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The Kruppel-like Factor Family, Adipose Tissue Metabolism and Related Diseases

Kemal Yuce[1*] and Ahmet Ismail Ozkan[2]

[1]*Department of Basic Medical Sciences, Selcuk University, Konya, Turkiye*

[2]*Department of Basic Medical Sciences, Artvin Coruh University, Artvin, Turkiye*

[*]**Corresponding author:** Kemal Yuce, Department of Basic Medical Sciences, Selcuk University, Konya, Turkiye, E-mail: yuce2020@hotmail.com

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Abstract

Obesity, diabetes, and cardiomyopathy are the leading causes of death in the world. Therefore, the genetic and transcriptional processes that influence these disease processes are important. Klfs are a transcription factor family with 3 Cysteine2Histidine2 zinc finger proteins and 18 members. Proadipogenic Klfs are Klf4, Klf5, Klf14, and Klf15, while antiadipogenic Klfs are Klf2, Klf3, Klf7, Klf10, and Klf16. Klfs directly associated with diabetes are Klf4, Klf5, Klf7, Klf11, and Klf15. Klfs directly associated with cardiomyopathy are Klf4 and Klf5. The purpose of this review is to shed light on the connections between Klfs and diabetes, obesity, cardiomyopathy, and adipose tissue metabolism.

Keywords: The Kruppel-like factor family; Obesity; Diabetes; Cardiomyopathy

Introduction

The Kruppel-Like Factor (KLF) family is an 18-member family of transcription factors. Klfs associated with adipose tissue and glucose metabolism are Klf2, Klf3, Klf4, Klf5, Klf6, Klf7, Klf9, Klf10, Klf11, Klf14, Klf15, and Klf16. Key players in the transcription network that regulates obesity, adipocyte differentiation, and adipogenesis have been identified as these [1,2]. Klf4, Klf5, Klf14, and Klf15 have been defined as proadipogenic, while Klf2, Klf3, Klf7, Klf10, and Klf16 have been defined as antiadipogenic [3]. Obesity, a worldwide epidemic, is characterized by an excess of adipocytes in both quantity and size. A significant risk factor for the onset of type II diabetes, hypertension, and cardiovascular disease is obesity. Dysregulation of the processes governing the expression of genes linked to metabolism and endocrine function in adipocytes is a result of obesity and associated diseases [4]. The purpose of this review is to shed light on the connections between KLFs and diabetes, obesity, cardiomyopathy, and adipose tissue metabolism.

Relationship of Klfs with Adipogenesis

The expression of Klf3 was reduced at all stages of adipogenic differentiation. Klf3 directly inhibited the expression of the C/EBPα gene by combining with C-terminal Binding Protein (CtBP), thus regulating adipogenic differentiation [5]. Adipose tissue growth is the cause of obesity, which leads to metabolic problems. *Garcinia cambogia* (*G. cambogia*), used for anti-obesity purposes and as a supplement, reduces high-fat diet-induced obesity by suppressing adipocyte size and inguinal subcutaneous and epididymal white adipose tissue mass in an obese animal model. The expression of CEBPB, an important adipogenic factor, was attenuated by *G. cambogia,* and its transcription was suppressed in differentiated cells.

