



Published in final edited form as:

Trends Endocrinol Metab. 2016 December ; 27(12): 881–892. doi:10.1016/j.tem.2016.08.006.

Sarcolipin: a key thermogenic and metabolic regulator in skeletal muscle

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Abstract

Skeletal muscle constitutes ~40 % of body mass and has the capacity to play a major role as thermogenic, metabolic and endocrine organ. In addition to shivering, muscle also contributes to nonshivering thermogenesis via futile sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase (SERCA) activity. Sarcolipin (SLN), a regulator of SERCA activity in muscle, plays an important role in regulating muscle thermogenesis and metabolism. Uncoupling of SERCA by SLN increases ATP hydrolysis, heat production and contributes to temperature homeostasis. SLN also affects whole body metabolism and weight gain, in mice, and is upregulated in various muscle diseases including muscular dystrophy, suggesting a role for SLN during increased metabolic demand. In this review we also highlight the physiological roles of skeletal muscle beyond contraction.

Keywords

Skeletal muscle; Sarcolipin; SERCA; Metabolism; Thermogenesis

Skeletal muscle beyond contraction

Fascination with skeletal muscle anatomy and function dates back to several centuries as seen from Michelangelo's classical paintings and Leonardo da Vinci's vivid sketches depicting architecture of human skeletal muscle. During the 20th century, scientists were more interested in the mechanics of muscle contraction, which led to the identification of many contractile proteins [1] and the sliding filament theory as the basis for muscle movement [2]. A large body of research was devoted to understanding striated muscle structure, organization, fiber types and performance. There has also been much interest in muscle growth (body building), hypertrophy, and adaptation to exercise due to its relevance

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The authors declare that they have no conflicts of interest with the contents of this article.

to health and sports medicine [3–4]. Despite significant advances in our understanding of muscle as a contractile organ, these early studies placed less emphasis on the importance of skeletal muscle in **thermogenesis** (see Glossary) and metabolism. These studies assumed that heat production and metabolic activity in the skeletal muscle are primarily due to contractile activity. However, emerging studies suggest that some of these functions are not exclusively dependent on muscle contraction. These studies provide evidence that muscle can also function as thermogenic, metabolic and endocrine organ (Box 1) (Figure 1). Table 1 shows study models (key genetically modified mouse models and cell lines) used to understand skeletal muscle functions beyond contraction.

Skeletal muscle occupies ~40% of mammalian body mass and consumes more than 70% of metabolites during extreme physiological demands such as exercise [5–6]. Therefore, muscle can play a dominant role in the regulation of the whole-body metabolic rate, and any perturbation in muscle health can have significant metabolic consequence. Pioneering studies in endothermic fish and birds suggested that **sarcoplasmic reticulum** (SR) calcium cycling in muscle can be activated to produce heat in these organisms and an increase in muscle metabolism is required to support this mechanism [7]. Recent studies demonstrated that **sarcoplipin** (SLN) a regulator of **sarcoplasmic/endoplasmic reticulum Ca²⁺ transport ATPase** (SERCA) is involved in heat production in skeletal muscle [8–10]. Even though, SLN was discovered more than 30 years ago [10–11], the physiological implications of SLN-SERCA interaction are only now beginning to emerge. Therefore, a major objective of this review is to highlight the role of SLN in skeletal muscle physiology, with a focus on thermogenesis and metabolism.

Muscle as a thermogenic organ- a historic account

The role of skeletal muscle in thermogenesis is well known ever since the earliest biological studies. Muscle shivering is recruited as the first line of defense during an acute exposure to cold [12]. Shivering is a repetitive contraction-relaxation process activated by repeated stimulation of the neuro-muscular junction that leads to elevation of cytosolic Ca²⁺ concentration thereby activating ATP hydrolysis to produce heat. During shivering, heat is primarily produced by the major ATP utilizing enzymes including Na⁺/K⁺ ATPase, myosin ATPase and SERCA [12–14]. Interestingly, it has been shown that mice and humans can maintain body temperature during acute cold exposure, even when shivering is minimized [8, 15]. Studies have also shown that during cold acclimation, shivering is gradually replaced by **nonshivering thermogenesis** (NST). This is because repetitive muscle contractions during constant shivering can cause muscle damage [16]. In addition, high intensity shivering relies predominantly on muscle glycogen that can become limiting after few hours [15].

Many studies using rodent models suggested that brown adipose tissue (BAT) is the major site of NST. BAT expresses **uncoupling protein 1** (UCP1), which functions to deplete the proton motive force developed in the mitochondrial inter-membranous space by the electron transport pathway, and is the basis for thermogenesis in BAT [17]. However, in large mammals including humans, although BAT is abundant in neonatal stages, it decreases in adulthood [14, 18]. The development of UCP1 knock out (KO) animals has revealed the

