



Histone Deacetylases as Modulators of the Crosstalk Between Skeletal Muscle and Other Organs

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Skeletal muscle plays a major role in controlling body mass and metabolism: it is the most abundant tissue of the body and a major source of humoral factors; in addition, it is primarily responsible for glucose uptake and storage, as well as for protein metabolism. Muscle acts as a metabolic hub, in a crosstalk with other organs and tissues, such as the liver, the brain, and fat tissue. Cytokines, adipokines, and myokines are pivotal mediators of such crosstalk. Many of these circulating factors modulate histone deacetylase (HDAC) expression and/or activity. HDACs form a numerous family of enzymes, divided into four classes based on their homology to their orthologs in yeast. Eleven family members are considered classic HDACs, with a highly conserved deacetylase domain, and fall into Classes I, II, and IV, while class III members are named Sirtuins and are structurally and mechanistically distinct from the members of the other classes. HDACs are key regulators of skeletal muscle metabolism, both in physiological conditions and following metabolic stress, participating in the highly dynamic adaptative responses of the muscle to external stimuli. In turn, HDAC expression and activity are closely regulated by the metabolic demands of the skeletal muscle. For instance, NAD⁺ levels link Class III (Sirtuin) enzymatic activity to the energy status of the cell, and starvation or exercise affect Class II HDAC stability and intracellular localization. SUMOylation or phosphorylation of Class II HDACs are modulated by circulating factors, thus establishing a bidirectional link between HDAC activity and endocrine, paracrine, and autocrine factors. Indeed, besides being targets of adipo-myokines, HDACs affect the synthesis of myokines by skeletal muscle, altering the composition of the humoral milieu and ultimately contributing to the muscle functioning as an endocrine organ. In this review, we discuss recent findings on the interplay between HDACs and circulating factors, in relation to skeletal muscle metabolism and its adaptative response to energy demand. We believe that enhancing knowledge on the specific functions of HDACs may have clinical implications leading to the use of improved HDAC inhibitors for the treatment of metabolic syndromes or aging.

Keywords: HDACs, tissue crosstalk, soluble factors, epigenetics, HDAC inhibitors (HDACi)

INTRODUCTION

Skeletal muscle significantly affects body mass and energy consumption, being characterized by a highly dynamic response to energy demand (Baskin et al., 2015). Indeed, skeletal muscle is the most significant metabolic organ, accounting for up to 30% of resting energy expenditure (Zurlo et al., 1990). Considered a key site for glucose uptake and storage, and a reservoir of amino acids, skeletal muscle exerts a crucial role in modulating energy and protein metabolism throughout the body (Turner et al., 2014; Ahima and Park, 2015). Adult skeletal muscles have a diverse pattern of myofibers (Staron, 1997): the slow-twitch, or type I, myofibers are characterized by a higher content of mitochondria and have an oxidative metabolism, as opposed to the fast-twitch, or type II, myofibers, which mostly rely on a glycolytic metabolism (Schiaffino and Reggiani, 2011; Talbot and Maves, 2016). Metabolic demand or a disease state both affect the composition of the skeletal muscle fiber type. For instance, insulin resistance correlates with an increase in the anaerobic and glycolytic capacities of muscle, similarly to what happens in obesity and diabetes (Simoneau et al., 1995). On the other hand, age-related sarcopenia is characterized by an increase in the relative amount of slow-twitch fibers and by the atrophy of the fast ones (Gannon et al., 2009; Daou et al., 2020; Berardi et al., 2021).

The mechanisms whereby skeletal muscle mediates metabolic changes in other tissues is a clinically relevant, dynamic avenue of investigation. An increasingly high number of muscle-derived soluble molecules is known to induce a plethora of effects in the whole body and to mediate inter-organ cross-talk (Severinsen and Pedersen, 2020) and numerous studies also reveal that changes in skeletal muscle factors can modulate metabolism systemically (Chen et al., 2010; Correia et al., 2015; Pereira et al., 2017). The expression of many muscle-derived soluble factors is reported as being altered in disease, including in cancer, type 2 diabetes, obesity, or heart failure (Liu et al., 2015; Berezin et al., 2021; Evans et al., 2021; Pin et al., 2021), suggesting the importance of these factors in the crosstalk between muscle and other organs/tissues in pathological conditions. However, the metabolic adaptations of the skeletal muscle, up to now often merely seen as a consequence of a disease state, may be exploited in a pro-active way to treat metabolic disorders. In this scenario,

Abbreviations: AcH3K9, Acetyl-Histone H3 (Lys9); AMPK, AMP-activated protein kinase; ANGPTL4, Angiopoietin-like protein 4; ATF4, Activate transcription factor 4; AP-1, Activator protein 1; BAIBA, β -aminoisobutyric acid; BDNF, Brain-derived neurotrophic factor; cAMP, Cyclic adenosine monophosphate; ER, Endoplasmic Reticulum; FGF-21, Fibroblast growth factor 21; GLUT4, Glucose transporter type 4; HAT, Histone Acetyltransferases; HDAC, Histone Deacetylases; HDACi, HDAC inhibitors; HFD, High fat diet; IL-1, Interleukin 1; IL-6, Interleukin 6; IL-15, Interleukin 15; IKK, Nuclear factor- κ B Kinase; JNK, c-Jun N-terminal kinase; LPL, Lipoprotein lipase; MDC, Muscle-derived cells; MEF2, Myocyte enhancer factor-2; Metrnl, Meteorin-like; mTOR, Mammalian target of rapamycin; MyoD, Myoblast determination protein 1; NAD, Nicotinamide adenine dinucleotide; NF κ B, Nuclear factor kappa-light-chain-enhancer of activated B cells; TNF α , Tumor Necrosis Factor- α ; TSA, Trichostatin-A; PGC-1 α , Peroxisome proliferator-activated receptor- γ coactivator-1 α ; PPAR- δ , Peroxisome proliferator-activated receptor- δ ; SIK1, Salt-inducible kinase 1; SIRT, Sirtuin; STAT3, Signal Transducer And Activator Of Transcription 3; VPA, Valproic acid; WAT, White adipose tissue.

exercise training as a preventive and therapeutic strategy in several diseases has already been proposed (Leal et al., 2018; de Lima et al., 2020; Severinsen and Pedersen, 2020). Indeed, muscle contraction represents a major physiological stimulus to activate the release of a variety of soluble factors, in a time- and intensity-dependent fashion (Hutchinson et al., 2019; Kurgan et al., 2019; Piccirillo, 2019; Florin et al., 2020).