The expression of Klf3, a negative regulator of adipogenesis, was significantly increased by *G. cambogia*. Increased Klf3 interacted with C Terminal Binding Protein (CTBP2) to form a transcriptional suppressor complex and inhibited the transcription of Cebpa and Pparg [6]. One of the most fundamental regulators of adipogenesis is Klf4. Klf4 knockdown suppresses adipogenesis and lowers C/EBPbeta levels. In conjunction with *Krox20*, Klf4 cooperatively transactivates a C/EBPbeta reporter and directly attaches to the C/EBPbeta (Cebpb) promoter. Knockdown of C/EBPbeta raises levels of *Krox20* and Klf4, indicating that CCAAT/Enhancer Binding Protein beta (C/EBPbeta) normally represses Klf4 and *Krox20* synthesis through a strictly regulated negative feedback. Klf4 is selectively activated in response to cyclic Adenosine Monophosphate (cAMP), which on its own can partially induce adipogenesis [7]. In adipose tissue, Klf5 expression was shown to be stimulated in the early stages of differentiation of preadipocyte cell lines. In the 3T3-L1 cell line, insulin-induced differentiation is inhibited by expression of the dominant negative form of Klf5, but overexpression of Klf5 promotes differentiation into adipocytes without the need for hormones. *In vivo* studies in which heterozygously suppressed mice exhibit reduced formation of mature adipose tissue due to reduced differentiation support this observation [8]. In the preadipocyte differentiation model, Klf9 expression was found to increase greatly with adipogenic induction. Expression of the adipogenic gene Adaptor Protein-2 (AP2) was downregulated in overexpression of Klf9, and consequently, triglyceride accumulation was impaired. Knockdown of Klf9 increased the expression of CCAAT Enhancer-Binding Protein Alpha (CEBPA), Peroxisome Proliferator-Activated Receptor Gamma (PPARG), and AP2 in intramuscular preadipocytes. Therefore, the present study suggested that Klf9 may regulate adipogenesis through the long noncoding RNAs (lncRNAs) [9]. During 3T3-L1 preadipocyte development, there was an increase in the expression of the glycoprotein Clusterin (CLU). The

CLU encouraged preadipocytes to differentiate into adipocytes. CLU increased mRNA levels of adipogenic indicators such as CCAAT enhancer binding protein α (Cebpa) and Peroxisome proliferator-activated receptor γ (Pparg). Conversely, knockdown of CLU decreased transcript levels of Cebpa and Pparg and attenuated adipogenesis. The cycloheximide follow-up experiment showed that the increased Klf5 level with CLU overexpression was due to reduced degradation of Klf5 protein. Overexpression of CLU increased the protein level of Klf5, an upstream transcription factor of Cebpa and Pparg involved in adipogenic development, but variations in the degree of CLU expression did not affect the mRNA level of Klf5 [10]. Adipocyte differentiation was found to be promoted by miR-324-5p. In a study aimed at the mechanism of this, miR-324-5p agomiR was injected into obese mice *in vivo* and found that adipogenic-related gene expression level, body weight, and adipocyte area were notably increased, but lipolytic genes were decreased. It was discovered that the underlying mechanism of this was that miR-324-5p agomiR directly stimulated Klf3 [11]. Klf7 expression was found to change during the differentiation of predadipocytes into adipocytes. Suppression of Klf7 formation reduced the synthesis of adipogenic markers in intramuscular and subcutaneous adipocytes and repressed lipid droplets. This shows that Klf7 may be a new regulator during adipogenesis [12].

Relationship of Klds with Fatty Acid and Glucose Metabolism

It is believed that Retinoid X Receptor α (RXRα) plays a crucial role in controlling gene expression, inflammatory response, lipid and glucose metabolism, and adipogenic differentiation. Intramuscularly, adenovirus-induced overexpression of RXRα promoted lipid accumulation and upregulated the expression of positive marker genes (PPARc and GLUT4). The positive effect of RXRα was found to be mediated by Klf8 [13]. Following platycodin D treatment, the expression levels of genes related to lipid metabolism, including lipoprotein lipase and fatty acid binding protein 4, were markedly reduced. A decrease in PPARγ expression and its binding to the target DNA sequence was seen upon treatment with Platycodin D. siRNA dramatically enhanced PPARy expression and binding to its target sequence by suppressing Klf2 overexpression. The anti-adipogenic effect of Platycodin D was stated to involve upregulation of Klf2, followed by downregulation of PPARγ [14]. It was found that Klf15 could stimulate adipocyte maturation and GLUT4 expression. Klf2/LKLF was confirmed to be a negative regulator of adipocyte differentiation. Mature adipocytes did not express Klf2, but preadipocytes did. Overexpression of Klf2 inhibited Peroxisome Proliferator-Activated Receptor (PPAR), but Klf15 did not elicit such an effect. In addition, Klf2 was shown to directly inhibit PPAR 2 promoter activity [15]. Klf3 and CtBP2 were shown to be directly stimulated by miR-144-3p. Suppression of CtBP2 and Klf3 by miR-144-3p was also confirmed by protein expression and mRNA. Adipocyte lipid accumulation was increased and adipogenesis was positively controlled by miR-144-3p overexpression [16,17]. Klf15 was found to play a role in regulating fuel exchange between fatty acids and glucose in response to energy status changes in brown adipose tissue. Fasting increased the expression of Pdk4, Klf15, and genes involved in fatty acid utilization in brown adipose tissue, while refeeding suppressed Klf15 and Pdk4 expression. Expression of the pyruvate dehydrogenase kinase 4 gene was increased or decreased, respectively, by overexpression or knockdown of Klf15 in differentiated brown HB2 cells [18].

