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Review

Role of kruppel-like transcription factors in adipogenesis

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ABSTRACT

The zinc-finger transcription factors of the kruppel-like factor family (KLF) are critical in many physiological and pathological processes including cell proliferation, differentiation, inflammation, and apoptosis. Recently, there is increasing evidence that suggests these KLFs have an important role in fat biology. This review summarizes the role of KLFs in lipid metabolism, especially in adipogenesis, and reveals the relationship networks among members of KLF family in differentiation.

Contents

Introduction

The worldwide prevalence of overweight and obesity is rapidly increasing, and this negatively impacts the health of humans (Flier, 2004). Obese individuals are more likely than their lean counterparts to develop cardiovascular disease, type 2 diabetes mellitus, metabolic disorders, and some cancers (Flier, 2004). Excessive fat accumulation reflects an imbalance between energy expenditure and caloric intake, which leads to an increase in the number and/or size of fat cells. Adipocytes can be enlarged by excessive lipid deposition or generated from precursor ones. The essential step of adipocyte differentiation is the commitment from preadipocytes to adipocytes.

Differentiation of preadipocyte into adipocyte is regulated by an elaborate network of transcription factors that coordinate expression of hundreds of genes responsible for fat-cell phenotype (Rosen and MacDougald, 2006; Rosen and Spiegelman, 2000). Peroxisome

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proliferator-activated receptor gamma (PPARγ) is considered a master regulator of adipogenesis among transcription factors in particular (Barak et al., 1999; Rosen et al., 1999; Tontonoz et al., 1994). Without it, precursor cells are incapable of expressing any known aspect of the adipocyte phenotype (Zhang et al., 2004). The CCAAT/enhancer-binding protein (C/EBP) family plays a vital role in promoting adipocyte differentiation. C/EBPβ and C/EBPδ are induced early during the differentiation of 3T3-L1 preadipocytes upon hormonal stimulation (Tanaka et al., 1997; Wu et al., 1996, 1995), which is followed by the induction of PPARγ and C/ERPα. C/EBPα, whose expression is highest during later stages of differentiation, is induced by PPARγ activation. Krox20 (Chen et al., 2005), sterol-regulatory element-binding protein (SREBP)-1c (Kim et al., 1998a, 1998b; Kim and Spiegelman, 1996), and Stat5 (Kawai et al., 2007; Meirhaeghe et al., 2003; Nanbu-Wakao et al., 2002) have also been shown to be important in adipogenesis.

Members of the Kruppel-like factor (KLF) family of zinc-finger transcription factors have recently been identified as key regulators of cell activity and have received intensive investigations in human health and disease (McConnell and Yang, 2010). KLF is derived from the Drosophila protein "kruppel" (meaning "cripple") which shares homology of proteins to the DNA-binding domains. Drosophila embryos deficient in kruppel die with consequences of abnormal thoracic and abdominal segmentation and thus appeared "crippled" (Nusslein-Volhard and Wieschaus, 2003; Zuo et al., 1991). The distinguishing feature of the KLF family is the presence of three highly conserved classical Cys2/His2 zinc fingers (Bieker, 2001; Dang et al., 2000b; Turner and Crossley, 1999), a motif that is the most abundant in transcription factors and the second most abundant in the human genome (Bieker, 2001). Zinc fingers 1 and 2 contain 23 residues, while the third finger has only 21 residues (Pearson et al., 2008). These fingers are located at the carboxyl terminus of the protein and enable KLFs to bind to related GC- and CACCC-boxes of DNA (Bieker, 2001; Dang et al., 2000b; Pearson et al., 2008; Turner and Crossley, 1999). In contrast to the zinc-finger regions, the non-DNA-binding regions are highly divergent, modulate transactivation and transrepression, and often mediate interaction with various co-regulators, giving KLFs unique tissue-specific roles (Pearson et al., 2009).