crucial importance of BAT in NST. Cold adaptation studies performed in UCP1 KO mice showed that UCP1-independent thermogenesis exists even in mice, because these mice could be gradually cold adapted and survive to full term [19]. These mechanisms include but are not limited to futile metabolic cycles like phosphocreatine cycling in beige fat, futile protein turnover and futile SERCA activity in muscle [8, 20–23]. Interestingly, BAT is either absent or inactive in certain endotherms including birds and in few mammals (boars and pigs) [24–25], suggesting that alternate thermogenic mechanisms must exist to maintain a constant body temperature (T_c). The predominant use of mice, which rely on BAT, as experimental animals for thermogenesis studies, often neglected the importance of skeletal muscle in temperature homeostasis. Initial cold adaptation studies performed in avian species provided evidence for the existence of NST in the skeletal muscle and suggested that the SR Ca^{2+} handling plays an important role in this process [24, 26]. It was elegantly shown that oxygen consumption increased in skeletal muscle of cold acclimated ducklings [27]. Dumonteil et al. demonstrated that muscle SERCA activity (measured as Ca^{2+} uptake rate) is significantly higher in cold acclimated ducklings compared to ducklings maintained at thermoneutrality [26]. More recent studies suggest that skeletal muscle SR Ca^{2+} cycling specifically uncoupling of SERCA activity by SLN could be an important mechanism for muscle-based thermogenesis in mammals including mice [8, 23, 28–29]. There is also evidence that NST mechanisms are activated during many other physiological contexts such as fear, fever, and caloric (diet)-overload [30–32]. However, it is currently not known to what extent NST pathways are recruited during each of these physiological conditions other than cold.

Calcium cycling and muscle heat production- early discoveries

Muscle function is intricately associated with oscillation of Ca^{2+} ion concentration in the cytosol. The role of SR calcium cycling in **excitation-contraction (EC) coupling** is well defined [33], while its influence on metabolic activity of skeletal muscle has not been adequately explored. During muscle contraction, Ca^{2+} cycling is initiated by membrane depolarization, activating dihydropyridine receptor (DHPR), a voltage dependent L-type calcium channels present on T-tubules. These channels can in turn activate the release of Ca^{2+} from SR through ryanodine receptor 1 (RYR1), whose activity is fine-tuned by modulatory proteins like triadin, junctin and calsequestrin that together form the calcium-releasing unit (CRU) [33]. When the cytosolic Ca^{2+} builds up, it binds to myofilaments and bring about contraction [34]. At the same time, a rise in cytosolic Ca^{2+} can trigger key Ca^{2+} dependent signaling pathways and also activate mitochondrial respiration. Once the cytosolic Ca^{2+} levels exceed the activation threshold of the SERCA, it transports the Ca^{2+} into the SR against the concentration gradient, utilizing energy from ATP hydrolysis thereby initiating relaxation [33]. Two major isoforms of SERCA are expressed in skeletal muscle: SERCA 1a and 2a. SERCA 1a isoform is expressed predominantly in fast glycolytic fibers, while SERCA 2a is predominantly expressed in slow twitch and fast-oxidative fibers. SERCA2a is the main isoform in cardiac muscle. The SERCA activity in muscle is regulated by two small proteins: phospholamban (PLB) and SLN, which will be discussed in detail below [35]. In addition to SLN and PLB, a new peptide regulator of SERCA, Myoregulin has been identified; however there is paucity of information and its physiological role is less well understood [36]. The first clear evidence that SR calcium cycling by SERCA can be

adapted to generate heat, comes from studies on deep-sea fishes called blue marlin. These fishes contain a special organ called “Heater Organ”, that is a modified extra ocular muscle tissue [7, 37]. The heater organ is enriched with SR and mitochondria to generate heat. The SR is highly specialized with an inherently leaky RyR that increases SERCA pump activity and therefore ATP hydrolysis and heat production. This is combined with enhanced mitochondrial oxidative metabolism to support ATP production and heat generation [38]. Another example where uncontrolled SR Ca^{2+} release and uptake can result in excessive heat is associated with a pathological condition called “malignant hyperthermia (MH)” found in pigs and humans [39]. MH is caused by mutations in the RYR1 that become leaky when exposed to volatile anesthetics (even exercise in some cases), causing excessive Ca^{2+} leak from the SR that leads to continuous cycling of SERCA pump and myosin ATPase, thereby generating excessive heat. Increased SERCA activity and SR remodeling has also been shown to be involved during cold adaptation in rabbits, where BAT is limited in amounts [40]. Studies in birds (BAT absent) further demonstrated that RYR1 and SERCA expression were upregulated after cold-adaptation, suggesting a role for SR Ca^{2+} handling in thermogenesis [26]. Despite these findings, the detailed mechanism that leads to increased heat production from SERCA activity during cold challenge remained unclear.

Sarcolipin, a regulator of SERCA pump, is essential for muscle thermogenesis and body temperature maintenance

As mentioned above, the activity of SERCA pump in cardiac and skeletal muscle is regulated by PLB and SLN. PLB is a 52 aa γ -phosphoprotein that inhibits SERCA activity at low cytosolic Ca^{2+} . Release of Ca^{2+} from SR and/or phosphorylation of PLB relieve inhibition of SERCA [35, 41]. Studies have shown that PLB is an important mediator of beta-adrenergic response in the heart and responsible for modulating the force frequency of heart [42]. On the other hand, SLN expression is relatively high in skeletal muscle, but its expression is restricted to atrial chamber in the heart. Compared to PLB, SLN is relatively small (31aa) and has distinct N and C-terminal residues [35, 43–44]. Recent studies have shown that SLN interaction with SERCA is unique in that it can bind to SERCA in the presence of high cytosolic Ca^{2+} [22, 43]. The mechanism behind SLN mediated muscle-based thermogenesis is not fully understood. However, recent studies have shown that when SLN binds to SERCA, it allows ATP hydrolysis to occur, but the Ca^{2+} transport into the SR is decreased due to “slippage” of Ca^{2+} back to the cytosol. This suggests that in the presence of SLN more ATP needs to be hydrolyzed by SERCA to transport the released Ca^{2+} than in the absence of SLN. There is also evidence that pre-treatment with the RYR inhibitor dantrolene, increases the sensitivity of mice to acute cold exposure [8]. Also, hyperphosphorylation of RyR1 sites, that can make it leaky, is observed in conditions when muscle-based thermogenesis is higher [16, 23]. This implies that Ca^{2+} leak from RYR is important for muscle-based thermogenesis. Taken together these data suggest that the mechanism behind SLN mediated NST is a result of futile SERCA activity leading to an increase in ATP hydrolysis and heat production. Interestingly, no such uncoupling based mechanism has been reported in MH or heater organ. Those mechanisms rely mostly on futile Ca^{2+} cycling. More recent X-ray crystallographic studies further confirmed SLN-SERCA interaction can occur in the Ca^{2+} bound state [45].

