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Research Article

Metformin: A Promising Outlook in Treatment of Acne Vulgaris

Azadi A[1,2*], Forouzani-Haghighi B[1,2], Dorvash M R[1,2]

[1]*Pharmaceutical Sciences Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.*
[2]*Department of Pharmaceutics, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.*

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ABSTRACT
Acne vulgaris is a common skin disorder in civilized countries that their diet consists of high glycemic load and high amount of dairy proteins**.** Recent studies have shown that this disease is derived from express of mTORC1 (the mammalian target of rapamycin) which also leads to increased body mass index (BMI) and Insulin resistance. mTORC1 complex, which is significantly increased in the skin of acne patients, is the mammalian target of rapamycin. We hypothesized that acne vulgaris can be treated by any drug that is able to suppress mTORC1 complex. Acne pathogenesis is mediated through mTORC1 over activation, so metformin may relieve acne symptoms by AMPK (5' adenosine monophosphate-activated protein kinase) dependent suppression of mTORC1. Actually, by applying a topical form of this drug on acne spots, mTORC1 over activation in skin cells can be inhibited which leads to disappear of acne spots.

Keywords: Acne vulgaris, mTORC1, Metformin

INTRODUCTION

Acne vulgaris is a common skin disorder in civilized countries that their diet consists of high glycemic load and high amount of dairy proteins[1], which is a result of increased sebum production, bacterial colonization and altered keratinization[2]. It has been claimed that there is a link between the pathogenesis of acne and the endocrine signaling, which is influenced by the diet[3]. Recent studies have shown that this disease is derived from over expression of mTORC1 (the mammalian target of rapamycin) which also leads to increased body mass index (BMI) and Insulin resistance (IR). Hyperglycemic carbohydrates and insulinotropic milk/dairy products both lead to increased IGF-1 (inslulinlike-growth-factor1) signaling[4]. One of the most important transcription factors, named FoxO1 (Forkhead box protein O1), has a key role in modulating the expression of the genes which are responsible for controlling the cell cycle, apoptosis, DNA damage and repair, oxidative stress management, glucose and lipid metabolism, inflammation, etc. Generally, it senses the external nutrient and internal growth factors (IGFs) and manages the body metabolism via regulating the FoxO1-dependent gene expression. FoxO1 also suppresses the lipid metabolism by antagonizing the expression of SREBP-1c (Sterol regulatory element-binding protein 1) which leads to decreased sized sebaceous glands (SGs) and mitigated skin inflammation. It has been reported that reduced IGF-1 serum level during acne treatment via isotretinoin is mediated by the inhibition of hepatic GHR (growth hormone receptor) expression by FoxO1 which leads to decreased hepatic IGF-1 synthesis. So, FoxO1 has a key role in linking the diet to acne pathogenesis. Sebaceous glands activity and acne proliferation depend on androgens serum level. IGF-1 stimulates gonadal and adrenal androgen synthesis as well as intracutaneous intracrine conversion of testosterone to tenfold more active dihydrotestosterone (DHT). Diet increases hepatic IGF-1 synthesis that may result in increasing endogens in the skin. The high IIS (increased insulin secretion) which is mediated by the diet will result in the suppression of FoxO1. Both AR (androgen receptor) and IIS synergistically increase SREBP-1-mediated lipogenesis and up-regulate lipogenic pathways and will cause the development of acne. There are two functionally different complexes of mTOR (mammalian target of rapamycin) in mammalian cells, mTORC1 which is responsive to rapamycin and mTORC2 which is non-responsive to rapamycin. The mTORC1 signaling network senses and relays diverse inputs of nutrients, growth factors and cellular energy to a central 'signaling core' that consists of Akt (Protein kinase B (PKB)), TSC1/TSC2 (the tumor-suppressor genes), Rheb (Ras homolog enriched in brain) and mTORC1 itself. Liver kinase B_1 and AMP-activated-protein kinase (AMPK), regulate mTORC1 expression[5].