Histone deacetylases (HDACs) work as epigenetic factors by repressing gene transcription through the removal of acetyl groups from the tails of histone proteins or, alternatively, modulate various cellular responses through their deacetylase activity on non-histone proteins (Glozak et al., 2005; Hyndman and Knepper, 2017). We find it intriguing that HDACs modify gene expression in the skeletal muscle tissue in response to humoral factors, and that, in turn, several HDACs modulate the expression of soluble factors, ultimately affecting their levels in the circulation. The fact that the genetic expression of secreted products is regulated by epigenetic factors adds up to the complexity of the regulatory network controlling myokine production. Also, that multiple tissues are responsible for the coordinated production of the same endocrine factors, such as certain adipo-myokines, highlights this phenomenon in all its complexity.

In this review article, first we introduce HDACs (paragraph 2) and their key role in skeletal muscle metabolic responses (paragraph 3), then we review the most recent findings on how myokines directly or indirectly regulate metabolic reprogramming (paragraph 4): in particular, we focus on those myokines that affect HDAC expression and activity (paragraph 5) and, vice-versa, on those HDACs that affect myokine synthesis and release (paragraph 6); lastly, we conclude with the clinical implications of the use of HDAC inhibitors (paragraph 7).

THE HISTONE DEACETYLASES AND THEIR CLASSIFICATION

Chromatin is a highly organized nucleoprotein complex, mainly composed by DNA and histone proteins that form nucleosomes. The DNA transcription rate depends, among other factors, on changes in the structure of the nucleosomes. Highly compact and dense chromatin, known as heterochromatin, is associated with the repression of transcriptional activity; whereas open chromatin, or euchromatin, is associated with transcriptional activation. The packaging of chromatin depends mainly on modifications, including acetylation, of the N-terminal histone tails, which protrude from the nucleosome. Histone acetylation levels are regulated through the interplay between two families of enzymes, namely histone acetyltransferases (HATs) and HDACs, and chromatin (Peserico and Simone, 2011). The deacetylation of histones increases their positive charge and consequently their affinity to the DNA, inducing the formation of a compacted, transcriptionally repressed chromatin structure. However, HDACs also target non-histone proteins and finely tune their activity and function by means of deacetylation

(Bannister and Kouzarides, 2011; Peserico and Simone, 2011; Hyndman and Knepper, 2017).

To date, 18 different mammalian HDACs have been identified and divided into four classes according to their sequence similarity to yeast counterparts (Seto and Yoshida, 2014; Park and Kim, 2020): Class I HDACs (HDAC1, 2, 3, and 8), Class II HDACs (HDAC4, 5, 6, 7, 9, and 10), Class III HDACs (Sirtuins), which differ from the others because they use NAD⁺ as a cofactor rather than Zn²⁺, and Class IV HDACs (HDAC11). Class II HDACs is further divided into two subgroups, Class IIa (HDAC4, 5, 7, and 9) and Class IIb HDACs (HDAC6 and 10), which differ significantly in many biological aspects, from subcellular localization to their involvement in diseases. Whereas most Class I HDACs are ubiquitously expressed and localized in the nucleus, the Class II HDACs are characterized by tissue-specific expression and stimulus-dependent nucleus-to-cytoplasm shuttling (Haberland et al., 2009). Class III HDACs, which are ubiquitously expressed in human tissues (Frye, 1999), have differential subcellular localizations: SIRT1, SIRT6, and SIRT7 are primarily detected in the nucleus, SIRT2 is mainly found in the cytosol, while SIRT3, SIRT4, and SIRT5 are present exclusively in mitochondria (Michishita et al., 2005). HDAC11, the only member of Class IV, seems to be mainly expressed in the kidney, heart, brain, skeletal muscle, and testis, and is localized in the nucleus of the cell (Michishita et al., 2005).

Histone deacetylases control essential phenomena such as cell cycle progression, cell survival and differentiation (Moresi et al., 2016). Consistently, HDAC deregulation plays a key role in many pathologies, including cancer, neurological, inflammatory and cardiac diseases, as well as metabolic and neuromuscular disorders (Haberland et al., 2009; Volmar and Wahlestedt, 2015; Li and Seto, 2016; Pigna et al., 2019). The involvement of HDACs in the regulation of skeletal muscle metabolism is highlighted below.

HISTONE DEACETYLASES ARE KEY REGULATORS OF SKELETAL MUSCLE METABOLISM

The interplay between epigenetics and skeletal muscle metabolism has been thoroughly described (Sharples et al., 2016; Tzika et al., 2018; Jacques et al., 2019). In particular, HDAC activity orchestrates the metabolic reprogramming of skeletal muscle in response to physiological challenges and in several disease states (Howlett and McGee, 2016; Bianchi et al., 2017; Astratenkova and Rogozkin, 2019).

The role of HDACs in muscle metabolism has been extensively studied over the years. Early evidence revealed that Class IIa HDACs have a main role in regulating myofiber identity in physiological conditions. Indeed, Class IIa HDACs associate with MEF2 transcription factors ultimately repressing their transcriptional activity thereby regulating the metabolism of oxidative, slow-twitch myofibers (Wu et al., 2000; Potthoff et al., 2007). In particular, HDAC5 directly binds to the promoter region of *GLUT4*, repressing the transcription of this gene. This

ultimately leads to the shift of muscle fibers toward oxidative metabolism promoting their glucose uptake (McGee et al., 2008).

The Class I members HDAC1 and HDAC2 are essential to skeletal muscle metabolism and homeostasis in physiological conditions. The deletion of HDAC1 and HDAC2 in skeletal muscle induces a shift toward a more oxidative metabolism and higher energy expenditure, caused by defects in the autophagy flux (Moresi et al., 2012). More recently, an important role in muscle energy metabolism was demonstrated for HDAC3 by means of its muscle-specific deletion: this causes an insulin resistance associated with higher endurance and fatigue resistance, due to a decrease in the uptake of glucose and an increase in the consumption of lipids (Hong et al., 2017; Song et al., 2019). The involvement of Class I HDACs in skeletal muscle metabolism was further demonstrated through the pharmacological inhibition of this class (Galmozzi et al., 2013), validating previous findings obtained through genetic approaches.

