreting PAPA syndrome [56–58]. In fact, PAPA syndrome responded well to anakinra, an IL-1 receptor antagonist [59, 60]. Growth factor signaling during puberty activates basal keratinocytes which release IL-1α [61], a primary signal initiating further suprabasal keratinocyte activation resulting in the expression of cytokeratins K6, K16 and K17 [62]. Indeed, upregulated expression of these cytokeratins has been detected in infundibular keratinocytes, the comedone wall, sebaceous duct cells and differentiated sebaceous cells of acne patients [63, 64].
The regulation of genes controling the cell cycle is a major functional role of FoxO proteins. In the absence of growth factors, FoxOs reside in the nucleus and upregulate genes that inhibit the cell cycle (p27KIP1 and p21WAF1), promote apoptosis (Fas ligand, Bim and TRAIL), and decrease oxidative stress (superoxide dismutase and catalase) [1]. Furthermore, a number of important genes controlling cell cycle checkpoints (cyclins D1 and D2) and matrix modulation (matrix metalloproteinases) are repressed by FoxOs [1, 65]. Intriguingly, increased concentrations of matrix metalloproteinases have been observed in sebum of acne patients. The derepression of FoxO-controled genes involved in cell cycle progression and matrix modulation by growth factor signaling might explain the increased cell proliferation of comedogenesis and increased levels of matrix metalloproteinases observed in sebum of acne patients [18, 51].

**FoxO1 and insulin resistance of puberty**

Increased pituitary secretion of growth hormone (GH) is the major endocrine change of puberty, a period of transient insulin resistance. GH induces hepatic synthesis and secretion of IGF-1, the most important mediator of growth. The GH/IGF system has been considered to be the major contributor of insulin resistance at puberty [66–72]. Insulin resistance is associated with a marked reduction in the intracellular pool of glucose transporter protein-4 (GLUT4) [73].
The expression of GLUT4 is regulated by FoxO1, PPARγ1 and PPARγ2. FoxO1 directly activates the GLUT4 promoter and suppresses the promoters of PPARγ1 and PPARγ2 [73]. PPARγ1 and PPARγ2 repress the GLUT4 promoter. In the absence of growth factors, high nuclear levels of FoxO1 increase insulin sensitivity by direct stimulation of the GLUT4 promoter and suppression of PPARγ1 and PPARγ2 expression. However, during increased growth factor signaling and decreased nuclear FoxO1, direct FoxO1-activation of the GLUT4-promoter is reduced and PPARγ-mediated repression of GLUT4 is increased resulting in diminished expression of GLUT4 leading to insulin resistance. Thus, high levels of nuclear FoxO1 induce directly and indirectly via PPARγ the expression of GLUT4 and improve insulin sensitivity and cellular glucose uptake [73]. Rosiglitazone and pioglitazone, two synthetic hypoglycemic agents of the thiazolidinedione family, are potent ligands of PPARγ. They alleviate PPARγ repression of the GLUT4 promoter, thereby enhancing insulin responsiveness with improved glucose uptake [73, 74]. However, chronic insulin/IGF-1-stimulation with increased phosphorylation of FoxO1 results in insulin resistance, an endocrine characteristic observed at puberty and in polycystic ovary syndrome (PCOS). Therefore, it is not surprising that PCOS is often associated with insulin resistance, acne and hirsutism. These data underline the pivotal role of FoxO1 in glucose metabolism and explain that the reduced nuclear content of FoxO1 during increased growth factor signaling is the cause of transient insulin resistance at puberty.

**FoxO1 and follicular inflammation**

*Toll-like-receptors*

*Toll-like receptor-2 (TLR2) and TLR4* expression was found to be increased in the epidermis of acne lesions [75]. TLR2 is also expressed on the cell surface of macrophages surrounding pilosebaceous follicles. *Propionibacterium acnes* induce cytokine production of monocytes through a TLR2-dependent pathway [76]. Distinct strains of *P. acnes* induced selective human β-defensin-2 and IL-8 expression in human keratinocytes through TLRs [77]. *P. acnes*, by acting on TLR2, may stimulate the secretion of IL-6 and IL-8 by follicular keratinocytes and IL-8 and IL-12 by macrophages, giving rise to inflammation [78]. There is no doubt that TLRs play an important role in the induction of innate immunity and inflammatory cytokine responses in acne [79].
Interestingly, TLR2 contains a PI3K binding motif and activation of PI3K is particularly important for TLR2 signaling [80] (Figure 4). In response to bacterial ligands, Src family kinases initiate

