6. Emerging Role of Kruppel-like Factors (KLFs) in Skeletal Muscle Biology

Saptarsi M. Haldar

Skeletal muscle displays remarkable phenotypic plasticity during development, physiological stress, and disease. At the molecular level, this plasticity is governed by powerful gene regulatory signaling pathways. In this review, we discuss the emerging role of the Kruppel-like Factor (KLF) family of transcription factors as essential regulators of muscle biology. Continues efforts in this exciting new field have the potential to advance our knowledge of disease pathogenesis and create therapeutic inroads for metabolic and myopathic conditions.

Skeletal muscle is a remarkably plastic tissue and can adapt to a wide range of physiologic and pathologic stimuli. For example, skeletal muscle has a robust capacity to hypertrophy during exercise, remodel its metabolic machinery in the face of nutritional/energetic stress, and regenerate when injured[1) 2)]. Furthermore, in addition to known primary disorders of muscle (e.g. muscular dystrophy), skeletal muscle dysfunction is increasingly appreciated to play an important role in common cardiometabolic diseases. At the molecular level, these physiological and pathological gene regulatory responses are governed by powerful transcription factors such as members of the basic helix-loop helix (e.g. MyoD), MADS-box (e.g. MEF2) and nuclear receptor (e.g. PPAR) superfamilies[1) 2)]. In this review, we will highlight recent evidence that adds to this list a new transcription factor family, Kruppel-like Factors (KLFs), as essential regulators of muscle biology. We will first provide an introduction to the general biology of KLFs followed by a discussion of this transcription factor family's role in myogenesis, postnatal muscle physiology, and muscle disease. Where applicable, we will highlight broader themes in transcriptional signaling and integrated mammalian physiology that are emerging from our increasing understanding of KLFs in skeletal muscle function.

[Keywords]
Kruppel, KLF, skeletal muscle, myogenesis, metabolism, transcription

1 Introduction to the KLF family of transcriptional regulators

KLFs belong to a subfamily of the zinc-finger class of DNA-binding transcriptional regulators that are capable of both gene transactivation and repression (Fig. 1). There are currently 17 known mammalian

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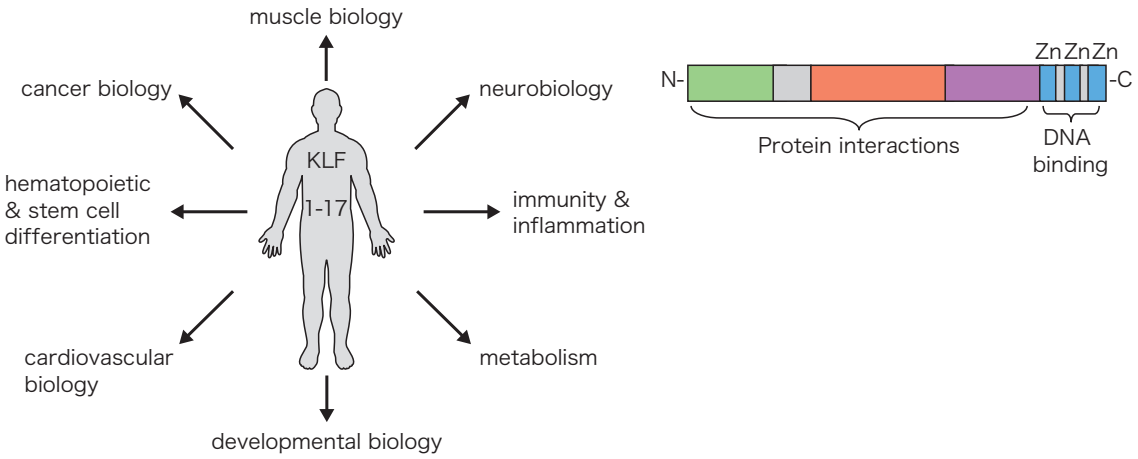

Figure 1 Overview of KLFs in physiology and disease
There are 17 known mammalian KLF family members which have been implicated in a broad range of physiological and pathophysiological processes. These transcription factors, which can both activate and repress target genes, share a highly homologous zinc finger (Zn) DNA-binding domain in their C-terminus