Being nicotinamide adenine dinucleotide (NAD⁺)-dependent enzymes, Sirtuins control gene transcription in response to changes in nutrient availability and energy demand. Indeed, an energy deficit increases the cellular NAD⁺/NADH ratio, thus activating Sirtuins which promote mitochondrial biogenesis and fatty acid oxidation in skeletal muscle, by deacetylating both histone and non-histone proteins (Houtkooper et al., 2012), as a response to the low energy condition (Ryall, 2012). It is worth noting that the deletion of SIRT1 in mice has modest effects on skeletal muscle metabolism (Menzies et al., 2013), implying a biological redundancy of this adaptive response.

In addition to regulating metabolic homeostasis in the whole body, by controlling insulin sensitivity and glucose tolerance (Bhaskara, 2018), the Class IV member HDAC11 has been recently reported to play a crucial role in skeletal muscle metabolism and function (Hurtado et al., 2021). HDAC11 localizes in muscle mitochondria and its deletion increases mitochondrial content, causing a glycolytic-to-oxidative muscle fiber switch (Hurtado et al., 2021).

Metabolic stresses, such as exercise, obesity, or a high fat diet (HFD), induce skeletal muscle adaptations through HDACs. Exercise modulates skeletal muscle metabolism *via* epigenetic reprogramming, partially through the phosphorylation-dependent nuclear export of Class II HDACs (McGee and Hargreaves, 2011). In addition, exercise also affects Sirtuin activity, as shown by the fact that a number of histone and non-histone Sirtuin targets are deacetylated during exercise (Cantó et al., 2009). Furthermore, obesity and HFD induce epigenetic reprogramming in skeletal muscle, involving Class I and II HDACs (Berdeaux et al., 2007; Sun et al., 2011; Moresi et al., 2012), although, the underlying mechanisms are not yet fully known.

Given the crucial role of HDACs in the regulation of muscle metabolism in various pathophysiological conditions, it is not surprising that not only HDACs in skeletal muscle are targeted by soluble factors, but also that they regulate the production of myokines affecting other tissues. The role played by myokines and adipo-myokines is outlined in the next paragraph, in which

we describe how these factors of muscle and non-muscle origin are able to reprogram the metabolic activity of several tissues, ultimately determining metabolic adaptations in the whole body.

MYOKINES AS MEDIATORS OF METABOLIC REPROGRAMMING

Skeletal muscle is an important source of secreted factors exerting autocrine, paracrine and endocrine effects (Di Felice et al., 2020; Florin et al., 2020). This skeletal muscle secretome varies in response to ever-changing metabolic demand, dependent on variable physiological and pathological conditions (Lecompte et al., 2017; Florin et al., 2020). Among the numerous circulating factors involved in the regulation of systemic metabolism we included in our overview those that are expressed in the skeletal muscle and also have a proved link to HDACs.

Myostatin was the first characterized skeletal muscle-derived circulating protein (McPherron et al., 1997), originally identified in mice as a regulator of muscle growth *via* a negative feedback. Further studies clarified that myostatin targets other tissues in addition to muscle. For instance, myostatin is involved in the crosstalk between skeletal muscle and adipose tissue, thereby modulating insulin sensitivity and fat accumulation, both in animals and humans (Argilés et al., 2012). Moreover, myostatin targets bone, affecting osteogenic differentiation and enhancing resorption, modulating overall bone mass (Hamrick et al., 2006, 2007). Follistatin is a myostatin-binding protein and an inhibitor of myostatin activity, capable of promoting muscle growth (Yakabe et al., 2020). In humans, following exercise circulating follistatin increases and targets several organs, regulating pancreatic cell function and survival and promoting insulin resistance in skeletal muscle and adipose tissue (Willis et al., 2019). In this regard, we have shown that the mechanical stretch of murine myotubes *per se* alters the amount of myokines produced by muscle cells *in vitro*, including follistatin (Baccam et al., 2019).

In the search for a consensus term to define peptides produced and released by skeletal muscle, the word “myokine” referring to Interleukin 6 (IL-6) was first introduced in 2003 (Pedersen et al., 2003). Ten years later, the term “adipo-myokine” was coined to indicate those myokines, such as IL-6, that are also expressed by adipose tissue (Raschke and Eckel, 2013). In humans, the level of circulating IL-6 is increased after exercise (Northoff and Berg, 1991), mainly due to its secretion by skeletal muscle (Steensberg et al., 2000). Studies conducted in mice and humans highlighted that in response to physical exercise IL-6 exerts a positive role in modulating muscle mass, insulin secretion and lipid metabolism (Rosendal et al., 2005; Serrano et al., 2008; Ellingsgaard et al., 2011; da Silva Vasconcelos and Fernanda Salla, 2018). In addition, IL-6 produces anti-inflammatory effects, inhibiting the expression of Tumor Necrosis Factor- α (TNF α) and Interleukin-1 (IL-1) (Pedersen et al., 2003). However, besides the above mentioned positive effects, other studies highlighted the pleiotropic functions of this factor and revealed the deleterious effect of IL-6 on muscle homeostasis, showing that it is also a promoter of muscle wasting (Moresi et al., 2019). Indeed,

IL-6 overexpression induces muscle atrophy in transgenic mice (Tsujiyama et al., 1996) and perturbs redox homeostasis (Forcina et al., 2019). Consistently, while the acute induction of IL-6 promotes muscle growth, sustained and elevated levels of IL-6 have been associated with muscle wasting in several human catabolic conditions (Yudkin et al., 2000; Kern et al., 2001; Pradhan et al., 2001; Ershler and Keller, 2003). All of the above shows how important it is to consider the complexity of a system where the kinetics and the source tissue of a given factor significantly influence its effects. To this regard IL-6 is emblematic and all these aspects should be taken into account when discussing the possible clinical implications of adipo-myokines.

Metrnl and BAIBA are two myokines whose expression is regulated by the transcriptional factor peroxisome proliferator-activated receptor-gamma coactivator-1 α (PGC-1 α) (Boström et al., 2012; Rao et al., 2014) and induced upon exercise in murine and human skeletal muscle (Rao et al., 2014; Roberts et al., 2014). These myokines target many tissues, exerting numerous physiological functions, such as promoting neural and osteocyte differentiation, preserving pancreatic β -cell functions and browning white adipose tissue (WAT), in addition to regulating glucose uptake and energy expenditure in skeletal muscle (Zheng et al., 2016; Darvin et al., 2018; Tanianskii et al., 2019; Rabiee et al., 2020).