Although *in vitro* studies suggested that SLN binding to SERCA could increase heat production [22, 46–48], its role in muscle thermogenesis remained unclear. Bal et al. first studied the importance of SLN in temperature homeostasis using a SLN knock out (SLN KO) mice [8, 49]. When challenged to acute cold (4°C), these mice were unable to maintain T_c [8], providing the first physiological evidence for SLN as a contributor in thermogenesis. Reintroduction of SLN in the SLN KO background, using skeletal muscle specific SLN overexpression, rescued the cold sensitive phenotype. Further, cold exposure studies using curare (a neuro-muscular junction inhibitor), and interscapular BAT removal surgery, suggested that SLN is a contributor in muscle-based NST [8]. Interestingly, SLN-mediated NST in muscle is recruited to a greater extent in mice lacking UCP1. In addition, mice lacking both SLN and UCP1 are much more sensitive to exposure to acute cold of 4°C, than UCP1 KO mice [28]. The role of SLN in muscle-based NST was further evidenced by the recent observation that neonatal mice acclimatized to cold retain higher levels of SLN in skeletal muscle [29].

SLN plays a critical role in whole body energy metabolism

Studies have shown that humans can produce heat in response to normal feeding, a phenomenon termed thermic effect of food or **obligatory diet-induced thermogenesis** (oDIT) [50]. Interestingly, overfeeding and high fat diet studies have demonstrated that rodents and humans can increase energy expenditure to prevent excessive weight gain. This is known as **facultative DIT** (fDIT) and has become an attractive target for combating obesity. [31, 51–52]. These studies also highlighted the role of BAT and UCP1 as a major mechanism for fDIT in rodents. However it remains unclear if BAT is an important component of fDIT in humans. The skeletal muscle being a major metabolic organ could be involved in fDIT. Since SLN was found to be involved in cold activated thermogenesis, it is possible that SLN might be recruited in fDIT. Bal et al. used mice with either null for SLN (SLN KO) or skeletal muscle specific overexpression (SLN OE) to investigate the role of muscle in fDIT, *in vivo*. SLN KO and SLN OE mice were fed on high fat diet (HFD) for 12 weeks. SLN KO mice on HFD, developed increased adiposity and insulin resistance compared to WT mice, which were less obese but exhibited upregulated SLN expression in selected muscle tissues [8]. Interestingly, SLN OE mice were found to be resistant to HFD-induced obesity and did not exhibit metabolic disease [53]. SLN OE mice on HFD exhibited a higher metabolic rate compared to their controls and their muscles showed enhanced oxidative capacity. This was accompanied by increased mitochondrial biogenesis and fatty acid transport protein expression. These studies highlighted that SLN is recruited in fDIT, and increased SLN level/activity in the skeletal muscle promotes increased fat oxidation and offers protection against diet-induced obesity (DIO). However, details are missing and the mechanism behind fatty acid based activation of SLN mediated NST is yet to be understood. Interestingly, mice overexpressing SLN in muscle were able to exercise better and were found to be resistant to fatigue [54]. Collectively these studies suggested that SLN is an important regulator of muscle metabolism.

The relevance of SLN expression in neonatal and adult skeletal muscle

In rodents SLN expression is regulated in a developmental and tissue specific manner. SLN expression is induced in all skeletal muscles during late embryonic development (~1 week before birth) and the level of expression increases right after birth reaching its maximum 1–3 days after birth in rodents [55]. Gradually, SLN expression is down regulated during neonatal development and by the weaning age (~21 day old) it becomes restricted to slow-twitch/oxidative fibers. In adult mice (8–16 week old) the relative SLN expression level can be ordered as follows: atria> diaphragm> soleus> tongue> red gastrocnemius> trapezius> oxidative fiber rich portion of quadriceps>oxidative fiber rich portion of tibialis anterior. It is interesting that one of the most critical challenges that a newborn mammal faces in the extra-uterine environment is triggering thermogenesis to maintain Tc on their own. Importantly, during neonatal stage the muscles are not mature enough to support shivering, neonates lack insulation by fur and their surface-to-body ratio is higher causing significant heat loss [56]. In spite of the above odds neonate mice are able to survive because they are equipped with abundant BAT. The presence of relatively high SLN expression in mouse and rat skeletal muscles during the first two weeks after birth, suggests that SLN is important for muscle-based NST in neonates that lack shivering ability [29, 55]. It was recently demonstrated that when neonatal mice are acclimatized and reared in cold, SLN expression is retained and continues to express at higher levels beyond weaning age, when compared to mice reared at thermoneutrality. Along with SLN, the expression of SERCA2a isoform is much higher in cold reared mice [29]. This delay in the isoform switch from SERCA 2a to SERCA 1a, as normally observed during development, has also been shown in cold acclimated ducklings [26]. As mentioned earlier, SERCA 2a isoform is expressed predominantly in slow twitch / fast oxidative muscle. In addition, SERCA 2a exhibits slower Ca²⁺ transport kinetics than SERCA 1a, possibly due to lower affinity for Ca²⁺ [57–58]. The upregulation of SERCA2a expression in cold adapted neonates suggests a shift in the fiber type towards slow oxidative. It is possible that the slow kinetics of SERCA2a along with interaction with SLN support the heat generating capacity of skeletal muscle. In a recent study Bal et al. have shown that conditional ablation of interscapular BAT in adult mice induces SLN expression in muscle, when exposed to cold challenge [23]. These studies provide convincing evidence that SLN-SERCA interaction is an important component of muscle-based thermogenesis. They further suggest that the expression of SLN is regulated by physiological demand.

