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THE DEVELOPING LINK OF METABOLIC GROWTH FACTORS IN INSULIN RESISTANCE

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ABSTRACT

Obesity has become a major problem in public health over the past few years. It is strongly associated with insulin resistance, the central pathological process in many metabolic disorders. Now it is generally acknowledged that adipose tissue plays a vital role in the obesity-induced insulin resistance as an active endocrine organ. Many "classic" adipokines such as TNF-α, IL-6, adiponectin, and leptin have been studied extensively but recently many novel metabolic regulators which belong to growth factor family, such as FGF21, VEGF, TGF-β superfamily, have gained much attention. While some of these growth factors have showed greater promise in palliating insulin resistance and type 2 diabetes mellitus (T2DM), the role of others' remains obscure or shrouded in mystery due to their pleiotropic nature. Plethora of research has been reported to trace their role in insulin-resistance in peripheral insulin-responsive tissues, like adipose tissue and skeletal muscle. In this review we attempted to analyze the role of various growth factors in insulin resistance as a result of mutual cross-talk between metabolic tissues.

Key words: Obesity, Insulin resistance, Adipokines, Growth factors

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INTRODUCTION

Obesity has a well-established role in numerous metabolic and non-metabolic diseases and now it is becoming a major problem in public health causing measureable increase in the morbidity and mortality of world's population. According to the global health statistics in recent past, 937 million people were found to be overweight that which is about 23.2% of the world's adult population while 396 million people were shown to be obese that makes around 9.8% of adult community. The same global statistics projected that the number will be 1.12 for obese and 2.16 billion for overweight subjects **[1]**. Obesity is considered as a major contributing factor for

cardiovascular diseases, metabolism syndrome (MS) and type 2 diabetes mellitus (T2DM) **[2, 3]**.

Over the past few years, the concept about adipose tissue for energy storage function is evolved and now it is well acknowledged that adipose tissue has a substantial involvement in body metabolism as a mobile endocrine tissue **[4]**. Moreover adipokines which are secreted from adipose tissues are off-balance in obesity **[5]**. As Dietze D et al **[6]** found that the co-culture between adipocytes and skeletal muscle cells can block the insulin induce signal transduction in skeletal muscle; the obesity induced insulin resistance is vitalized in key metabolic organs e.g. white adipose tissue (WAT), liver and skeletal muscle **[7]**. Various adipokines and cytokines have been studied extensively **[8]** and novel metabolic mediators (MCP-1, chemerin, DPP-4, endocannabinoids, HSP60) have shown to play their role in insulin resistance recently **[9-12]**.

Growth factors like nerve growth factor (NGF), insulin-like growth factor (IGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and transforming growth factor (TGF), are having key involvements in different cell functions like development, proliferation and differentiation. These all have showed to play a part in energy metabolism. This article is primarily concentrated on the influence of specific growth factors like VEGF, FGF21 and TGF-β superfamily in the development of obesity-associated insulin resistance in peripheral insulin-responsive tissues (skeletal muscle and adipocytes).

FIBROBLAST GROWTH FACTOR 21(FGF21)

Cytokines such as adiponectin, leptin and resistin possess prominent involvement in the regulation of energy metabolism and cellular homeostasis. In addition to these, some newer metabolic regulators have been discovered periodically which comprise fibroblast growth factor 21 (FGF21). Conventional FGFs encompass heparin-binding domain in their structure which is a characteristic of this family **[13, 14]**, but FGF21 lack this domain and hence considered different FGF family member. This unique structural feature gives FGF21 hormone-like actions unlike other FGFs. it is present abundantly in liver, white adipose tissue (WAT), and pancreas **[15, 16]**. Under normal circumstances, FGF21 synthesis and secretion is induced in the WAT by feeding and in liver by prolonged fasting. Though dominant source of it is liver **[15, 17]**.