The Relationship of Klfs with Obesity

Obesity is a serious public health issue that is linked to several illnesses, including diabetes and arteriosclerosis. Therefore, it is crucial to comprehend the processes that govern the differentiation and function of adipose tissue [15]. Research has shown that renal Klf4 is crucial in the fight against obesity-related nephropathy and that in chronic kidney disorders, Klf4 and mitochondrial function contribute to energy homeostasis. Overexpressed Klf4 alleviated diet-induced renal dysfunction, abnormal structural remodeling, and inflammation. When mouse endothelium cells were exposed to palmitic acid, the overexpression of renal Klf4 reduced the inflammatory response. Diet-induced renal impairment, including elevated creatinine and blood urea nitrogen levels, was positively linked with decreased renal Klf4 levels [19]. Transcriptional activation of Klf15 on PPARγ can be inhibited by Diallyl Trisulfate (DATS). This inhibition occurs by preventing Klf15 from binding to PPARγ. DATS was found to significantly decrease lipid accumulation and renew dysregulated metabolism *in vivo* by restricting lipogenesis and adipogenesis and promoting fatty acid oxidation and lipolysis in white adipose tissue. DATS inhibits lipogenesis and adipogenesis, particularly in the late stage, which reduces the buildup of lipids. Klf15 was found to be knocked down in 3T3-L1 cells, abolishing the inhibitory effect of DATS on lipogenesis and adipogenesis. Through controlling Klf15's transcriptional activation effect on PPARγ, DATS reduces obesity [20]. In obese patients, CD4+T cells regulate metabolism and inflammation. An imbalance in CD4+T regulatory cells (Tregs) is essential for the emergence of insulin resistance and diabetes. A tendency towards insulin resistance, fatty liver, and obesity was determined in a mouse model in which CD4+T cell-specific Klf10 was suppressed. This was attributed to damage to the passage of CD4+T cells to adipose tissue and liver and decreased secretion of Tissue Growth Factor (TGF) beta3. In normal mice, healthy transfer of CD4+ Tregs to relevant tissues completely prevented fatty liver, obesity, and insulin resistance [21]. Klf5 (+/-) mice were found to be more resistant to glucose intolerance, hypercholesterolemia, and high-fat-induced obesity than normal mice. This may be due to increased energy expenditure because the expression of genes involved in energy expenditure and lipid oxidation, including genes encoding Uncoupling protein 2 (Ucp2), Ucp3, and Carnitine palmitoyltransferase-1b (Cpt1b), was upregulated in the soleus muscles of Klf5 (+/-) mice. Klf5 was desumoylated and linked to transcriptional activation complexes that included both CREB-Binding Protein (CBP) and liganded Peroxisome Proliferator-Activated Receptor delta (PPAR-delta) in response to agonist stimulation of PPAR-delta. Ucp3, Cpt1b, and Ucp2 were all more highly expressed as a result of this activation complex [22].