Among other myokines, irisin production (Maak et al., 2021) has been shown to be induced by exercise in mice and humans (Boström et al., 2012; Jedrychowski et al., 2015). Studies with gain- (Boström et al., 2012) and loss- (Xiong et al., 2019) of function approaches demonstrate the ability of irisin to mediate the positive effects of physical activity in mice. These effects were not confirmed in humans (Maak et al., 2021).

The role of irisin, or even its existence in humans (Albrecht et al., 2015), is still debated, mainly in relation to: (1) the accuracy and reliability of the methods used to detect circulating irisin levels (Albrecht et al., 2015; Jedrychowski et al., 2015; Pourteymour et al., 2017; Bretland et al., 2021); (2) the positive effects of irisin on target organs or tissues (Raschke et al., 2013; Elsen et al., 2014; Maak et al., 2021). The debate on irisin exemplifies how difficult it is to study the crosstalk between tissues.

Metabolic stresses, such as acute bouts of exercise, fasting and caloric restriction, induce the expression of ANGPTL4 in human skeletal muscle (Catoire et al., 2014), likely by increasing plasma free-fatty acid levels and activating the peroxisome proliferator-activated receptor- δ (PPAR- δ) (Staiger et al., 2009). ANGPTL4 stimulates lipolysis in WAT, determining a shift from fat storage to fat release, and triggers AMP-activated protein kinase (AMPK) in skeletal muscle, thereby mediating an increase in its mitochondrial oxidative capacity and ATP production (Norheim et al., 2014; Chang et al., 2018; Li et al., 2020). It should be noted that besides skeletal muscle, adipose tissue and the liver express higher levels of ANGPTL4 following exercise, likely contributing even more than skeletal muscle to ANGPTL4 exercise-mediated effects (Norheim et al., 2014). Interestingly, human studies showed that ANGPTL4 mRNA in skeletal muscle is lower in men than in women at basal conditions, probably due

to differences in the utilization of glucose and fat mass in the two genders (Barja-Fernandez et al., 2018; Li et al., 2020). Moreover, a positive correlation between muscle ANGPTL4, obesity and glucose metabolism has been reported: indeed, ANGPTL4 muscle and serum levels are significantly higher in obese patients with an abnormal glucose tolerance (Barja-Fernandez et al., 2018; Li et al., 2020).

Fibroblast growth factor 21 targets several organs including: (1) the liver, where it activates important metabolic responses, such as the induction of hepatic fatty acid oxidation, ketogenesis, and gluconeogenesis; (2) the pancreas, where it is necessary to maintain the digestive and endocrine functions of this organ; (3) WAT, where it promotes insulin sensitivity, glucose uptake, fatty acid storage, and oxidative capacity (Cuevas-Ramos et al., 2019; Martínez-Garza et al., 2019; Keinicke et al., 2020; Watanabe et al., 2020; Xie and Leung, 2020). Several cellular stress-signals, such as autophagy impairment, mitochondrial dysfunction and ER stress, induce FGF21 release from murine skeletal muscle (Kim and Lee, 2014; Pereira et al., 2017; Oost et al., 2019). All these induce FGF21 expression *via* the activation of transcription factor 4 (ATF4) (Keipert et al., 2014; Miyake et al., 2016). In addition, both mammalian target of rapamycin (mTOR) complex 1 (mTORC1) and mTORC2 have been reported to induce FGF21 expression in murine skeletal muscle (Guridi et al., 2015; Pereira et al., 2017). Furthermore, the secretion of FGF21 from human skeletal muscle is strongly induced upon exercise or in pathophysiological conditions including in mitochondrial myopathies and aging, suggesting the involvement of muscle-derived FGF21 in both healthy and pathological conditions (Hanks et al., 2015; Tanimura et al., 2016; Villarroya et al., 2018; Tezze et al., 2019). Despite its beneficial effect on body metabolism, the therapeutic role of FGF21 to the advantage of human health is still under debate, due to its paradoxical effects on different tissues. Indeed, FGF21 has negative effects on bone mass and mineral density both in mice and humans (Wei et al., 2012; Fazeli et al., 2015). Moreover, the long-term increase of circulating FGF21, triggered in skeletal muscle by stress conditions, contributes to systemic inflammation, precocious senescence, and premature death in mice (Tezze et al., 2017). Additional studies are required to clarify the specific role of FGF21 secreted from other organs and its effect on the whole body under physiological and pathological conditions.

Data available on rodents and humans highlight a rapid increase of IL-15 in circulation in response to exercise, improving whole body insulin sensitivity and decreasing adiposity (Carbó et al., 2001; Nadeau and Aguer, 2019). The data regarding IL-15 expression and release from skeletal muscle upon exercise in humans are controversial, probably due to the use of different exercise protocols in different studies or to differences in the subjects analyzed (Nielsen et al., 2007). In rats, autocrine IL-15 release induces a shift toward an oxidative skeletal muscle phenotype through the induction of PPAR- δ and PGC-1 α (Carbó et al., 2001; Busquets et al., 2006; Pistilli and Quinn, 2013), contributing to the beneficial adaptations to exercise of the metabolism (Hennigar et al., 2017). IL-15 also inhibits muscle protein degradation (Pistilli et al., 2007), however, since its levels

decline progressively with aging, this contributes to age-related sarcopenia (Quinn, 2008; Quinn et al., 2010). In addition, IL-15 directly targets adipose tissue modulating the WAT mass and lipid metabolism probably because it decreases lipoprotein lipase (LPL) and leptin activities (Alvarez et al., 2002). A positive effect of a greater amount of circulating IL-15 on bone mineral content has been reported, likely due to the ability of IL-15 to interfere with TNF- α signaling (Quinn et al., 2009).