FGF21 Levels are interestingly related to diseases like NAFLD, cardiovascular disease, metabolic syndrome and diabetes **[18-20]**, and correlated with body mass index (BMI) **[18, 21]**, serum leptin and insulin levels **[21, 22]**, liver and systemic insulin resistance, and lipid disturbances **[23, 24]**. These results suggest that obesity is a FGF21-resistant state and this has been verified by at least two independent animal studies **[25, 26]**. Conclusively these reports imply that there is association between elevated FGF21 levels and metabolic abnormalities.

Kharitonenkov et al **[27]** initially reported the involvement of FGF21 in the regulation of metabolism regulation. Their studies showed that glucose uptake can be stimulated by FGF21 in mouse. During *in vivo* studies FGF21-transgenic mice raised the human protein i.e. fibroblast growth factor 21 from the liver. This protein was found to improve insulin sensitivity and raise glucose tolerance. Administration of recombinant FGF21 in various rodent models was studies, like diet-induced obese (DIO) mice, db/db mice, ob/ob mice, and Zucker diabetic fatty (ZDF) rats, that have affirmed its usefulness in obesity induced T2DM in relation with the phenotypes of FGF21-transgenic mice **[28, 29]**. FGF21-KO has also showed to regulate

the insulin-sensitizing effect of rosiglitazone **[30]**. Similarly in LIRKO mice FGF21 administration reversed hyperglycemia in these diabetic animals **[31]**. FGF21 is directly involved in glucose uptake, cell metabolism, and inducing fatty acid oxidation, improving insulin sensitivity in liver and other fatty tissues **[32, 33]**. In rodent models, Atg7 (encoding autophagy-related 7) gene knockout mice promoted the FGF21 expression which exhibited prevention of diet-induced obesity and ameliorated the autophagy deficiency in the liver and insulin resistance in mice **[34]**. The author concluded that FGF21 provides shield from development of insulin resistance and diet-induced obesity. Camporez et al **[35, 36]** confirmed that FGF21 intake can spare mice from insulin resistance associated with decreased myocellular diacylglycerol level and reduced protein kinase Cθ activation. Similar results were found in humans by Mashili et al **[37]** who discovered that FGF21 affects the glucose uptake in human skeletal muscle. Evidences were also found that FGF21 can prevent palmitic acid-induced insulin resistance by inhibiting the activation of NF-κB **[38]**. The actions of FGF21 are blocked in adiponectin knockout mice. These effects include diminution in impaired insulin signaling in skeletal muscles caused by obesity and also prevention of obesity-associated insulin resistance, atypical elevations in glucose and triglycerides. FGF21 treatment in rodents showed increase in adiponectin level and increased the serum levels, which may suggest that is involved in the downstream signaling of FGF21 **[39, 40]**. It can also be suspected that FGF21 may be vital in the cross-talk between the skeletal muscle and the adipose tissue **[41]**.

Although FGF21 is believed to act on key metabolic organs but studies have exhibited that it can also act on brain via blood-brain barrier (BBB) **[42]**. It requires further studies to fully comprehend the spectrum of potential and its mechanisms of actions.

VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)

The effects of vascular endothelial growth factor (VEGF) family on metabolism remained unknown **[43, 44]**. Much of the clinical data support the correlation of VEGF and obesity **[45, 46]**. Levels of VEGF are also positively correlate with with serum insulin level **[47]**. However few of the data also suggests the expression of VEGF and its receptors in metabolic tissues **[48, 49]**. Bosch and colleagues **[43]** found the protective effects of VEGF in adipose tissue. Similar results were received from mice with doxycycline-inducible overproduction of VEGF model, and these are in line with the results from adipose-tissue specific VEGF deleted ($VEGF^{Ad\triangle}$) mice, exhibiting hypoxia, decreased adipose vasculature, inflammation and insulin resistance **[50, 51]**. However, Lu et al. **[52]** found paradoxical actions of VEGF-A in regard that suppression of VEGF-A, along with elevation in VEGF-B, causes the protection against development of high fat diet-induced obesity. The complexity of VGEF signaling system is verified by the similar results in both repression and overexpression of VEGF-A.