Significance of increased SLN expression in dystrophic/diseased skeletal muscle

Dystrophic muscle disease has a major effect on muscle structure/function and metabolism. It is often associated with poor muscle function but with increased energy demand [59]. Further, the calcium cycling is altered due to membrane instability and disorganization of SR structure. In Duchenne muscular dystrophy (DMD) the glycolytic muscles are more severely affected and there is an increase in oxidative fiber type [60]. Recent studies have shown that expression of SLN is upregulated several folds in the mouse models of DMD [61]. In addition, there is an upregulation in protein expression of SERCA 2a in these dystrophic muscles. Few studies have highlighted the impact of DMD on muscle and whole body

metabolism [62–63]. In addition to DMD, SLN expression is also upregulated in rodent skeletal muscles in various **dysferlinopathies**, α -tocopherol deficiency, myotonic dystrophy and dynamin dependent centronuclear myopathy [64–67]. Since metabolic demand is high in these muscles, the upregulation of SLN could be part of a global process promoting the oxidative metabolism to cope with the compromised muscle function.

SLN promotes oxidative metabolism in skeletal muscle in response to increased metabolic demand

DIO, muscle disease, exercise and cold impose a metabolic demand on the body, which necessitates reallocation of energy (and/or substrate) utilization between different organs. Under such conditions the skeletal muscle shows flexibility in substrate utilization to accommodate the needs of other organs including brain. It is well known that oxidative muscles can cope with greater energy demand and are less vulnerable to fatigue than glycolytic fast twitch muscles [68]. Their machinery is ideally suited to support long enduring physical tasks. During cold exposure, oxidative muscles are better suited to generate heat, because of their ability to maintain high-energy demand. Shifting to oxidative metabolism is also beneficial in redistributing fuel sources and energy consumption between different organs. Conditions of high/altered energy demand impose metabolic stress and trigger the release of stress hormones like glucocorticoids that are known to activate mitochondrial biogenesis in skeletal muscle [69]. Interestingly, glucocorticoids are also known to upregulate the expression of SLN in skeletal muscle [70]. The presence of SLN in slow twitch / oxidative fibers, in rodents, indicates that there is a physiological connection between SLN expression and oxidative metabolism. The fact that SLN overexpression in fast twitch glycolytic muscle promoted mitochondrial biogenesis and oxidative metabolism further supports this connection [53]. An interesting finding was that SLN overexpression increased **PGC-1 α** and **PPAR δ** expression and resulted in higher calcineurin activity, which are in line with higher mitochondrial biogenesis. These studies also suggested that SLN regulates muscle metabolism by altering cytosolic Ca^{2+} (Figure 2). Specifically, SLN uncoupling of SERCA leads to an elevation in cytosolic Ca^{2+} that serves as a powerful signal 1) to facilitate Ca^{2+} entry into mitochondria and activate mitochondrial metabolism and 2) to activate Ca^{2+} dependent signaling pathways including calcineurin and Ca^{2+} / Calmodulin dependent protein kinase II (CamKII), important for programming the muscle into an oxidative phenotype through the activation of PGC1 α and PPARs [71–73].

Concluding remarks and future perspectives

In the mammalian body, skeletal muscle is one of the most abundant tissues and serves as a major metabolic organ. Because of its ability to generate heat through shivering and nonshivering mechanisms, muscle can play important homeostatic roles, in thermogenesis as well as in whole body metabolism by regulating fuel utilization. Therefore, future research should explore how NST in muscle can be exploited to regulate whole body energy metabolism. Recent discoveries have uncovered the importance of cross talk between muscle and other organs in the regulation of energy metabolism both under healthy and diseased conditions [51, 74]. Muscle also has enormous flexibility in substrate utilization and can

switch back and forth between fat and carbohydrate to accommodate energy demand and substrate availability during various patho-physiological conditions. Studies using mouse models have highlighted that SLN mediated SR Ca^{2+} cycling and hence intracellular Ca^{2+} plays an important role in integrating muscle energy demand with energy production. Although, significant progress has been made recently in understanding the function of SLN, much remains to be understood regarding its regulation and mechanism of heat production (see Outstanding Questions). The importance of SLN in human physiology remains relatively unknown. A recent study has shown that SLN-mediated metabolism is downregulated in obese humans [75]. These data are exciting and warrant further studies, to discover the full potential of SLN-SERCA mediated muscle-based thermogenesis in humans. Determining the factors that can directly regulate SLN's expression and/or function will provide attractive therapeutic targets for enhancing skeletal muscle metabolism and opportunities to counter obesity related metabolic diseases.