KLF isoforms that share several common features[3]. First, members of this subfamily are characterized by three consecutive C_2H_2 containing zinc finger motifs at the extreme C-terminus of the protein. Second, KLFs share a highly conserved seven residue sequence between the zinc fingers, TGEKP(Y/F)X. Third, KLFs generally bind to genomic DNA consensus sequences such as the *CACCC* element or *GT* box, with target sequence specificity determined, in part, by a handful of critical residues within each zinc finger. In contrast to the C-terminal zinc finger domains, which are similar across the KLF family, the non-DNA-binding regions are highly divergent. These divergent regions are increasingly appreciated to mediate specific transactivation and transrepressive functions of individual KLF proteins via their ability to form protein interactions and undergo post-translational modification[3].

The name "Kruppel-like Factor" is derived from the shared homology of these proteins to the DNA-binding domain of the Drosophila gene *kruppel*, which means "cripple" in German. In the fly, *kruppel* is an early developmental gene whose role in body patterning was first described in the pioneering work of Nusslein-Volhard and Weischaus who observed that Drosophila embryos deficient in this gene died as a result of abnormal thoraco-abdominal patterning and thus appeared physically "crippled" [4]. The first mammalian kruppel homolog, termed erythroid Kruppel-like factor (EKLF/KLF1), was identified in the early 1990's in the laboratory or Stuart Orkin as a factor specifically expressed in the red blood cell lineage that is essential for β-globin expression and erythroid differentiation[5]. Since the discovery of KLF1, a total of 17 mammalian KLFs have been identified (designated KLF1 through 17, corresponding to chronologic order of identification). The 17 KLFs display both overlapping and non-overlapping patterns of spatiotemporal expression across a broad range of cell types and developmental stages. Studies over the last decade have defined essential roles for several members of this family in a diverse array of cellular processes including embryonic stem cell differentiation, hematopoiesis, cardiovascular biology, neoplasia, immunity/inflammation, and metabolism[3]. Ironically, despite the initial description of the Drosophila *kruppel* gene as a critical determinant of myogenic fate in the gestating fly, the role of vertebrate KLFs in skeletal muscle biology has only recently been appreciated. In this review we will discuss published studies that implicate KLFs as essential regulators of skeletal muscle biology.

2 KLFs in myogenesis and muscle maturation

Myogenesis is the process of muscle generation, which occurs during embryonic development (from mesodermal progenitors) and also during adult life (muscle regeneration from a pool of tissue-resident myogenic precursors termed satellite cells)[2]. Myogen-

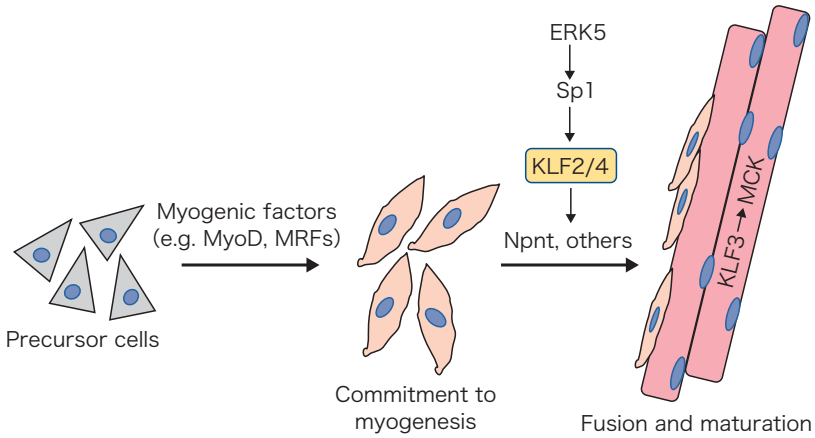

Figure 2　KLFs in muscle differentiation
MRF：myogenic regulatory factors, *Npnt*：Nephronectin, MCK：muscle creatine kinase