Bonner et al **[53]** argued that VEGF deletion in transgenic mice in skeletal muscles generates about 40-45% less glucose uptake by skeletal muscle which is quite significant. Whole-body glucose disposal, stimulated by insulin, was also found to be reduced up to 45%. Inhibition of VEGF-B signaling in mice, both genetic and pharmacological, have exhibited to raise the muscle glucose uptake, improve peripheral insulin sensitivity and reduce ectopic lipid accumulation **[44]**.

Taken together, these findings validate the crucial role of VEGF system in the energy metabolism and highlight a new approach which

targets VEGF to treat obesity-associated metabolic dysfunction.

TRANSFORMING GROWTH FACTOR-B (TGF-B) SUPERFAMILY

The transforming growth factor-β (TGF-β) superfamily is composed of over 30 family members which play key part in proliferation, differentiation, and apoptosis **[54]**. Drugs against TGF-β family have been playing an important role in human ailments, especially in cancer tratement **[55]**, however, recent studies hint an rising role in modulation of metabolism and energy expenditure **[56, 57]**. In this part of review, we have focused on TGF-β, myostatin and activins for their participation in diabetic disease.

Transforming Growth Factor -β

The TGF-β subfamily is composed of TGF-β1, TGF-β2, TGF-β3 and their action is mediated via single receptor signaling pathways. TGF-β signals are primarily facilitated by Smad3 **[58]**. Interestingly TGF-β levels are linked obesity in humans **[59]**, mathed with animal studies as well **[60]**. TGF-β levels were also increased in insulin-resistant adipose tissue **[61, 62]**; and correlation was also found with BMI, leptin levels and obesity in hypertensive individuals **[63]**.

Lin HM et al **[64]** has showed TGF-β/Smad3 pathway as important regulator of insulin gene transcription and beta-cell function. In other experiments Smad3-deficiency raised glucose uptake in White Adipose Tissues, and blocked HFD diet induced obesity and insulin resistance **[65, 66]**. This phenomenon is accompained with the low expressions of PPARγ2, which promotes lipid storage **[67]**. Although, in comparison to skeletal muscles adipose tissue is not a considerable consumer of energy **[68]**. Similarly Smad signaling is enhanced in insulin resistant skeletal muscle in obese individuals **[69]**. Except TGF-β family, another key regulator myostatin also play a vital role in enegry homeostasis **[70, 71]**.

Myostatin

Myostatin is a growth factor secreted from skeletal muscle and adipose tissue **[72]**. Myostatin is known as a negative modulator of skeletal muscle progression **[73]**. It is also acknowledged that myostatin serves as a link between skeletal muscle and adipose tissue **[74]**. The actions of Myostatin in muscle are well acknowledged. Mstn-deficient mice exhibited raised GLUT1 and GLUT4 levels in skeletal muscle **[71]** and resulted in a maintaining normal energy metabolism **[75, 76]**. It can also enhance the levels of adiponectin which is a vital regulator of energy **[77, 78]**. This also implies that skeletal muscles and adipose tissues are well connected **[79]**. In 3T3-L1 adipocytes, myostatin suppressed the pre-adipocyte differentiation and modulate the lipid metabolism of full grown adipocytes **[80]**. Feldman et al **[81]** studied the actions of Mstn in transgenic mice and cell culture. Moreover, obese mice exhibited the up-regulated expression of Mstn, which indicates that the response of adipocytes to obesity is potentially mediated by Mstn **[82]**. The results above implied that generation of adipocytes with favorable metabolic effects by adipogenesis can be modulated by myostatin **[83]**. As Myostatin is robustly expressed in skeletal muscle, it needs more investigation to clarify the complex but potential mechanisms of actions of Myostatin.

Activin

Activins is a part of TGF-β subfamily and is highly expressed in adipose tissue **[84]**. Activins acts via activation of trans-membrane receptors with serine/threonine kinase activity. The biological effects are exerted through Smad **[85]**. Activin is in turn modulated by follistatin (FST), which is a established adipokine important for adipogenesis **[86]**, and follistatin like-3(FSTL-3) **[87]**.