The expression of myonectin in murine skeletal muscle is regulated by the availability of nutrients and by exercise (Seldin et al., 2012; Laurens et al., 2020). In addition, patients with type 2 diabetes mellitus or those affected by obesity exhibit higher levels of circulating myonectin compared to healthy individuals (Li et al., 2018). Circulating myonectin has been shown to decrease the levels of circulating non-esterified fatty acid, through the promotion of fatty acid uptake both in hepatocytes and in adipocytes (Seldin et al., 2012). Moreover, the exercise-induced myonectin release from skeletal muscle protects cardiac myocytes from apoptosis, leading to a reduction of acute myocardial ischemia-reperfusion injury in mice (Otaka et al., 2017, 2018). Taken together, these data underline the role of myonectin in regulating systemic fatty acid metabolism and in mediating a cross-talk between muscle and other metabolic compartments (Seldin et al., 2012), suggesting possible therapeutic applications.

Brain-derived neurotrophic factor is a member of the neurotrophic factor family, whose expression is increased in human and rat skeletal muscles in response to muscle contraction (Dupont-Versteegden et al., 2004; Matthews et al., 2009). In human skeletal muscle, BDNF activates AMPK and promotes lipid oxidation following exercise (Matthews et al., 2009). In addition to skeletal muscle, exercise greatly increases the expression and release of BDNF from the brain, in both humans and mice (Liu and Nusslock, 2018), which, most likely, accounts for most of the BDNF-mediated effects, since the brain is the major source of this soluble factor.

The aforementioned studies taken together indicate that major metabolic adaptations to physiological or pathological alterations are regulated by soluble factors, mediating a complex crosstalk involving a network of tissues. Many of these circulating factors involve changes in HDAC expression or activation in skeletal muscle. The next paragraph focuses on this aspect.

MYOKINES AFFECT HISTONE DEACETYLASE EXPRESSION AND ACTIVITY

Myokines and other soluble factors control tissue homeostasis through a variety of signaling pathways including the regulation of HDAC expression or activity (Table 1). For instance, a correlation between the exercise-induced hormone irisin, known to regulate energy metabolism and to protect against numerous diseases, and HDAC4 has already been proposed. In rodents irisin protects the cardiomyocytes of rats exposed to hypoxic stress (Zhao et al., 2016) and the myocardium of type II diabetic db/db mice (Zhao et al., 2016; Wang et al., 2020). This protective role of irisin correlates with the degradation of HDAC4

(Zhao et al., 2016; Wang et al., 2020), which causes cell death and mitochondrial dysfunction in these cells. These findings highlight the principle, in rodents at least, that a systemic factor, namely irisin, produces its effects partially involving epigenetic mechanisms. Since the relevance of irisin-mediated effects in humans is still debated, more studies are needed to clarify whether the protective role of irisin on muscle in our species exists, and whether it involves epigenetic mechanisms.

The secretion of Metrnl by skeletal muscle, increased during muscle contractions, improves glucose tolerance by inducing glucose uptake *via* the AMPK-dependent phosphorylation of HDAC5, a transcriptional repressor of *Glut4* in mice (Lee et al., 2020): the phosphorylated HDAC5 interacts with 14-3-3 proteins, is sequestered in the cytoplasm, and results in the activation of *Glut4* transcription (Figure 1). Glucose uptake by the musculature represents a paradigmatic behavior, which usually occurs in response to the classic insulin signaling. The interesting aspect of the alternative Metrnl signaling stems from the fact that the upregulation of the *Glut4* gene involves an energy-sensing factor, AMPK, as well as an epigenetic factor, HDAC5. In addition, the delivery of recombinant Metrnl improves glucose tolerance in mice with HFD-induced obesity or type 2 diabetes (Lee et al., 2020), suggesting the potential use of this myokine as a therapeutic tool to treat metabolic disorders.

Fibroblast growth factor 21 activates a SIRT1-AMPK-PGC1 α pathway in skeletal muscle, thereby promoting myoblast differentiation and aerobic metabolism, and is also possibly involved in starvation-induced muscle atrophy (Liu et al., 2017). In adipocytes the same axis has been proven to be responsible for increasing mitochondrial oxidative capacity (Chau et al., 2010). Additionally, the protective role of the FGF21-SIRT1 axis in different pathological conditions has been reported in multiple cell types, suggesting that this pathway may be a potential target for therapeutic approaches. Indeed, FGF21 activates SIRT1 in hepatocytes, thereby ameliorating multiple metabolic parameters in alcoholic fatty liver disease (Zhu et al., 2014) or cafeteria-diet induced steatohepatitis (Abd Elwahab et al., 2017). In addition, FGF21 also activates SIRT1 in germ cells reducing their oxidative stress and apoptosis in diabetes (Jiang et al., 2015). A similar TGF21-induced SIRT1 activation in cardiomyocytes has a protective effect on type 1 diabetes-induced inflammation and fibrosis in the heart (Zhang et al., 2016), on doxorubicin-induced cardiomyopathy (Wang et al., 2017) as well as on angiotensin-II induced cardiomyocyte apoptosis and cardiac hypertrophy (Li et al., 2019).

Interleukin 15, a myokine which contributes to the benefits of physical exercise on muscle metabolism, is responsible for the post-exercise induction of SIRT1 in muscle, which, in turn, mediates many of the metabolic effects of physical exercise (Quinn et al., 2013, 2014). IL-15 Tg mice also exhibit an induction of the SIRT1 protein and changes in oxidative metabolism, which may be involved in their phenotype, i.e., the resistance to diet-induced obesity and higher insulin-sensitivity (Quinn et al., 2011).

Differently from FGF21 and IL-15, ANGPTL4 represses *Sirt1* expression in hepatocytes, thus mediating the inflammatory response in acute lung injury (Guo et al., 2015).

Leptin has been shown to target multiple tissues, including skeletal muscle. Evidence of a direct effect of leptin on muscle cells comes from *in vitro* experiments showing that, in murine myotubes, leptin induces the expression of genes involved in metabolism (including PGC-1 α , uncoupling protein 3, muscle carnitine palmitoyltransferase 1) in addition to that of myokines such as IL-6 and IL-15 (Nozhenko et al., 2015). Interestingly, leptin affects SIRT1-mediated PGC-1 α deacetylation (Garcia-Carrizo et al., 2016; Figure 1), even though contradictory data have been reported. This is probably due to dissimilar leptin and nutrient concentrations in the culture media, as well as to different timing of the analyses. *In vivo*, leptin receptor deficiency in skeletal muscle leads to muscle atrophy and compromised primary myoblast proliferation and differentiation (Arounleut et al., 2013), indicating a possible role for this adipokine in skeletal muscle homeostasis. Whether or not leptin influences adult skeletal muscle *via* modulating HDACs has not been investigated yet. However, an initial link between leptin and HDACs has been reported: indeed, the administration of leptin in conjunction with a HFD induces HDAC4 dephosphorylation and its nuclear import in macrophages in white adipose tissue, thereby reducing inflammation (Luan et al., 2014). The molecular mechanism described for leptin-induced HDAC dephosphorylation consists in a catecholamine-dependent increase in cAMP, triggered by leptin, which inhibits salt-inducible kinases. This ultimately promotes HDAC4 dephosphorylation; the dephosphorylated HDAC4 then shuttles to the nucleus where it inhibits NF- κ B transcriptional activity on pro-inflammatory genes (Luan et al., 2014).