Acknowledgments

This work was supported in part by NIDDK-National Institutes of Health Grants R01 DK098240-01, American Diabetes Association Basic Science Research Award (7-13-BS-131) (to M. Periasamy.) and Award DK102772 (to N. C. B.). N.C.B. is recipient of a Ramalingaswamy Re-entry Fellowship from the Department of Biotechnology, India.

Glossary

Adipokines

Peptide hormones secreted from fat tissues

Brown adipose tissue (BAT)

is a highly specialized organ enriched with mitochondria that express the mitochondrial transmembrane protein uncoupling protein 1 (UCP1)

Dysferlinopathies

A neuromuscular disorder that is caused by a deficiency of the muscle repair protein dysferlin

Excitation-Contraction Coupling

The process in which the action potential generated by motor neurons causes the muscle to undergo contraction

Facultative Diet-induced Thermogenesis (fDIT)

The increase in energy expenditure in BAT and skeletal muscle in response to overfeeding that helps to protect against weight gain

Indirect Calorimetry

A technique that measures the amount of oxygen inhaled and carbon dioxide exhaled by the body. The volume and ratio of these two gasses helps to determine the metabolic state of the body

Myokines

They include cytokines or other small peptides secreted by muscle cells that can have autocrine, paracrine or endocrine effects

Nonshivering thermogenesis (NST)

is thermogenic activity that occurs in BAT and muscle that is independent of the repetitive muscular contraction (shivering). The mechanism of activation could be hormonal and or neuronal

Obligatory Diet-induced thermogenesis (oDIT)

is the post-prandial increase in energy expenditure above basal metabolism that is required for the digestion, absorption and storage of nutrients

PPAR gamma coactivator 1 α (PGC1 α)

is a transcriptional co-activator that regulates the expression of genes involved in metabolism. It is an important regulator of mitochondrial biogenesis

Peroxisome proliferator-activated receptor δ (PPAR δ)

is a nuclear hormone receptor and plays an important role in regulating glucose and lipid metabolism

Sarcolipin (SLN)

is a small protein that coexists with SERCA in the muscle sarcoplasmic reticulum

Sarcoplasmic reticulum (SR)

It is a specialized endoplasmic reticulum present in striated muscle cells. It acts as a Ca^{2+} store and regulates Ca^{2+} concentration in the cell

Sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase (SERCA)

It is a P- type Calcium ATPase present on SR. It transports calcium from cytoplasm into the SR and hydrolyzes ATP in the process

Thermogenesis

The process of heat generation in the body

Uncoupling protein 1 (UCP1)

A transmembrane protein present in the mitochondrial membrane of brown adipose tissue (BAT). It uncouples the oxidative phosphorylation from ATP synthesis, generating heat in the process

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BOX 1**Muscle also serves as an important metabolic and endocrine organ**

Muscle is a major consumer of metabolites due to constant maintenance and renewal of its mass, therefore serves as a key determinant of the basal metabolic rate, and metabolic homeostasis. For example, under normal physiological conditions skeletal muscle crosstalk with liver is responsible for regulating glucose levels in the body. However, during intense exercise muscle metabolic rate can be swiftly upregulated to utilize a substantial percentage of whole body glucose [5]. Additional metabolic flexibility allows muscle to use fat or ketones depending on availability and physiological demand [76]. During infection or starvation, muscle can switch to fatty acid utilization allowing continued glucose utilization by other organs like brain that rely on it exclusively. When challenged with prolonged starvation, skeletal muscle can trigger degradation of its proteins to provide amino acids for gluconeogenesis in liver (Figure 1). The role of skeletal muscle in the whole body metabolic demand is also supported by recent studies using high-precision **indirect calorimetry** that measured oxygen consumption in resting forearm of human subjects and demonstrated that skeletal muscle accounts for at least 20% of whole body oxygen uptake [6]. These results provided evidence that energy expenditure in skeletal muscle is much higher than accounted by only the contractile status of the muscles recruited.

Skeletal muscle also serves as an important endocrine organ and secretes several “**myokines**” in a muscle activity-dependent or -independent manner. For example, it is known that interleukin 6 (IL-6) level is increased several folds in the circulation during intense physical exercise [77]. IL-6 plays a key role in the substrate utilization by enhancing lipolysis in white adipose tissue (WAT), glycolysis in the liver, and insulin secretion from the pancreas. The importance of IL-1, IL-8 and IL-15 as myokines is also becoming clear during basal metabolism, diet overload, exercise and cold adaptation [78]. More recent studies have identified several other myokines including leukemia inhibitory factor (LIF), insulin-like growth factor (IGF)-1, fibroblast growth factor (FGF)-2, and FGF-21, that play an important role in energy homeostasis by regulating function of multiple organs. The role of these myokines in general and in particular the role of FGF-21 as a key regulator of metabolism in liver, heart, WAT, BAT and pancreas function, is an emerging area of research [79]. A better understanding of the regulation of skeletal muscle metabolism and its crosstalk with other organs will provide insight towards manipulating whole body energy expenditure (Figure 1, Table 1)