Relationship of Klfs with Diabetes and Cardiomyopathy

One of the causative genes of mature-onset diabetes is Klf11. Klf11 binds to the promoter's GC box to control the expression of the insulin gene [23]. Klf11 is an insulin gene regulator that is glucose-inducible. Thus, Klf11 is implicated in the regulation of pancreatic beta cell physiology, and both functional and genetic analyses show that variations in it could lead to the onset of diabetes [24]. Diabetes-induced heart failure and vascular atherosclerotic lesions were

associated with Klf5 expression [25]. Adipose tissue-specific Klf15 deletion mice have reduced adiposity, elevated adiponectin, decreased leptin, improved insulin sensitivity, improved endurance during exercise, and increased liver ketogenesis. In fact, diet-induced obesity is prevented in both systemic Klf15-deficient mice and Klf15-deficient mice specific to adipose tissue. Through a Signal Transducer and Activator of Transcription (STAT)-mediated mechanism, leptin inhibits endogenous Klf4 expression; on the other hand, elevated Klf4 expression in the rat arquat nucleus decreases sensitivity to exogenous leptin [26]. Adiponectin and leptin expression were decreased in human adipocytes overexpressing Klf7 compared to control cells, while IL-6 expression was increased. In the insulin-secreting cell line (HIT-T15 cells), the expression of insulin and glucose-induced insulin secretion were significantly suppressed in Klf7 overexpressing cells compared with control cells, which was accompanied by a decrease in sulfonylurea receptor 1, glucose transporter 2, pancreatic duodenal homeobox factor 1, and Kir6.2 expressions. Therefore, Klf7 is also associated with type 2 diabetes [27].

It was stated that fatty acid oxidation was triggered by Klf5, and that genetic and pharmacological inhibition of Klf5 protected diabetic mice from heart failure. Cardiomyocyte Klf5 was found to be a novel regulator of fatty acid metabolism, and its expression was found to be reduced in the early stage of type 1 diabetes and increased later in a mouse model of streptozotocin-induced type 1 diabetes. Isolated cardiomyocytes from patients with aortic stenosis showed higher levels of Klf5mRNA in individuals with diabetes [28]. In a study in which streptozotocin-induced cardiomyopathy and diabetes were induced, the synthesis of Astrocyte Elevated Gene-1 (*AEG-1*) and Klf4 was notably higher in the streptozotocin group compared to the control group. Suppression of *AEG-1* increased left ventricular ejection fraction, suppressed autophagy, and upregulated Klf4 expression. Suppression of *AEG-1* downregulated Klf4 expression and suppressed autophagy in diabetic cardiomyopathy [29]. Cardiac Klf5 expression was lower in diabetic mice with suppressed cardiomyocyte-specific Forkhead box protein O1 (*FOXO1*) gene, protecting these mice from diabetic cardiomyopathy. *FOXO1* was found to bind directly to the Klf5 promoter and increase Klf5 expression. Likewise, cardiac dysfunction was brought about by constitutive cardiomyocyte-specific Klf5 overexpression. By directly attaching to the NADPH Oxidase 4 (*NOX4*) promoter and promoting *NOX4* expression, Klf5 produced oxidative stress. In diabetic mice, pharmacological or genetically induced Klf5 suppression reduced superoxide generation, enhanced heart function, and avoided ceramide accumulation. Diabetes-induced activation of cardiomyocyte *FOXO1* stimulated *NOX4* expression and ceramide accumulation, increased Klf5 expression, and caused diabetic cardiomyopathy [30].

Conclusion

Obesity, diabetes and cardiomyopathy are major health problems for the world. The processes in which these diseases emerge in the body are important. The proteins, enzymes and hormones associated with these diseases are genetically determinants of a person's susceptibility to these diseases. The amounts and activities of proteins, enzymes and hormones in the body are controlled by transcription processes.

The Klf family, which contains 3 Cysteine2Histidine2 zinc finger proteins, is one of the largest transcription factor families. Klfs are associated with adipose tissue metabolism, obesity, diabetes and cardiomyopathy. Klfs are determinants of genetic susceptibility to these diseases in humans. The mechanisms and molecular pathways by which Klfs control the development of these diseases are important. The current review was written in this context and will be a guide for future studies on this subject.

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