esis is a multistep process in which mononucleate myoblasts withdraw from the cell cycle, initiate the expression of muscle genes, and fuse with each other to form multinucleate myotubes[6]. It is now generally accepted that the processes of embryonic myogenesis and postnatal muscle regeneration via satellite cells are governed by very similar signaling pathways[2]. A broad spectrum of extracellular signaling molecules and cytosolic signaling cascades instruct myogenesis. These signaling pathways ultimately converge on a battery of transcription factors that translate extracellular cues into a gene expression program that assigns myogenic identity and drives muscle differentiation[2]. Pioneering studies over the last 25 years have identified "master" myogenic regulatory factors (MRFs, e.g. MyoD, Myf5, Myogenin) that are organized into hierarchical networks which display tightly controlled spatiotemporal patterns of patterns induction/repression during the differentiation process. Once a commitment to myogenic identity has been established by these MRFs, a network of secondary transcription factors drive expression of contractile proteins, metabolic machinery, and signaling modules that together fashion the mature, multinucleate myotube[2]. There is no published evidence to date that defines a role for a KLF family member in the very early events that commit precursor cells to a myogenic fate. However, recent studies now implicate three members (KLF 2,3,4) in later stages of muscle development and maturation (**Fig. 2**)[6,7].

1）KLF3 in late myogenic gene expression

KLF3 was identified in a proteomic screen designed to detect muscle proteins capable of recognizing a key regulatory region of the Muscle Creatine Kinase (*MCK*) promoter, termed the MPEX site[7]. Consistent with its ability to bind the *MCK* promoter, KLF3 expression was found to be initiated in the terminal stages of muscle differentiation at a time when many genes that define the maturing myotubes are induced. Using chromatin immunoprecipitation (ChIP) studies, these investigators found KLF3 to enrich at the MPEX locus in the MCK promoter as well as in many other muscle gene promoters. KLF3 was shown to directly transactivate the MCK gene via physical association and cooperation with serum response factor (SRF). Interestingly, this synergy occurred independently of SRF binding to its cognate CArG-box on the MCK promoter, suggesting that KLF3 could mediate CArG independent modes of SRF signaling. Considering the previously described role of KLF3 as a potent transcriptional repressor, this study demonstrates a context in which KLF3 functions as a direct transactivator and suggests a more generalizable mechanism for CArG-independent SRF signaling[7]. In addition to its gene-inductive function, it is likely that KLF3 also plays an important role in gene repression during late stages of muscle development. Interestingly, mice systemically deficient in *Klf3* have prominent abnormalities in adipogenesis[8], however do not demonstrate any overt muscle defects. While a more detailed physiologic assessment of Klf3-null mice may reveal functional muscle abnormalities,

it remains possible that other KLF family members play important compensatory roles in this setting.

2) KLF2/4-dependent signaling pathway in muscle cell fusion

Elegant work from the laboratory of Dr. Eisuke Nishida has elucidated a novel, cell autonomous role for a KLF2/4 transcriptional module in muscle cell fusion[6]. This study began by demonstrating that ERK5, a member of extracellular signal-regulated kinase (ERK) family was required for muscle cell fusion. Surprisingly, unbiased transcriptomic profiling revealed that ERK5 regulated a downstream gene program that was distinct from those directly regulated by classical myogenic factors. Using *in silico* transcription factor binding site prediction algorithms for ERK5 inducible genes, the investigators found no significant enrichment for MyoD- or MEF2-binding consensus motifs. Unexpectedly, the profiles revealed that *Klf2* and *Klf4* were induced by ERK5 during myogenesis and that there was significant overrepresentation of the KLF motifs (CACCC or GGGTG) in the promoters of the 189 genes induced by ERK5. Further experiments demonstrated that silencing of either *Klf2* or *Klf4* attenuated muscle cell fusion downstream of ERK5, while overexpression of both these factors together could increase the abundance of myotube nuclei during the differentiation process. Importantly, overexpression of KLF2/4 in ERK5-inhibited cells could restore capacity for muscle fusion. To link these signaling pathways together, the investigators find that *Klf2/4* are direct targets of the ERK5-activated transcription factor Sp1. Finally, the gene *Nephronectin* was shown to be an important direct downstream target of KLF2/4 capable of mediating effects on muscle fusion. Together, these studies define an ERK5-Sp1-KLF2/4 pathway that, along with master myogenic regulatory factors, is essential for muscle cell fusion and myotube maturation in cultured cells (**Fig. 2**)[6]. Interestingly, ERK5 activation has also been shown to mediate KLF2 induction in endothelial cells subject to laminar flow[9], suggesting that a similar signaling axis might operate across multiple cell types. As systemic deficiency of either *Klf2* or *Klf4* in mice results in embryonic or perinatal lethality, it will be interesting to explore the role of endogenous *Klf2/4* in muscle development *in vivo* using conditional targeting approaches. In addition to KLF2,3, and 4, a number of other KLFs are differentially expressed during the various stages of myogenesis and muscle maturation[6]. Considering the emerging data implicating KLF networks in embryonic stem cell pluripotency[10], erythropoiesis[11], and adipogenesis[12], it is likely that similar networks of KLFs are involved in stage specific gene expression during myogenesis.