Outstanding Questions

- How does muscle integrate contractile, thermogenic and metabolic functions? Is it through Ca^{2+} regulation or myokines or through mechanisms yet to be defined?
- During metabolic overload, how does muscle interact with other organs including liver? Is it entirely through myokines or through other mechanisms including metabolites?
- How does SLN-SERCA interaction modify overall Ca^{2+} homeostasis in muscle? What is the impact of increasing SLN on plasma membrane and mitochondrial regulators of Ca^{2+} entry and efflux?
- How does SLN interaction with SERCA leads to increased oxidative metabolism? Is prolonged increase in SLN expression beneficial or detrimental?
- Does SLN promote mitochondrial biogenesis through known or novel signaling mechanisms?
- Is upregulation of SLN beneficial under diseased conditions? What roles inflammatory pathways play in upregulating SLN expression?
- Is there a relationship between myokine production and SLN expression? Is muscle thermogenesis synchronized by autocrine or paracrine action of slow-twitch muscles, where SLN expression is more abundant?
- Is SLN-SERCA interaction an ideal target to increase energy metabolism and combat metabolic disorders? Can SLN levels be manipulated pharmacologically?

Trends Box

- Recent studies have highlighted that skeletal muscle plays important roles as a metabolic, thermogenic and endocrine organ.
- It has been known that the SR calcium ion transport is recruited in muscle-based thermogenesis, but the mechanistic details were missing.
- Uncoupling of SERCA by SLN increases ATP hydrolysis, enhances muscle metabolism and promotes heat generation. It also alters cytosolic calcium levels, which act as a powerful signal to regulate mitochondrial metabolism and architecture.
- Overexpression of SLN in muscle improves muscle energetics, providing resistance to diet induced obesity.
- SLN protein levels are upregulated during diet overload, cold adaptation and in dystrophic skeletal muscle suggesting that SLN might be involved in promoting oxidative metabolism during conditions of metabolic stress.

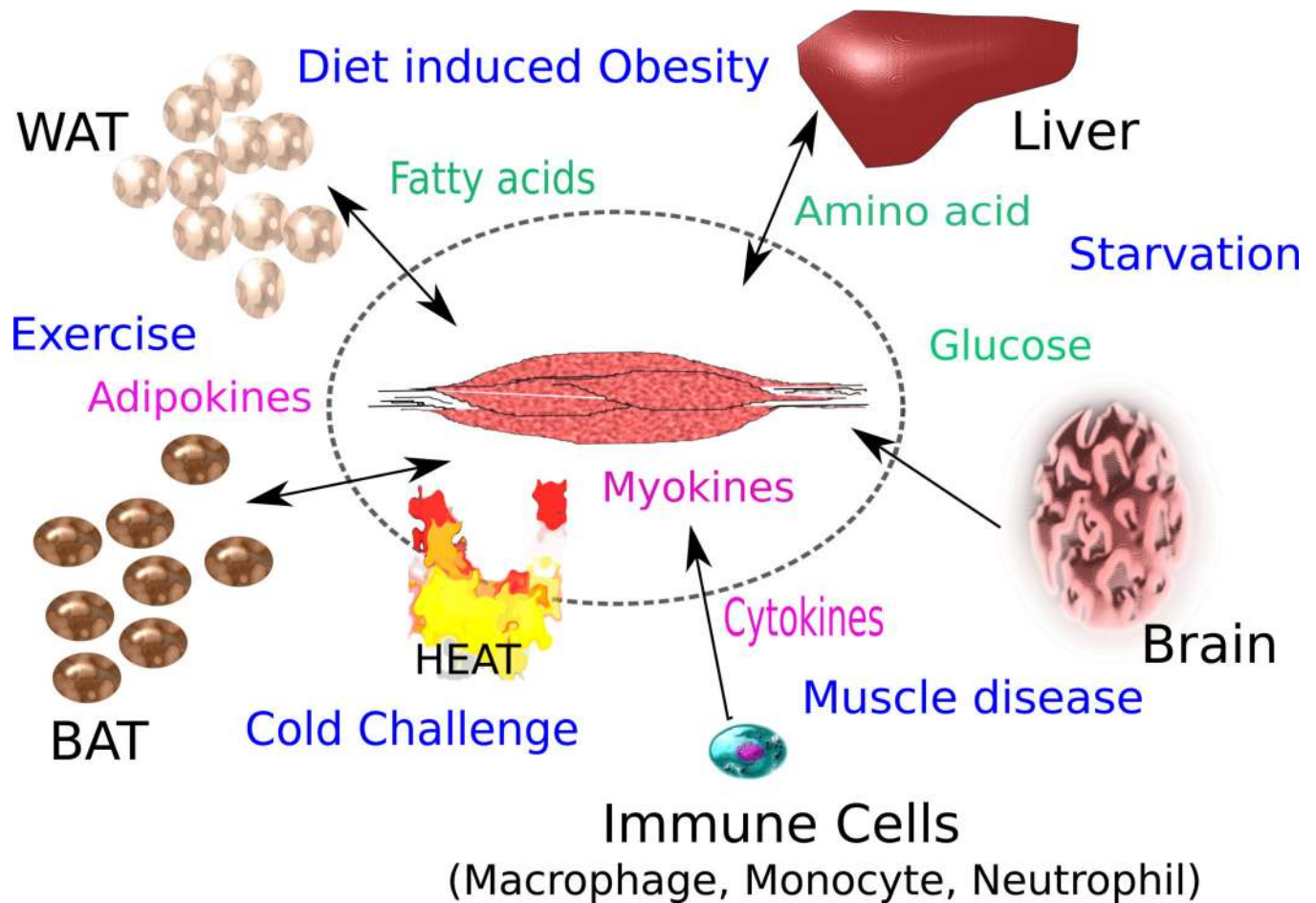


Figure 1. Skeletal muscle also serves as an important thermogenic, metabolic and endocrine organ