Seborrhea and SG (sebaceous gland) hyperplasia are produced by Increased SG lipid biosynthesis. The key transcription factor of lipid bio synthesis is SREBP-1 which is depended on mTORC1 activation. So, the over activation of mTORC1 will result in acne producing. $FoxO_1$ act as mTORC1 inhibitor and regulates the activity of mTORC1 and Akt. It activates AMPK by inducing the expression of sestrin-3 which leads to the inhibition of mTORC1. TSC1/TSC2 complex is dissociated by the Akt-phosphorylated cytoplasmic FoxO1, so the FoxO1 complex will be inhibited, but it directly activates mTORC1 which leads to increased protein, lipid synthesis and insulin resistance that all will result in producing acne

**Author for Correspondence:*

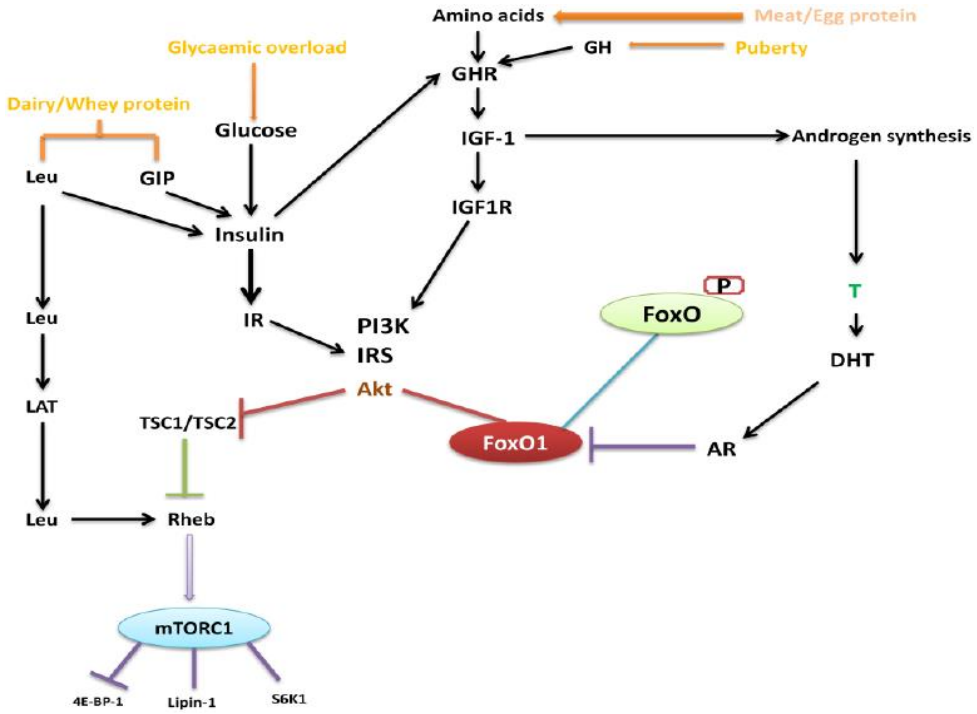

Figure 1: Leu (leucine); LAT (L-type amino acid transporter); 4E-BP-1 ((eIF4E-binding protein); S6K (Ribosomal protein S6 kinase); IR (insulin resistance); PI3K (Phosphoinositide 3-kinase); IRS (insulin receptor substrate); GH (growth hormone); DHT(Dihydrotestosterone); AR (androgen receptor).