3 KLFs in postnatal muscle plasticity and integrated metabolic function

In addition to the roles described above in myogenesis, KLFs are emerging as important regulators of physiologic muscle function in the adult. In this section we will first highlight the role of KLF15 in muscle physiology and metabolism, with emphasis on how this factor serves as a nodal integrator of nutrient flux across key tissues. Second, we will discuss the role of KLF5 in the regulation of muscle metabolic genes, with emphasis on its essential role as a nuclear receptor co-regulator.

1) KLF15 in muscle metabolism and integrated control of substrate flux

KLF15 is expressed in skeletal muscle, cardiac muscle, smooth muscle, brown/white adipose, kidney and liver[13]. In skeletal and cardiac muscle, KLF15 is minimally expressed during development and robustly induced during postnatal maturation[14] and *Klf15*-null mice do not display any overt developmental abnormalities[13,14]. Across numerous tissues, including skeletal muscle, KLF15 is robustly induced by fasting and is induced by acute endurance exercise in skeletal muscle of mice and humans[14]. Together, these expression patterns are consistent with a role for KLF15 in adult skeletal muscle metabolism. Indeed, earlier reports demonstrated that KLF15 regulates metabolic targets such as GLUT4[13] and Acetyl-CoA synthetase-2[15] in skeletal muscle cells and recent studies in *Klf15* null mice have begun to elucidate this gene's endogenous role in muscle metabolism and physiologic function *in vivo*. The first of these studies demonstrated that *Klf15* null mice develop severe fasting hypoglycemia due to a defect in hepatic gluconeogenesis via a novel mechanism that did not center upon direct regulation of PEPCK[16]. Rather, KLF15 was shown to directly regulate key genes involved in the catabolism of skeletal muscle branched chain amino acids (BCAAs, the body's predominant store of glucogenic precursors) into alanine, and subsequent entry of these BCAA-derived carbons into hepatic gluconeogenesis (via the alanine cycle). In other words, KLF15 is induced with fasting in muscle and liver and drives

enhanced flux of BCAAs-derived carbon into the gluconeogenetic pathway. Therefore, this transcriptional pathway is required to guard against severe hypoglycemia during starvation[16]. It should also be noted that the catabolism of BCAA into their carbon skeletons also requires coordinated disposal of the nitrogen group via the hepatic urea cycle. To this end, we have also demonstrated KLF15 to be a key direct regulator of ornithine trasncarbamylase (OTC), the rate limiting step in the hepatic urea cycle[17]. Therefore, KLF15 is essential not only for physiologic amino acid catabolism during metabolic stress, but also for coupled disposal of the amino acid derived nitrogen groups and thus, global nitrogen balance[17]. In addition to its role in BCAA homeostasis, KLF15 also regulates the metabolism of several other amino acids *in vivo* (e.g. proline, tyrosine, tryptophan, arginine) suggesting an even broader role in metabolic homeostasis and metabolite-based signaling[17].