The first mammalian kruppel homolog, termed erythroid Kruppel-like factor (EKLF/KLF1), was identified in 1993 as a factor specifically expressed in the red blood cell lineage (Bieker, 1996; Miller and Bieker, 1993; Parkins et al., 1995). With the first KLF isolation and identification, a new subfamily of Kruppel-like proteins, which has a total of 17 mammalian KLFs, has emerged. These factors have been shown to have important roles in a diverse array of cellular processes including hematopoiesis (Nuez et al., 1995; Parkins et al., 1995), organ development (Wani et al., 1999b), cardiac remodeling (Fisch et al., 2007; Shindo et al., 2002), angiogenesis (Bhattacharya et al., 2005), monocyte activation (Das et al., 2006; Feinberg et al., 2005), neoplasia (Rowland et al., 2005; Wei et al., 2005), gluconeogenesis (Gray et al., 2007), cell growth regulation (Black et al., 2001), and endothelial cell function (Lin et al., 2005; Sen-Banerjee et al., 2005). In recent years, many members of KLF have been identified to be involved in both adipogenesis and lipogenesis. This review focuses on the role of the KLF family members as promoters or inhibitors in fat biology and also their role in brown adipocyte tissue (summarized in Table 1).

KLFs that promote adipogenesis

KLF15

Kruppel-like factor 15 (KLF15) is the first KLF found to be involved in adipogenesis (Uchida et al., 2000), which is initially identified as a protein that binds to CLC-K1 promoter, a kidney-specific CLC chloride channel, thus formerly designated kidney KLF (KKLF). Northern blot analysis shows KLF15 expression to be more abundant in adipose, muscle (heart, skeletal muscle, and aorta), kidney, and liver in mouse tissues (Uchida et al., 2000).

KLF15 is increased maximally at Day 6 in 3T3-L1 preadipocytes differentiation (Mori et al., 2005). The time course of KLF15 mRNA up-regulation during adipocyte differentiation is in the late phase of adipogenesis, about 4 days after the adipogenic stimulation, 2 days later than the initial expression of PPARγ and aP2 mRNAs, which is similar to the pattern of C/EBPα mRNA.

Table 1
Current findings in Kruppel-like factors associated with fat biology.

	Other name	mRNA appear time in adipogenesis	Function/observation
Promoters			
KLF4	Gut-enriched Kruppel-like factor GKLF/ZIF	30 min postinduction	• Interact with Krox20 • Transactivate C/EBPβ • Binding to the C/EBPβpromoter
KLF5	Intestinal-enriched Kruppel-like factor Basic transcription element-binding protein2 BTEB2, IKLF	1 h after stimulation	• Interact with C/EBPβ/δ • Bind to the PPARγ2 promoter
KLF6	Core promoter binding protein Zf9, CPBP/GBF	Within 30 min	• Associated with HDAC3 • Bind to the pre-1 promoter
KLF15	Kidney-enriched Kruppel-like Factor KKLF	4 days after induction	• Regulate GLUT4 • Involved in gluconeogenesis • Involved in amino acid catabolism • Downstream of C/EBPβ or C/EBPδ • Maintain differentiated state by mediating PPARγ in cooperation with C/EBPα
KLF9	Basic transcription element-binding protein1 BTEB1	4 days after induction	• Activate the PPARγ2 promoter • Act in concert with C/EBPα
Suppressors			
KLF3	Basic Kruppel-like factor BKLF	Most highly at day 0 Diminished upon differentiation	• Recruite the corepressor protein CtBP • Associate with the C/ebpα promoter
KLF2	Lung Kruppel-like factor LKLF	Most highly at day 0 Diminished upon differentiation	• Inhibite PPARγ promoter • Inhibite ADD1/SREBP1c expression • Inhibite C/EBPα expression
KLF7	Ubiquitous Kruppel-like factor UKLF	Most highly at day 0	• Effect the adipocytokine genes