They are known to stimulate the release of follicle from the pituitary **[88]**. In recent years, many additional functions including modulating growth, survival **[89]**, inflammation **[90]**, immunity, and cancer **[91]** have been put forward. Researchers have converged their focus on activins as vital modulators of metabolic disorders **[92]**. Activins levels are, interestingly, elevated in adipose tissue of obese patients **[93, 94]** and positively associated with insulin resistance(HOMA-IR) **[95]**. As FSTL-3 is a physiological activin antagonist, it reveals that activin have key roles in enhancing insulin resistance **[96]**. Further, activin can increase hepatocyte insulin response by upregulating insulin signaling and increasing glucose uptake **[97]**. Both human **[98]** and murine adipose tissue **[99]** show high expression of INHBB, a gene that code for it. In 3T3-L1 adipocytes, recombinant activin B was found to intracellular triglyceride content and decrease lipolysis **[100]**. There are certain other studies which have found a negative correlation between activin and whole-body glucose homeostasis **[101]**.

CONCLUSION

It is paluasible to conclude that above stated growth factors play a vital role in energy homeostatsis and various metabolic states in the body. But despite of all details the nature of action they exert on metabolic system is not clarified yet. Further research is required in this direction to elucidate the exact mechanism.

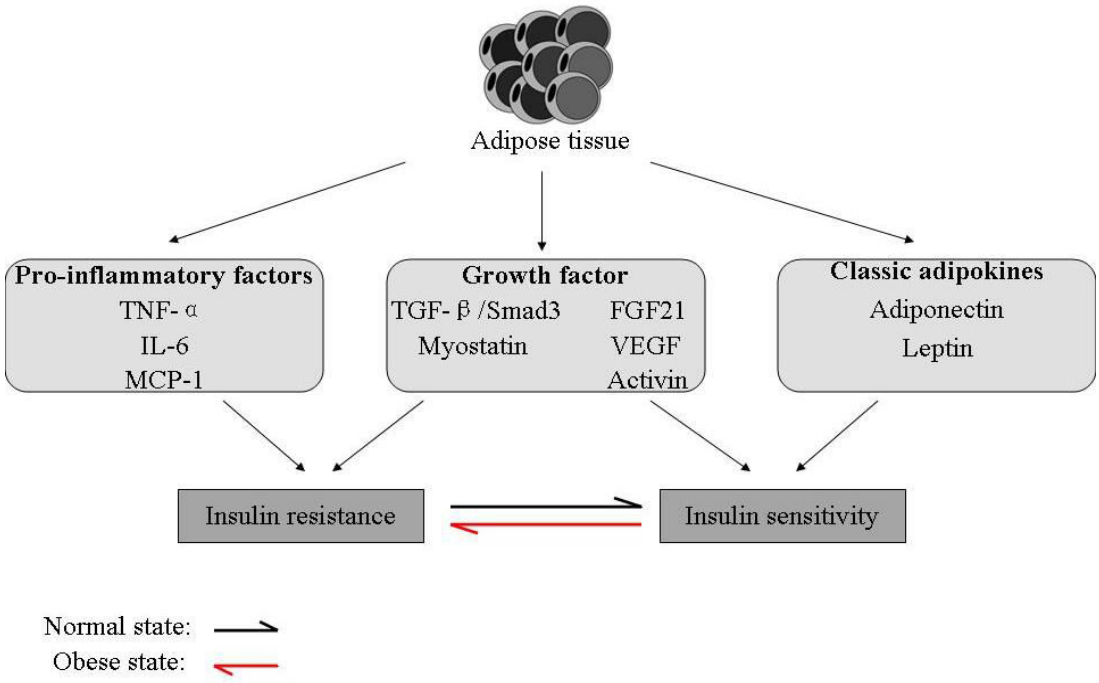

Figure 1: Figure analyzes the summary of actions of growth factors (FGF21, TGF-β, and VEGF) on insulin resistance and insulin sensitivity.

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