Although experimental evidence in skeletal muscle cells is still lacking, it is interesting to note that BDNF activates the salt-inducible kinase 1 (SIK1), a member of the AMPK family, in rat neurons, leading to the phosphorylation-dependent nuclear extrusion of HDAC5 and the consequent MEF2-dependent gene activation (Finsterwald et al., 2013). It would be important to investigate this signaling in skeletal muscles as well, since it may underly the beneficial effects of BDNF on muscle metabolism.

So far, we have reported that myokines control the metabolic shifts occurring in multiple tissues in response to physiological or pathological stress conditions, and that, at least in muscle tissues, myokines are capable of inducing epigenetic responses through HDACs. Conversely, HDACs influence the release of several factors from skeletal muscle, as outlined next.

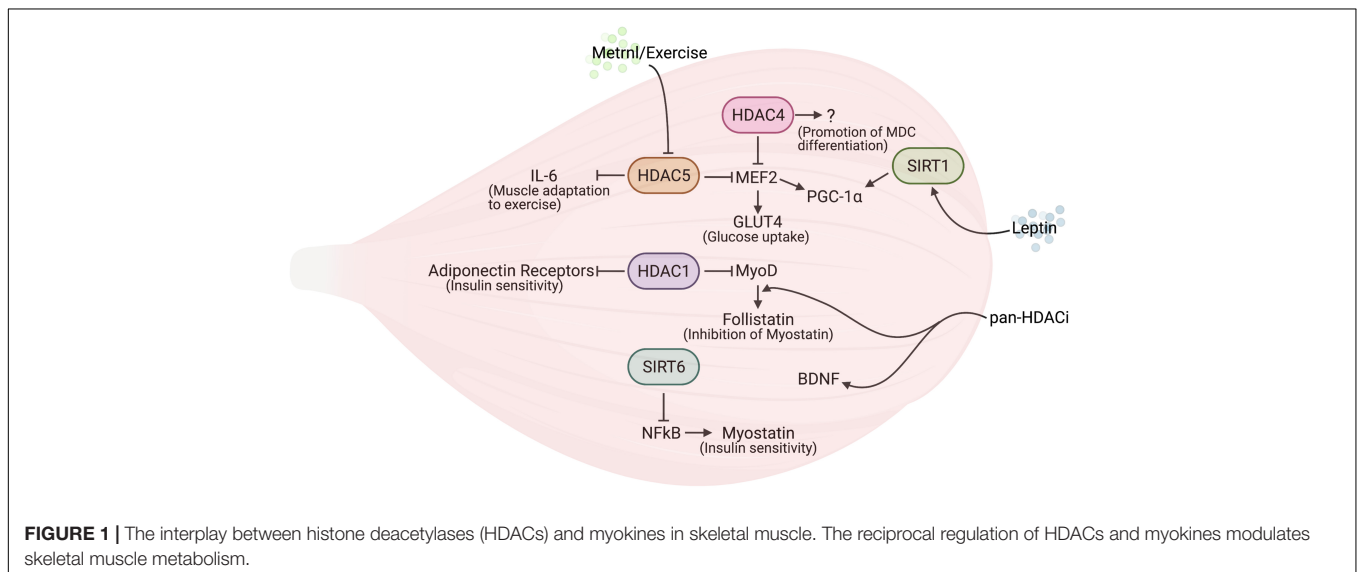
HISTONE DEACETYLASES AFFECT MYOKINE SYNTHESIS

Histone deacetylases regulate the expression of chemokines, cytokines and adipo-myokines, or that of their receptors, under physiological and pathological conditions in several tissues (Gatla et al., 2019). In particular, recent studies highlighted this role of HDACs in skeletal muscle—and in other cells to a lesser extent (Table 2). A paramount example of this is the fact that HDAC4 regulates factors secreted by skeletal muscle upon injury, thus regulating muscle-derived cell (MDC) myogenic potential and muscle regeneration (Renzini et al., 2018). Indeed, the deletion of

TABLE 1 | Circulating factors affect histone deacetylase (HDAC) expression or activity in various tissues.

Species	Circulating factors	Target tissue	Downstream effects	Link with HDAC	References
Rat	BDNF	Neurons	Activation of MEF2	HDAC5 nuclear export	Finsterwald et al., 2013
Mouse	Fgf21	Skeletal muscle	Myoblast differentiation, improved aerobic metabolism	SIRT1 activation	Liu et al., 2017
Mouse	Fgf21	Adipocytes	Increased mitochondrial oxidative capacity	SIRT1 activation	Chau et al., 2010
Mouse	Fgf21	Hepatocytes, germ cells, cardiomyocytes	Protection from oxidative stress, apoptosis, and fibrosis	SIRT1 activation	Zhu et al., 2014; Jiang et al., 2015; Zhang et al., 2016; Abd Elwahab et al., 2017; Wang et al., 2017; Li et al., 2019
Mouse	IL-15	Skeletal muscle	Improved oxidative metabolism	SIRT1 activation	Quinn et al., 2011, 2013, 2014
Rodents	Irisin	Cardiomyocytes	Protection from death	HDAC4 degradation	Zhao et al., 2016; Wang et al., 2020
Mouse	Leptin	Skeletal muscle	Acetylation of PGC-1 α	SIRT1 activation	García-Carrizo et al., 2016
Mouse	Leptin	Macrophages	Reduction of inflammation	HDAC4 nuclear import	Luan et al., 2014
Mouse	Metrn1	Skeletal muscle	Glucose uptake	HDAC5 nuclear export	Lee et al., 2020

The table represents an overview of the correlation between circulating factors and changes in the HDAC expression or activation (Link with HDAC) in a given tissue (Target tissue). The final output (Downstream effects) is also reported, as well as the species where the observations were made and the corresponding references.