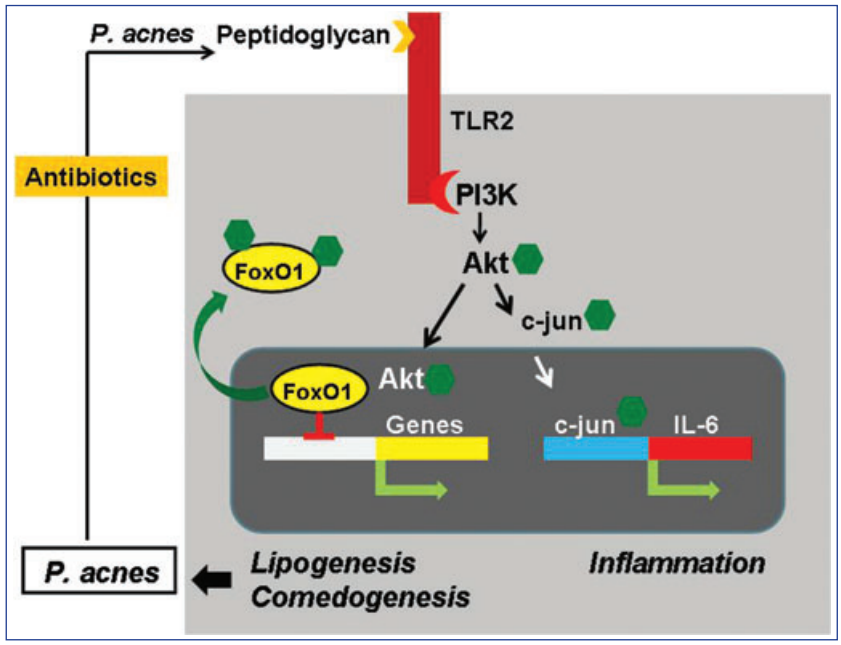


**Figure 4:** Toll-like receptor-2 has a binding motif for PI3K. TLR2/PI3K/Akt activation might reduce nuclear content of FoxO1 thereby activating lipogenesis, comedogenesis as well as inflammatory cytokine synthesis. Antibiotic treatment would interfere with this signaling pathway. TLR2 = Toll-like receptor-2; PI3K = phosphoinositol-3 kinase; IL-6 = interleukin 6.

TLR2-associated signaling, followed by recruitment of PI3K and phospholipase Cγ necessary for the downstream activation of pro-inflammatory gene transcription [81–83]. Thus, PI3K is not only activated by tyrosine kinase receptors, but also by TLRs and cytokine receptors like IL1-R [84]. A direct interaction between PI3K and TLRs or their adaptor proteins, such as MyD88, has been reported. Additionally, YxxM motifs in TLRs and MyD88 are required for their interaction with the p85 regulatory subunit of PI3K [80, 85, 86]. TLR2-mediated activation of transcription factor NFκB also requires YxxM motifs [80], suggesting that recruitment of PI3K to the cytosolic domain of TLR2 is important for downstream signal transduction. Furthermore, phosphorylation of Akt is detected upon stimulation of most TLRs [87].

*Toll-like receptor-2 and lipogenesis*

PI3K activation by growth factor signaling of puberty and the decrease of nuclear FoxO1 levels followed by derepression of PPARγ and LXRα and induced expression of SREBP1c is associated with increased lipogenesis. An increase of lipid synthesis of the sebaceous follicle provides a most favorable milieu for growth and biofilm formation of *P. acnes*. In a vicious cycle, *P. acnes* might stimulate TLR2 on sebocytes which further increase PI3K-mediated sebaceous lipogenesis. SZ95 sebocytes were found to constitutively express TLR2 and TLR4 augmented by exposure to components of Gram-positive (lipoteichonic acid) and Gram-negative (lipopolysaccharide) bacteria [88]. Most intriguingly, *P. acnes* exposure has recently been shown to augment lipogenesis in hamster sebaceous glands [90].

This observation implicates that TLR2-mediated PI3K activation might not only be involved in the stimulation of inflammatory responses to *P. acnes* but also to *P. acnes*/TLR2-stimulated sebaceous lipogenesis and comedogenesis.