While clearly important, KLF15's ability to augment alanine cycle flux for hepatic glucose production represents only one part of a coordinated response to metabolic stress. For example, during the stress of starvation or endurance exercise, this increase in hepatic glucose production must also be accompanied by a shift towards increased lipid utilization in skeletal muscle. This augmentation of peripheral lipid utilization allows mammals to efficiently fuel working skeletal muscle during periods of carbohydrate depletion while sparing glucose for the brain (which is glucose dependent)[14]. This significance of this physiologic circuit is best illustrated by the presence of fasting induced hypoglycemia and exercise intolerance in patients with certain inborn errors of lipid metabolism[18]. We have recently confirmed that KLF15 indeed plays a key role in augmenting skeletal muscle lipid flux during metabolic stress, such as endurance exercise[14]. KLF15 was shown to directly regulate a broad transcriptional program spanning all major segments of the lipid-flux pathway in muscle, including sarcolemmal partitioning, mitochondrial transport, beta oxidation, and peroxisomal function. Consequently, Klf15-deficient mice displayed abnormal lipid and energy flux, inappropriate reliance on carbohydrate fuels, exaggerated muscle fatigue, and impaired endurance exercise capacity. Together, these studies in liver and skeletal muscle illustrate a fundamental mechanism by which animals couple amino acid catabolism, glucose production and increased lipid utilization during metabolic stress[14) 16) 17)]. Given the important role of KLF15 in these two metabolic tissues, we suspect that this gene also participates in physiologic substrate flux across other key organs systems (e.g. white/brown adipose, kidney, heart). Considering the integral role of KLF15 in adaptive metabolism, understanding the signaling pathways governing its upstream regulation will shed important additional insights into its physiologic function. Recent studies by our group and others have identified several neurohormonal pathways as important regulators of Klf15 expression and function. Signals known to drive nutrient catabolism, such as glucocorticoids[19] and CREB activation[20] have been shown to induce Klf15 while anabolic signals such as insulin can suppress its expression[21]. In addition to these neurohormonal inputs, we have recently demonstrated that KLF15 can be directly regulated by BMAL1[17], a core component of the mammalian circadian clock. Therefore, it is likely that balance between such catabolic and anabolic signals, with addition synchronization by the circadian clock, regulate KLF15 function in a coordinated manner across tissues. **Fig. 3** provides a schema for our current understanding KLF15 as an integrator of adaptive substrate flux across key metabolic tissues.

As KLF15 is a bona fide direct target of the glucocorticoid (GC) receptor[19] and is known to regulate BCAA catabolism[16], it has been suggested that KLF15 can participate in GC-induced muscle wasting. A recent study has demonstrated that the GC-KLF15 signaling axis in skeletal muscle cells regulates BCAA catabolism, in part, via induction of the gene Branched Chain Aminotransferase 2 (BCAT2)[19]. Subsequently, the KLF15 mediated depletion of muscle BCAA leads to diminished activity of mTORC1, a key anabolic signaling complex involved in the maintenance of muscle mass. In addition, these authors demonstrate that enforced adenoviral overexpression of KLF15 in focal regions of rat muscle can induce several canonical atrogenes and decrease muscle cross sectional area. While provocative, this study lacks any *in vivo* loss of function experiments and draws conclusions that are largely based on enforced adenoviral KLF15 overexpression. Therefore, it remains unknown whether endogenous KLF15 is actually involved in GC mediated muscle atrophy or global regulation of muscle mass *in vivo*. Interestingly, *Klf15*$^{-/-}$ mice, which have significantly reduced muscle *Bcat2*[16) 17)], have unaltered baseline muscle mass in the basal state[14]. Given the