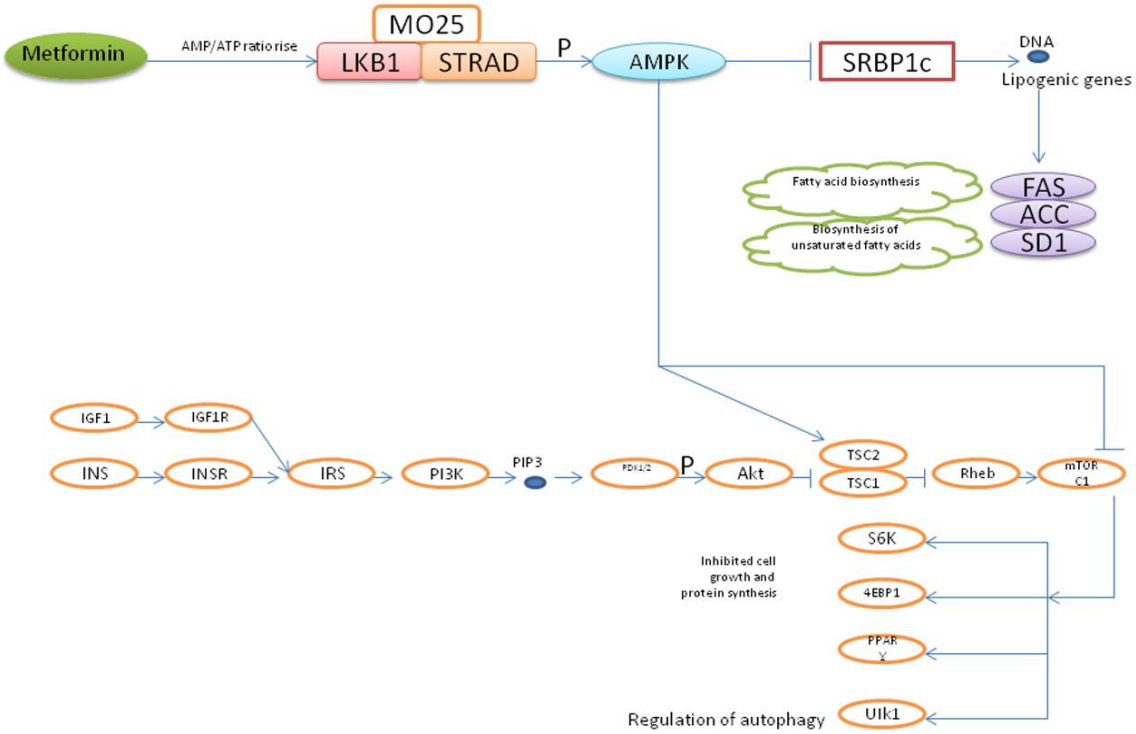

Figure 2: MO25 (master regulator of SPAK/OSR1 and MST3/MST4/YSK1 protein); LKB1 (liver kinase B1) ;FAS(an important cell surface receptor protein of the TNF receptor family known also as CD95, that induces apoptosis) ; STRAD (ste20 related kinase) ; ACC (acetylCoA carboxylase) ;SCD1(*Stearoyl-CoA desaturase-1)* ;IGF(insulin like growth factor) ; IGFR(insulin like growth factor receptor) ; INS(insulin) ; INSR (insulin receptor) ; IRS(insulin receptor substrate) PI3K (Phosphoinositide 3-kinase) ; PIP3(Phosphatidylinositol (3,4,5)-trisphosphate) ; PDK1/2 (Phosphoinositide-dependent kinase1/2) ;S6K(Ribosomal protein S6 kinase beta-1) ; 4EBP1 (eIF4E-binding protein 1); PPAR-Ɣ (Peroxisome Proliferator-Activated Receptor Gamma) ;ULK1 (Serine/threonine-protein kinase involved in autophagy in response to starvation).