*FoxO1, toll-like receptors and adaptive immune response*

TLR stimulation mimics the action of IL-1α and promotes the production of pro-inflammatory cytokines, prostaglandins, leukotrienes and chemokines [76]. Selected IL-1 receptor associated kinases (IRAK-1, 2, M and 4) are bifunctional. They can be recruited either to the TLR complex and thus mediate TLR signaling. On the other side, they can associate with adapter proteins involved in T- and B-cell receptor-mediated signaling pathways linking TLR/IRAK signaling to innate as well as adaptive immune responses [89, 91, 92]. Growth factor-mediated signaling as well as TLR2-signal transduction increases the activity of PI3K/Akt, thus decreasing nuclear content of FoxO1. Therefore, it is conceivable that antibiotic treatment might decrease *P. acnes*/TLR2-mediated upregulation of sebaceous lipogenesis [90]. In a synergistic fashion, ATRA has been shown to downregulate TLR2 expression and function [93]. TLR2/PI3K-signaling appears to be the connecting element between upregulated innate and adaptive immune responses in acne. Antibiotic treatment of acne might reduce peptidoglycan-mediated stimulation of TLR2/PI3K/Akt signaling and increases nuclear levels of FoxO1.

**FoxO1 and the therapeutic effect of retinoids**

Isotretinoin is the most potent inhibitor of sebum production, yet its mechanism of action remains largely unknown [94–96]. Oral isotretinoin is isomerized in 20–30 % to ATRA and reduces comedogensis, sebogenesis and inflammation [94–96]. Topical ATRA and other retinoid derivatives is the mainstay of anti-comedogenic external acne therapy [97, 98]. There is substantial evidence that isotretinoin interferes significantly with the regulation of cell cycle control mechanisms. Isotretinoin causes a significant dose- and time-dependent decrease of viable SEB-1 sebocytes. Part of this decrease could be attributed to cell cycle arrest as evidenced by decreased DNA synthesis, increased p21 protein expression and decreased cyclin D1 [99, 100]. The isotretinoin-induced apoptosis of SEB-1 sebocytes was associated with increased cleaved caspase 3 protein. The ability of isotretinoin to induce apoptosis could not be recapitulated by *9-cis* RA or ATRA. Isotretinoin-induced apoptosis was not inhibited in the presence of a RA receptor (RAR) pan-antagonist. These data indicate that isotretinoin causes cell cycle arrest and induces apoptosis in SEB-1 sebocytes by a RAR-independent unknown mechanism [99, 100]. Recent studies concerning isotretinoin-induced changes in gene expression focused on the regulatory role of RAR and RXR confirmed that isotretinoin induces apoptosis [101].

There is accumulating evidence that retinoids alter the expression of FoxO transcription factors. It could recently be shown in neuroblastoma cells that ATRA

induced the expression of FoxO3 [102]. FoxO3 is the strongest activator of the FoxO1 promoter, thus increasing the transcription of FoxO1 [65]. In ATRA-treated neuroblastoma cells, the upregulation of FoxO3 correlated with the expression of FoxO target genes p27, p130, and MnSOD [102]. These data show that ATRA activates genes associated with cell cycle arrest comparable to the changes observed in isotretinoin-treated SEB-1 sebocytes [99]. Retinoid-induced expression of FoxO3 augments the expression of FoxO1 as well as FoxO1-dependent target genes, like upregulation of p21WAF1 and p27KIP1 and downregulation of cyclins D1 and D2.

There is more indirect evidence supporting the role of isotretinoin for upregulation of FoxO1, which is a corepressor of the TAD of AR [10].

An isotretinoin-induced upregulation of FoxO1 would suppress the activity and expression of AR protein. In fact, reduced levels of AR protein have been observed in skin of acne patients after oral isotretinoin treatment: a 2.6-fold decrease in AR binding capacity constant and a 4-fold reduction in AR protein expression [103].

Retinoids at pharmacological doses increase plasma triglycerides and induce overt hypertriglyceridemia in more than 20 % of the patients [104–106]. Hepatic very low density lipoprotein (VLDL) production is facilitated by *microsomal triglyceride transfer protein* (MTP) in a rate-limiting step that is regulated by insulin. FoxO1 plays a key role in hepatic insulin signaling. In HepG2 cells, MTP expression was induced by FoxO1 and inhibited by exposure to insulin. This effect correlated with the ability of FoxO1 to bind and stimulate MTP promoter activity. Mice that expressed a constitutively active FoxO1 transgene revealed enhanced MTP expression, augmented VLDL production and elevated plasma triglyceride levels [107]. These data suggest that FoxO1 mediates insulin regulation of MTP expression and augmented MTP levels appear to be a causative factor for VLDL overproduction and hypertriglyceridemia [107]. Hepatic VLDL production is suppressed in response to increased insulin release after meals. Thus, insulin acts via PI3K/Akt activation and reduces nuclear levels of FoxO1 [108].