HDAC4 in skeletal muscle hampers skeletal muscle regeneration, even though MDCs from HDAC4 KO mice differentiate well when cultured *in vitro*, i.e., isolated from their muscle niche. Conversely, sera from injured HDAC4 KO mice negatively affect MDC differentiation, which proves that HDAC4 affects the release of soluble factors from skeletal muscle upon injury, which, in turn, are important for muscle regeneration (Renzini et al., 2018; **Figure 1**). The characterization of the secretome of HDAC4 KO will clarify this new important function of HDAC4 in skeletal muscle and provide new insights for a potential therapeutic application to muscle regeneration.

Myostatin is a member of the transforming growth factor-beta (TGF-beta) superfamily, expressed and released by skeletal muscle and that negatively influences muscle growth (McPherron et al., 1997). Myostatin expression is controlled by SIRT6, which regulates the binding of NF- κ B to the myostatin promoter (Samant et al., 2017; **Figure 1**). Indeed, SIRT6 KO mice

display muscle degeneration and atrophy, in addition to reduced fat and bone density. Conversely, the SIRT6 overexpression counteracts cytokine-induced myostatin expression in muscle cells, promoting myogenesis. Therefore, increasing SIRT6 activity or expression has been proposed as a potential therapeutic tool to counteract many disease states characterized by muscle cachexia, thanks to the ability of SIRT6 to influence myostatin expression and possibly act on multiple tissues.

Follistatin is a secreted protein able to bind with and neutralize the actions of many members of the TGF-beta family of proteins (Patel, 1998). General Pan-HDAC inhibitors (HDACi), such as valproic acid (VPA) or Trichostatin-A (TSA), have been shown to increase the expression of follistatin in muscle cells, through the binding of MyoD to the follistatin promoter, a process which is fostered by local hyperacetylation (**Figure 1**); in turn, the release of the soluble factor follistatin counteracts myostatin activity, enhancing myogenesis (Iezzi et al., 2004). Further studies clarified

TABLE 2 | HDACs regulate the production of myokines.

HDAC	Circulating factor	Target tissue	Downstream effects	References
HDACs	Follistatin	Skeletal muscle, FAPs	Promotion of myogenesis	Iezzi et al., 2004; Minetti et al., 2006; Mozzetta et al., 2013
HDACs	BDNF	Skeletal muscle, motor neurons	Improvement of the myofiber maturation and of the motor unit morphology and function	Avila et al., 2007
HDACs	ANGPTL4	Adipose tissue	Improved lipolysis	Zhang et al., 2021
HDAC1	Adiponectin	Skeletal muscle	Protection from HFD-induced obesity and insulin resistance; stimulation of mitochondrial function	Jian et al., 2016
HDAC2, HDAC3	Fgf21	Glia cells, adipocytes	Regulation of the outgrowth of extending processes and of the fatty acid utilization	Li et al., 2012; Leng et al., 2016
HDAC4	Unknown	Skeletal muscle	Promotion of muscle cell differentiation	Renzini et al., 2018
HDAC5	IL-6	Skeletal muscle	Muscle adaptation to exercise	Klymenko et al., 2020
SIRT1	Fgf21	Hepatocytes, heart	Improved energy expenditure	Li et al., 2014; Furukawa et al., 2020
SIRT6	Myostatin	Skeletal muscle	Promotion of myogenesis	Samant et al., 2017

The table shows how the activity of members of different HDAC classes affect the production of myokines (Circulating Factors) ultimately eliciting multiple responses (Downstream effects). For each of these findings the corresponding reference is cited.

that pan-HDACi improve muscle regeneration in dystrophy by increasing the expression of follistatin in both muscle stem cells and fibro-adipogenic progenitors (Minetti et al., 2006; Mozzetta et al., 2013)—a finding that led scientists to suggest the use of HDACi in clinical trials for the treatment of Duchenne Muscular Dystrophy. Although pan-HDACi increase the expression of follistatin in cancer cachexia as well, this is not sufficient to prevent muscle wasting in this disease state (Bonetto et al., 2009). Also, pan-HDACi have been shown to increase BDNF expression in the skeletal muscles and spinal cord in a murine model of Spinal Muscular Atrophy (SMA) (Avila et al., 2007; **Figure 1**). Since BDNF is an important contraction-induced secreted factor for the neurogenesis, growth, and survival of neurons (Murawska-Ciałowicz et al., 2021), its increase may explain the beneficial effects of HDACi on SMA progression.

Interleukin 6 was recognized in the past as a principal mediator of muscle adaptation to exercise (Ostrowski et al., 1998). Muscle contractions induce an increase of IL-6 gene expression that leads to a release of IL-6 protein in the circulation (Reihmane and Dela, 2013). An epigenetic modulation of IL-6 expression driven by HDAC5 has been recently reported in exercised skeletal muscle. Genetic murine models helped clarify the metabolic changes, including that of glucose metabolism, regulated by the HDAC5 activity on the IL-6 promoter (Klymenko et al., 2020): in resting conditions, HDAC5 negatively modulates IL-6 transcription by removing histone H3 acetylation at lysine 9 (AcH3K9), while upon exercise, HDAC5 is exported to the cytoplasm and results in an increased expression of GLUT4, thus prompting skeletal muscle cells to uptake glucose in response to insulin (Klymenko et al., 2020; **Figure 1**).

Histone deacetylases regulate ANGPTL4 expression in different cell types. ANGPTL4 is a secreted glycoprotein which inhibits the activity of lipoprotein lipases, thereby increasing circulating triglyceride levels (Fernández-Hernando and Suárez, 2020). HDACi sodium butyrate activates lipolysis in pigs, in part by downregulating ANGPTL4 gene expression in the adipose tissue (Zhang et al., 2021). In human cells, HDAC3 mediates

a NCOR-dependent transcriptional repression of the ANGPTL4 gene, as shown by using a renal cancer cell line, while additional investigations are needed to unveil the potential role of HDAC in regulating ANGPTL4 expression in skeletal muscle.