Skeletal muscle is involved in both shivering and nonshivering thermogenic mechanisms, which are recruited during cold adaptation and facultative diet induced thermogenesis (fDIT). Skeletal muscle also serves as an endocrine organ by secreting several myokines to communicate with other participating organs (BAT, WAT, Liver and Brain) to maintain energy homeostasis under different metabolic and patho-physiological stress conditions, including exercise, inflammation and muscle disease. Exercise induced increase in energy expenditure has been shown to be beneficial in treating metabolic disorders. Crosstalk between adipose tissues and skeletal muscle through **adipokines** and myokines facilitate metabolic homeostasis. Neuro-hormonal input from the central nervous system plays a central role in coordinating muscle physiology and metabolism. WAT- White Adipose Tissue, BAT- Brown Adipose Tissue

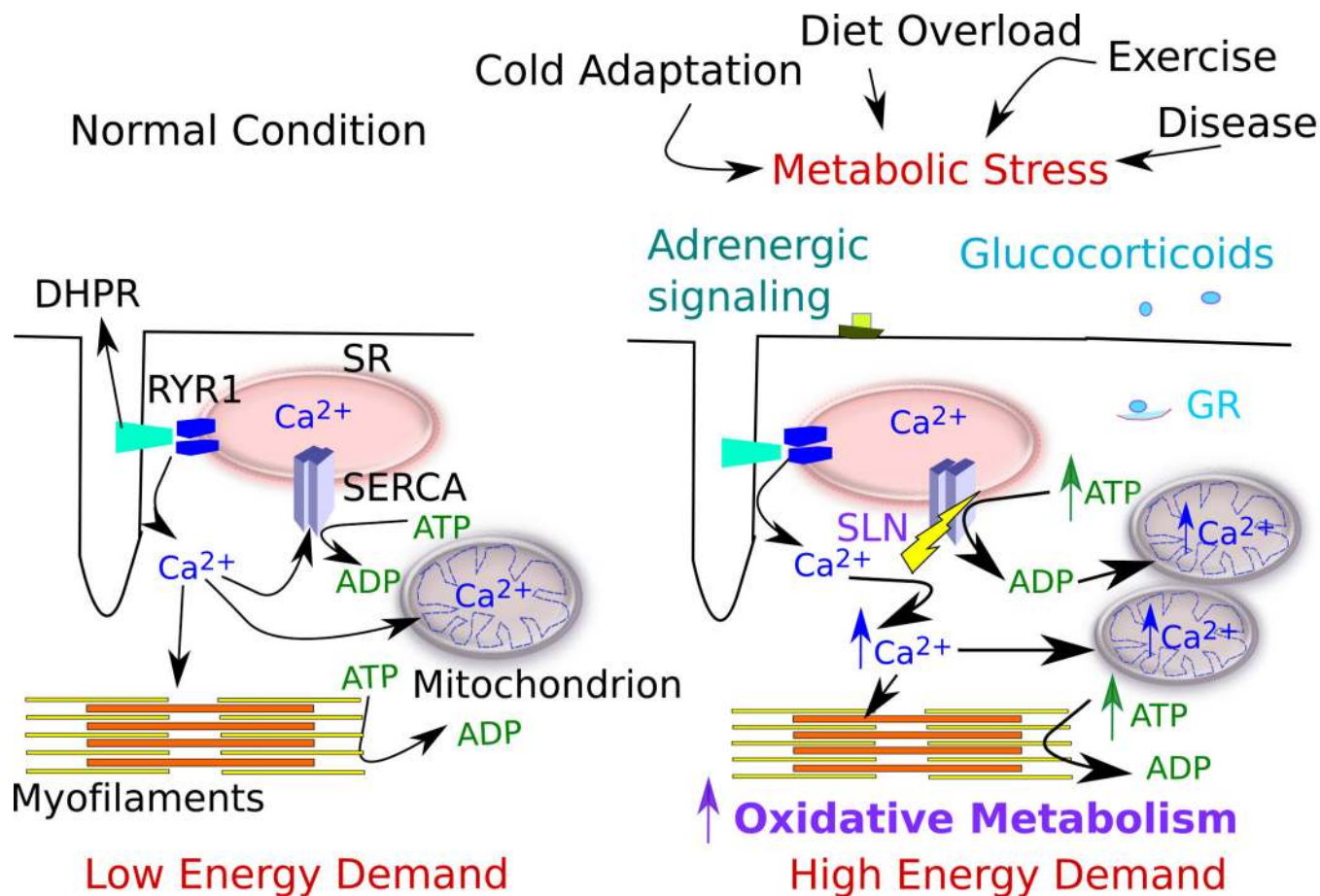


Figure 2. Sarcolipin promotes oxidative metabolism under conditions of increased energy demand