There is a second mechanism of retinoid-induced hypertriglyceridemia underlining the regulatory role of FoxO1. Retinoids increase the expression of *apolipoprotein C-III*, an antagonist of plasma triglyceride catabolism as apo C-III functions as an inhibitor of lipoprotein lipase and hepatic lipase [109–111]. Isotretinoin treatment in men (80 mg/d; 5 d) resulted in elevated plasma levels of apo C-III [112]. In HepG2 cells, retinoids increased apo C-III mRNA and apo C-III-protein production. Recent evidence links apo C-III expression to FoxO1 regulation, as FoxO1 stimulated hepatic apo C-III expression and correlated with the ability of FoxO1 to bind to the apo C-III promoter. Deletion or mutation of the FoxO1 binding site abolished insulin response and FoxO1-mediated stimulation [113].Thus, elevated FoxO1 production in liver augmented hepatic apo C-III expression [113].

From these data it can be deduced that isotretinoin or its isomerized derivatives induce the expression of FoxO1 in hepatocytes explaining retinoid-induced hypertriglyceridemia. Accumulated evidence supports the view that retinoids exert their beneficial therapeutic effects in acne by upregulation of nuclear FoxO1 thereby down-regulating increased AR-mediated signal transduction, down-regulating infundibular keratinocyte hyperproliferation (comedogenesis), suppressing increased sebaceous lipogenesis and reducing increased TLR2 signaling (inflammation), the major pathogenic events in acne.

## Conclusion and perspectives

All major steps in the pathogenesis of acne, i. e., increased AR-mediated signaling, cell proliferation of androgen-dependent infundibular keratinocytes, increased AR- and PPARγ-dependent sebaceous lipogenesis, upregulation of TLR2 signaling with local activation of the innate and adaptive immune responses, insulin resistance of puberty, the therapeutic effect of retinoids, retinoid-induced hypertriglyceridemia, the effectiveness of retinoids and antibiotics via reduction of TLR2-stimulation are all integrated at the activity level of PI3K/Akt, which finally determines the activity and localization of the nuclear transcription factor FoxO1.

Thus, all growth factors or acneigenic stimuli mimicking growth factor signaling might have a common denominator, the reduction of the nuclear content of FoxO1. Growth factor-mediated release of FoxO1 from "acne target genes" and nuclear receptors, especially AR, might be the fundamental mechanisms in acne pathogenesis. All measures, which elevate the nuclear content of FoxO1, especially retinoid treatment, reduction of *P. acnes*-mediated TLR2 stimulation by antibiotics, dietary intervention with reduction of insulinotropic food will most likely have beneficial counterregulatory effects on acne.

Remarkably, the proposed *growth factor-PI3K/Akt-FoxO1 acne pathway* is the well-known *oncogenic pathway*, which might explain the epidemiologic association between long-lasting acne and prostate carcinoma [114]. Chronically upregulated PI3K/Akt might explain the increased incidence of cancer in patients with acne-associated diseases like acromegaly [115], PCOS [116, 117], Apert syndrome [118–120] and dioxin intoxication. In this regard, persistent acne in adulthood should be recognized as an important clinical indicator of dysbalanced growth factor signaling with insufficient levels of nuclear FoxO1, an unfavorable condition which increases mitogenic stimulation and cell survival but reduces apoptosis, well-recognized processes in cancer promotion [121, 122].

Acne, certainly a disease with a genetic background, is among other factors induced by environmental growth factors in industrialized countries due to growth factor-mediated imbalances of the key transcription factor FoxO1. Acne pathogenesis is linked to multiple systemic and environmental risk factors demonstrating that acne is not just a simple skin disease. The presented concept of a *nuclear FoxO1 deficiency* explains and links for the first time major pathogenic factors of acne at the genomic level. These insights could improve our understanding of retinoid action in dermatology and may provide novel therapeutic strategies in the treatment of acne and other hyperproliferative skin disorders based on upregulation of nuclear levels of FoxO1. <<<

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