Different HDACs exert opposite effects on the expression of *Fgf21*, an important regulator of carbohydrate and lipid metabolism, in different cell types. HDAC2 and HDAC3 inhibit *Fgf21* expression in glia cells, thus regulating the outgrowth of their processes (Leng et al., 2016), and in adipocytes, affecting fatty acid utilization and ketogenesis (Li et al., 2012). On the contrary, SIRT1 induces *Fgf21* expression in hepatocytes, preventing fat-induced liver steatosis while promoting white adipose tissue browning and higher energy expenditure (Li et al., 2014). SIRT1 also induces *Fgf21* expression in the heart, improving energy metabolism and increasing the contractile efficiency of pressure-overloaded hearts (Furukawa et al., 2020).

A correlation between SIRT1 expression and irisin serum levels has been reported in type 2 diabetic patients and mice (Safarpour et al., 2020; Jiang et al., 2021), suggesting the involvement of SIRT1 in PGC-1 α -mediated irisin release. The treatment of obese type 2 diabetes patients with vitamin D also induces higher serum levels of SIRT1 and irisin, further pointing to the SIRT1-mediated release of irisin (Safarpour et al., 2020). The SIRT1 activator resveratrol, alone or in combination with all-trans retinoic acid (ATRA), significantly induces the expression of irisin in skeletal muscle cells (RongXia et al., 2017; Abedi-Taleb et al., 2019). Consistently, metformin, another compound activating SIRT1, increases irisin expression and its release from skeletal muscle in diabetic mice (Yang et al., 2015). In spite of the limited evidence to date, it seems likely that the positive effects of SIRT1 activation on body metabolism (Feige et al., 2008) are at least in part due to its ability to increase the levels of circulating irisin.

In skeletal muscle HDACs regulate signaling in response to adiponectin. This is an adipokine involved in controlling glucose levels and fatty acid breakdown (Yamauchi et al., 2001), which, interestingly, also plays a role in skeletal muscle (Fruebis, 2001).

Here HDAC1 represses the transcription of the genes encoding adiponectin receptors and uncoupling protein 2 and 3. Since the latter are important mitochondrial proteins involved in heat generation and energy expenditure, the inhibition of HDAC1 contributes to the beneficial effects of the pan-HDACi sodium butyrate on HFD-induced obesity in mice (Jian et al., 2016; **Figure 1**).

Based on the substantial experimental evidence above, it is apparent that myokines, cytokines and adipokines control the homeostatic and metabolic responses of tissues at organismal level, while their dysregulation is responsible for many diseases. Since HDACs affect the synthesis and ultimately the release of these factors in various organs or, vice-versa, modulate the organ response to endocrine factors through the regulation of their receptors, HDACs are very promising pharmaceutical targets. However, the first attempts to interfere with the activity of HDACs by means of HDACi must be further supported by additional investigations on the specific role of each HDAC family member. This approach alone will provide a solid ground for the development of HDACi-based therapies for human diseases. The studies on HDACi performed so far are summarized below.

CLINICAL IMPLICATIONS OF THE USE OF HISTONE DEACETYLASE INHIBITORS

Several preclinical studies highlighted the positive effects of HDACi in regulating the whole-body metabolism in various diabetic or insulin-resistance rodent models, thus providing the rationale for the inclusion of HDACi in clinical trials targeting metabolic disorders. For instance, pan-HDACi sodium butyrate and TSA, which improve insulin sensitivity and energy expenditure in HFD-fed mice (Gao et al., 2009; Li et al., 2012; Lin et al., 2012; Henagan et al., 2015; Xu et al., 2020), increase the liver expression of FGF21 and its serum concentration (Li et al., 2012). Consequently, FGF21 mediates the increase in fatty acid utilization and ketogenesis, in response to butyrate treatment, causing resistance to HFD. An added value offered by this study is the fact that it represents an additional proof of principle that many HDACi effects on body metabolism may be achieved through the regulation of soluble factors, such as FGF21 itself. Butyrate improves glucose and pyruvate tolerance in aged mice, reducing fat and preserving skeletal muscle mass (Walsh et al., 2015)—a result that suggests the use of HDACi to counter aging. Butyrate also increases mitochondrial biogenesis and oxygen consumption in the skeletal muscle of aged mice; notably, the use of this HDACi does not affect the HDAC4-myogenin axis, which is significant in neurogenic muscle atrophy (Moresi et al., 2010). In addition, another pan-HDACi, Scriptaid, modulates adaptive metabolic responses to exercise (Gaur et al., 2016). Considering the beneficial effects of exercise on aging, all these findings further suggest new future applications for HDACi in the context of sarcopenia (Pasyukova and Vaiserman, 2017).

In spite of the numerous positive effects that HDACi exert on metabolism control, additional considerations are needed

concerning the use of pan-HDACi in clinical trials for metabolic disorders. The use of general HDACi is usually discouraged, since their use is normally associated with numerous side effects and since they target a broad range of proteins. This makes drawing any biological conclusion on the action of specific HDACs difficult. Indeed, contradictory data were reported on the effectiveness of specific Classes of HDACi in ameliorating insulin resistance in obese mice (Sharma and Taliyan, 2016), probably due to the different concentrations used in the various studies or to the fact that Class II enzymatic activity depends on Class I HDACs, which can bias the effects of HDACi (Fischle et al., 2002).

Thus, further investigations should be carried out, both at the pre-clinical and clinical level, before proposing the unspecific pharmacological inhibition of this important enzyme family. The two major avenues of research in this field should be aimed at defining: (1) expression and activity of the different members of the HDAC family, under pathophysiological conditions, and (2) the functions of each single HDAC member in different tissues. Only by undertaking this approach will it be possible to design enzyme- and tissue-specific pharmacological treatments.

CONCLUSION

Myokines are mediators of the crosstalk between skeletal muscle and other tissues of pivotal importance for body metabolism and they support the central role of skeletal muscle as a metabolic hub. HDACs not only are regulators of muscle metabolism, they also affect other tissues, including liver and fat tissues, by controlling myokine production. The effects of this production can be muscle-centered, as is the case of myostatin and related factors, or have a broader action, such as in the case of pro- and anti-inflammatory cytokines. In turn, HDAC activity is regulated in response to the humoral milieu, a fact which suggests how important epigenetic control is to fine-tune the genetic response of tissues to hormones or other circulating factors. Given the broad and pleiotropic effects of HDACs, these may be targets in the treatment of metabolic and systemic pathological conditions.

AUTHOR CONTRIBUTIONS

VM conceived the manuscript. AR and MD'O generated the figure. DC supervised the content of the text. All authors contributed to the writing.

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