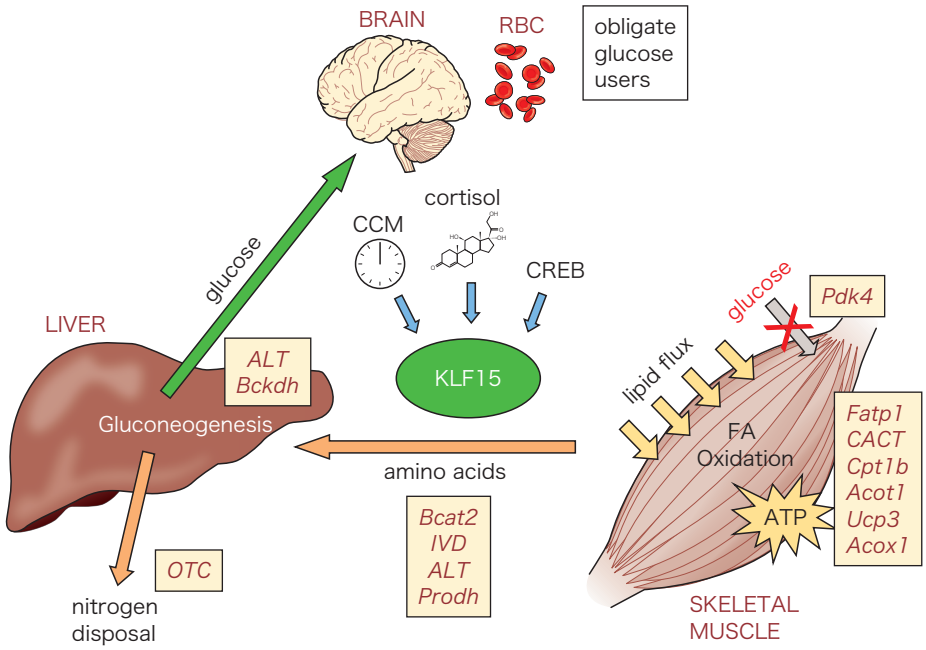

Figure 3 Integrated role of KLF15 in adaptive substrate flux
KLF15 regulates catabolism of BCAA and their flux into the gluconeogenetic pathway, increased lipid utilization in skeletal muscle, and nitrogen disposal via the urea cycle (via regulation of *OTC*). Major upstream regulators that induce/activate KLF15 include the central circadian clock machinery (CCM), glucocorticoids such as cortisol, and signals like glucagon that activate cyclic AMP response element binding protein (CREB). Images of organs adapted from Barish, G. D. et al., J. Clin. Invest., 2006[23]

complex metabolic effects of systemic *Klf15* deficiency, it will be important to use muscle-restricted genetic gain/loss of function approaches to definitively establish the role of the GC-KLF15 axis in adaptive nutrient catabolism, mTOR signaling, and regulation of muscle mass.

2) KLF5 in muscle metabolism and nuclear receptor function

Elegant studies from the laboratory of Dr. Ryozo Nagai have implicated KLF5 as an important regulator of muscle lipid metabolism and systemic energy homeostasis[22]. KLF5 is expressed in skeletal myocytes, but not in cardiomyocytes or hepatocytes. These investigators found that mice heterozygous for *Klf5* were resistant to diet induced obesity and insulin resistance, at least in part due to increased systemic energy expenditure. Consistent with this finding, skeletal muscle tissue from high-fat diet fed *Klf5*$^{+/-}$ mice had heightened expression of several key genes involved in lipid utilization (e.g. *Ucp3*, *Cpt1b*, *Acox1*), findings that were recapitulated with knockdown of *Klf5* in cultured muscle cells. Importantly, many of these KLF5 regulated genes are also known targets of the ligand activated nuclear receptor PPARδ, a central regulator of muscle lipid metabolism and energy utilization[23]. Interestingly, KLF5 was found to be post-translationally regulated by small ubiquitin like modifiers (SUMOs) on key lysine residues, a modification well known to dynamically modulate transcription factor function[24]. The authors demonstrate that a transcriptional complex containing SUMOylated KLF5, unliganded PPARδ, and the NCoR/SMRT co-repressors exerts tonic repression of these targets in the absence of synthetic PPARδ ligand. However, in an unusual twist, they demonstrate that the same target genes repressed by KLF5 under basal conditions are induced by KLF5 after PPARδ ligand stimulation. Using ChIP assays, they show that PPARδ ligands do not alter the enrichment of KLF5 or PPARδ themselves, but rather dynamically recruit the SUMO-protease SENP1 which subsequently de-SUMOylates KLF5. This ligand-mediated deSUMOylation of KLF5 facilitates loss of co-repressors, recruitment of classical nuclear receptor co-activators (e.g. CBP), and assembly of a protein