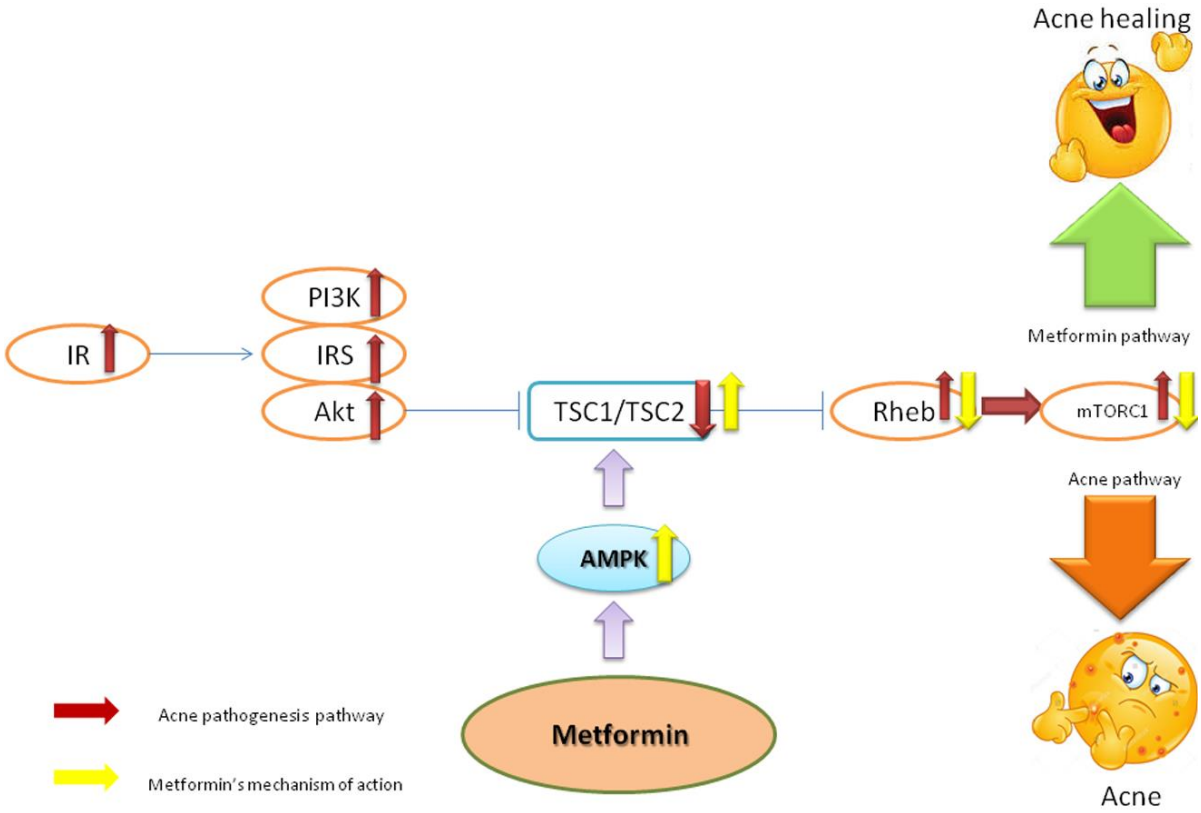

Figure 3: Schematic view of our hypothesis.

on skin[6]. The signaling pattern which is shown in Fig. 1 summarizes the acne pathogenesis.

Hypothesis

mTORC1 complex, which is significantly increased in the skin of acne patients, is the mammalian target of rapamycin. We hypothesized that acne vulgaris can be treated by any drug that is able to suppress mTORC1 complex. Recent studies have shown that metformin can be the best choice for mTORC1 suppression in acne patients. It is a biguanide that can increase cells' sensitivity to insulin and decrease insulin resistance[7] which has a key role in mTORC1 activation and pathogenesis of acne[8].

Evaluation of hypothesis

Metformin suppresses mTORC1 activity via AMPK pathway. AMPK is a cellular energy homeostasis regulator which senses ATP (adenosine triphosphate) cellular level and its activation can regenerate cellular ATP supplies. So, it suppresses ATP consuming activities such as gluconeogenesis, protein and lipid synthesis and regulates activities such as autophagy and fatty acid oxidation which can improve cellular ATP level. In fact it tries to decrease AMP (adenosine monophosphate)-ATP ratio in cells. Metformin signaling pathway is shown in Fig. 2. AMPK is able to suppress mTORC1 in two ways: directly or indirectly (by the activation of TSC1/TSC2 which will result in inhibition of Rheb so, mTORC1 can't be activated any more)[9]. As we discussed before, acne pathogenesis is mediated through mTORC1 over activation, so metformin may relieve acne symptoms by AMPK dependent suppression of mTORC1.

CONCLUSION

Many studies show that acne vulgaris is mediated by insulinotropic diet which leads to over expression of mTORC1 and suppression of FoxO1 regulating genes. So, this disease is supposed to be treated by mTORC1 suppression or FoxO1 activation (Fig. 3). Metformin can be a drug of choice for this condition. Actually by applying a topical form as a conditional or a novel drug delivery system[10-15] of this drug on acne spots, mTORC1 over activation in skin cells can be inhibited which leads to disappearance of acne spots.

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