During muscle contraction, membrane depolarization leads to activation of DHPR/RYR1 complex leading to release of Ca²⁺ from the SR. As the cytosolic Ca²⁺ concentration rises, it binds to myofilaments and triggers muscle contraction. Elevated cytosolic Ca²⁺ activates SERCA which pumps Ca²⁺ back into the SR. The energy demand during normal activity (routine functions) is relatively low. On the other hand, many different patho-physiological states increase energy demand in muscle. In addition, several cytokines and neuro-hormonal mechanisms (including glucocorticoids and adrenergic signaling) are activated to orchestrate muscle metabolism. SLN expression is also upregulated under these high-energy demand conditions. Higher SLN/SERCA level leads to higher cytosolic Ca²⁺ and facilitates its uptake into mitochondria, which serves as a trigger for oxidative metabolism. In addition Ca²⁺-signaling pathways activate increased transcription of genes involved in oxidative metabolism. DHPR- dihydropyridine receptor, GR- glucocorticoid receptor, RYR1- ryanodine receptor 1, SERCA-sarco/plasmic/endoplasmic reticulum calcium ATPase, SLN-sarcolipin, SR- sarcoplasmic reticulum.

Table 1

Role of skeletal muscle beyond contraction

Function	Regulator	Study model	Phenotype	Ref.
Ca²⁺ handling proteins	SLN	SLN KO mice	Sensitivity to cold induced thermogenesis and diet induced obesity (DIO)	[8]
	SLN	Skeletal muscle specific SLN overexpression in mice	Rescue of cold sensitive phenotype, resistance to DIO, increased fatty acid metabolism and fatigue resistance	[8, 53]
	PLB	PLB skeletal muscle overexpression in mice	Centronuclear myopathy like phenotype	[80]
	RYR1	Mice with leaky RYR1	Malignant hyperthermia, increased skeletal muscle metabolism	[39]
Metabolic Regulators	PPAR δ/β	Treatment with PPAR δ agonist in mice	Increased fatty acid oxidation, resistance to HFD induced obesity in mice	[81]
	PPAR α	Skeletal muscle specific PPAR α overexpression in mice	Resistance to obesity, glucose intolerance	[82]
	PGC1 α	Skeletal muscle specific PGC1 α overexpression in mice	Increased oxidative fibers, Increased fatigue resistance and endurance capacity	[83–84]
	PGC1 α	Skeletal muscle specific PGC1 α KO mice	Decreased oxphos genes, abnormal glucose homeostasis	[85–86]
	PGC1 β	Skeletal muscle specific PGC1 β overexpression in mice	Increased oxidative fibers, increase oxidative work capacity	[87]
	PGC1 β	Skeletal muscle specific PGC1 β knock out in mice	No effect on glucose homeostasis	[88]
	PGC1 α , PGC1 β	Skeletal muscle specific double knockout	Decreased exercise performance, decreased oxidative capacity, mitochondrial structural derangements	[88]
	Estrogen-related receptor γ (ERR- γ)	Skeletal muscle specific ERR- γ overexpression in mice	Increased exercise capacity, increased mitochondrial enzyme activity	[89]
	Leptin/AMP activated kinase (AMPK)	Leptin treatment \pm AMPK inhibitor	Decreased mitochondrial respiration when AMPK is inhibited	[90]

Function	Regulator	Study model	Phenotype	Ref.
	Leptin/ Phosphoinositide 3 kinase (PI3K)	Leptin treatment± PI3K inhibitor	Decreased mitochondrial respiration when PI3K is inhibited	[90]
	Nur77	Skeletal muscle specific Nur77 overexpression in mice	Increased oxidative metabolism, improved cold tolerance	[91]
	Lipoprotein lipase (LPL)	Skeletal muscle specific LPL overexpression in mice	Increased cold tolerance	[92]
Mitochondrial dynamics regulators	Mitofusin 2 (Mfn2)	Muscle specific expression analysis	Decreased skeletal muscle Mfn2 expression in obese humans	[93]
	Mfn2	Mfn2 repression in myotubes	Decreased glucose oxidation, decreased respiration	[93]
	Dynamin-related protein 1 (Drp1)	Ceramide induced Drp1 over expression in myotubes	Decreased mitochondrial respiration, disrupted insulin signaling. Drp 1 knockdown prevented these effects	[94]
Myokines	IL-6	Il-6 KO mice	Develop late onset obesity, impaired glucose homeostasis	[95]
	Irisin	Increased FNDC5/Irisin in human myocytes/ adipocyte culture	Increased energy expenditure	[96]
	FGF 21	Muscle specific constitutive activation of mTORC1 in mice	Increased plasma FGF 21, lean mice, increased insulin sensitivity, increased fatty acid oxidation	[79]
Hormones	Thyroid	Thyroid receptor α Knockouts	Muscle LPL and deiodinases are recruited to compensate for reduced BAT function	[97]
	β 2-adrenoceptor	β 1,2 and 3-adrenoceptor global knockout mice	Enhanced insulin sensitivity, increased adiposity and glucose intolerance	[98]
	Glucocorticoid	Treatment of rats with dexamethazone	Mitochondrial biogenesis in skeletal muscle	[69]
Ca²⁺ signaling regulators	Ca ²⁺ /Calmodulin dependent protein kinase kinase (CamKK α)	Increased expression in mice skeletal muscle using vectors	Increased glucose uptake in skeletal muscle	[99]
	Calcineurin	Activated Calcineurin in mice skeletal muscle	Increased lipid oxidation, increased glycogen synthesis, increased oxidative phosphorylation, increased expression of PPAR α and δ and	[73]

Function	Regulator	Study model	Phenotype	Ref.
			PGC1 α	

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