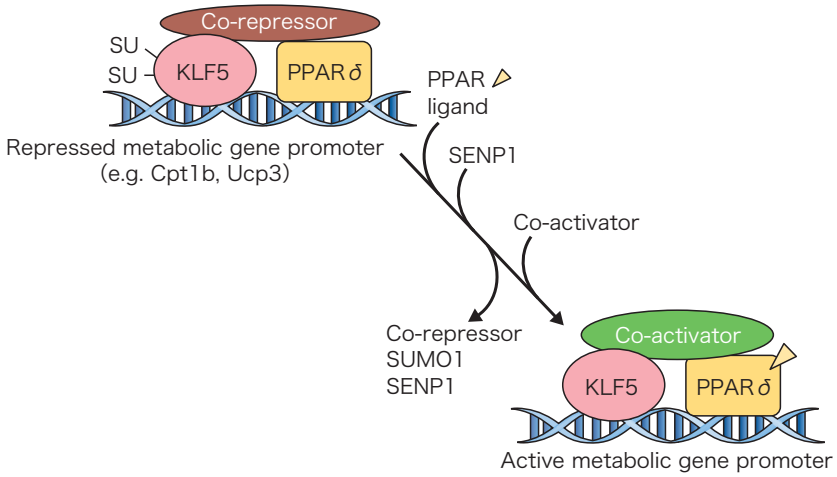

Figure 4　KLF5 as a co-regulator of PPARδ signaling in muscle metabolism
SU：SUMO. Adapted from Jain, M. K., Nat. Med., 2008[24]

complex that favors promoter transactivation. Essentially, SUMO–KLF5 cooperates with unliganded PPARδ to mediate repression, while de–SUMOylated KLF5 synergizes with liganded PPARδ during transactivation on the very same promoter. Alternatively stated, dynamic deSUMOylation of KLF5 (by SENP1) acts in concert with PPAR ligands in facilitating the switch from gene repression to activation and therefore represents an elegant molecular mechanism for finely tuning the output of these nuclear receptor dependent transcriptional switches (**Fig. 4**)[24]. As modulation of PPARδ has been considered as an attractive pharmacologic approach against metabolic syndrome[23], further understanding of KLF5–PPARδ crosstalk may help refine such therapeutic strategies. We note that KLF15, like KLF5, also regulates many lipid-metabolic genes that are known targets of nuclear receptors[14]. Thus, the body of work highlighted above supports a growing notion that important functional interactions between the KLFs and nuclear receptors families are pervasive.

4 KLFs in muscle disease

There is very little information on the role of KLFs in primary muscle diseases. One study using cultured muscle cells has suggested that excessive KLF15 expression/activity might contribute to the pathogenesis of facioscapulohumeral muscular dystrophy (FSHD)[25]. FSHD is a rare genetic muscle disorder with an autosomal dominant inheritance pattern that has been associated with partial genomic contraction of an integral number of 3.3-kb tandem repeats (D4Z4) present within the subtelomeric regions of the chromosome 4q35[26]. This genomic abnormality is associated with inappropriate upregulation of several genes during myogenic differentiation, a number of which have been implicated in FSHD pathogenesis, including DUX4c (Double homeobox 4, centromeric) and FRG1/2[26]. A potential mechanism for excessive induction DUX4c/FRG2 in differentiating FSHD myoblasts involves excessive enhancer function of the truncated D4Z4 region. Using a yeast one-hybrid screen, the authors identified KLF15 as a factor capable of interacting with and directly activating a minimal D4Z4 enhancer[25]. Importantly, KLF15 expression was found to be induced by MyoD during myogenic differentiation and increased in muscle cells/tissues derived from FSHD patients. Finally, the authors demonstrate that MyoD dependent activation of the D4Z4 enhancer, and subsequent induction of DUX4c/FRG2 was mediated by KLF15. While MyoD can initiate a transcriptional cascade that ultimately induces KLF15 in myoblasts, the precise upstream signaling pathways that mediate KLF15 overexpression in FSHD cells remain unclear. As the KLF15 promoter contains a functional E-box shown to mediate its circadian regulation by the central clock gene BMAL1[17], it is possible that it is also a direct target of the myogenic basic helix-loop-helix factors. In addition to potential roles in muscular dystrophies such as FSHD, the importance of KLFs in muscle metabolism[14) 16) 17)] also raise the pos-

sibility that dysregulation of these factors may also be involved in the pathogenesis of metabolic myopathies, sarcopenia, and diabetes.

5 Conclusion

KLFs have recently emerged as essential regulators of muscle development and postnatal physiology. Inasmuch as these factors are essential for muscle homeostasis, we anticipate that dysregulation of their expression and activity will be critically involved in the pathogenesis of muscle disease. Future studies elucidating the function of various KLF family members in physiology and disease, with a focus on cell/tissue-specific genetic manipulation and detailed molecular characterization of chromatin-level transcriptional mechanisms, will greatly advance this exciting field and may provide new therapeutic insight.

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ライフステージに応じた変容と破綻

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