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Commentary

miRNA-myokine crosstalk: Emerging therapeutic strategies for skeletal muscle diseases

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Abstract

The incidence of skeletal muscle disorders and chronic diseases leading to skeletal muscle atrophy have been increasing worldwide due to sedentary lifestyle, poor quality of life and dietary modifications. This results in impaired metabolic homeostasis by increasing morbidity and in turn leading to increased mortality. In skeletal muscle, miRNAs regulate expression and secretion of myokines. Myokines, the bioactive molecules, influence miRNA expression profiles in muscle and distant tissues such as liver, adipose tissue, bone, brain, and immune cells. Dysregulation of myokines and miRNAs leads to obesity, insulin resistance, sarcopenia, neurodegenerative disorders, and cardiovascular diseases. Recent research has established the role of myokines and miRNAs as potential targets in combating skeletal muscle atrophy but no promising and effective treatment strategy has been developed yet. In this article, gene targets of miR-1 and miR-320 have been retrieved in *Homo sapiens* and *Rattus norvegicus* using miRDB 6.0, miRTarBase 10.0, TargetScan 8.0 and miRWalk 2.0 version databases, out of which all myokines have been screened and scrutinized. FNDC5 (irisin, a positive regulator of skeletal muscle mass) in hsa-miR-1 and hsa-miR-320; and MSTN (myostatin, a negative regulator of skeletal muscle mass) in hsa-miR-1 and rno-miR-320 were found to be the crucial targeting myokines. The miRNAs regulating the irisin and myostatin might play dynamic role in maintaining skeletal muscle homeostasis. Further, our own experimental validation of miRNA-myokine interactions has shown miRNAs might regulate levels of myokines under normal or stress conditions. While the role of myokines in regulating miRNA expression in skeletal muscle is still inadequately explored. Further investigation of miRNA–myokine network might help in identifying molecular targets for therapeutic interventions to improve clinical management of skeletal muscle disorders.

Keywords: Skeletal muscle atrophy, Skeletal muscle diseases, Myokine, miRNA, Therapeutics

Introduction

Being the most abundant tissue, skeletal muscle comprises 40–50% of the total mass in healthy-weight individuals and regarded as the protein reservoir in the human body. It acts as a vital organ for metabolic homeostasis, physical performance and for maintaining a high quality of life. To estimate health loss from death and disability due to musculoskeletal disorders, the Global Burden of Disease (GBD) 2020 data revealed that musculoskeletal disorders were the second-highest cause of non-fatal disability, and more than 1.63 billion people live with musculoskeletal impairments worldwide [1]. Skeletal muscle atrophy is a global health burden and highly prevalent in several chronic pathophysiological conditions, such as obesity, diabetes, cancer cachexia, chronic obstructive pulmonary disease, cardiovascular diseases, renal failure, and aging. Impairment in skeletal muscle homeostasis and decline in skeletal muscle strength and function negatively affect everyday life with increased morbidity and mortality. Physical activity, exercises, healthy diet and nutritional supplements are widely acknowledged to prevent skeletal muscle atrophy but till date there is no promising treatment strategy. Therefore, it is very crucial to discover novel therapeutics to combat skeletal muscle diseases.

Skeletal muscle undergoes remodeling from birth until death to adapt stimuli such as contractile activity, resistance, exercise, endurance training, innervation, denervation, and hypoxia. This plasticity nature allows physiological changes to alter the structural and functional properties of skeletal muscle to adapt itself for the imposed environmental conditions. Skeletal muscle has high regenerative capacity to repair damaged tissue and regenerate new muscle fibers upon injury or consequence of degenerative diseases. Muscle stem cells or satellite cells in adult skeletal muscle differentiate into myofibers during muscle growth, repair (exercise or trauma), injury or aging due to their high proliferative and myogenic nature (**Figure 1**). Recently, skeletal muscle as secretory organ is an emerging area of research as the muscle fiber releases hormones, myokines, proteins, peptides, miRNAs, and metabolites to exert its effects through autocrine/paracrine and/or endocrine mechanisms.

Exploring Skeletal Muscle as Secretory Organ: Myokines and miRNAs

Skeletal muscle secretes myokines (cytokines or peptides) which crosstalk within itself or with other organs such as brain, liver, skin, bone, adipose tissue, etc. Myokines regulate oxidative stress, redox homeostasis, inflammation, mitochondrial function, and metabolic balance across multiple organs [2]. Irisin, decorin, FGF21, BDNF, myonectin are myokines which positively regulate muscle mass, strength and function by stimulating PI3K/Akt/mTOR pathway, have been evidenced to promote hypertrophy whereas myostatin, IL-6, IL-15 negatively regulate the muscle mass by stimulating Smad2/3 or FoxO pathway to induce atrophy [3].

Exercise induces PGC-1α expression in skeletal muscle which in turn stimulates the secretion of irisin from skeletal muscle into the bloodstream. The physiological level of irisin decreases with age but irisin expression is reported to be higher in elderly high-fitness men than in elderly low-fitness men [4]. Exercise-induced irisin and supplementation of recombinant irisin might be a successful strategy to ameliorate muscle atrophy, obesity, osteoporosis, liver injury, cardiovascular diseases, age-associated sarcopenia and metabolic dysfunction [5,6]. Irisin induces myogenic differentiation and myoblast fusion by increasing expression of a number of pro-myogenic and exercise response genes in myotubes via activation of IL-6 signaling pathway. In addition, irisin supplementation induces hypertrophy, enhances grip strength of uninjured muscle, repairs damaged fibers, rescues loss of skeletal muscle mass in case of muscle injury and improves regeneration by enhancing protein synthesis pathway (Akt/mTOR and Erk1/2 pathway), satellite cell activation and reducing protein degradation (ubiquitin proteosome pathway, including Atrogin-1 and MuRF-1) pathway [7].

Myostatin downregulates PI3K/Akt/mTOR pathway and decreases skeletal muscle protein synthesis. It negatively regulates the myogenic differentiation, proliferation, growth and development by stimulating myodegradation mediated by ubiquitin, autophagy-lysosomal system, FoxO-dependent, and Smad2/3/4 mediated protein degradation pathway [8]. Myostatin induces the expression of atrogin-1, MuRF-1, and several atrogenes that inhibits the development of skeletal muscle fibers by limiting the number and size of muscle fibers. Myostatin level is found to be elevated in the serum of individuals suffering from obesity, type 2 diabetes mellitus, cancer cachexia, sarcopenia and heart failure [9]. Regulating skeletal muscle mass through myostatin inhibition is emerging as a therapeutic tool for the treatment of skeletal muscle loss/atrophy. Both preclinical and clinical approaches that inhibit the myostatin signaling pathway can enhance the muscle mass and combat muscle wasting associated with cancer and other disorders. Many interventions

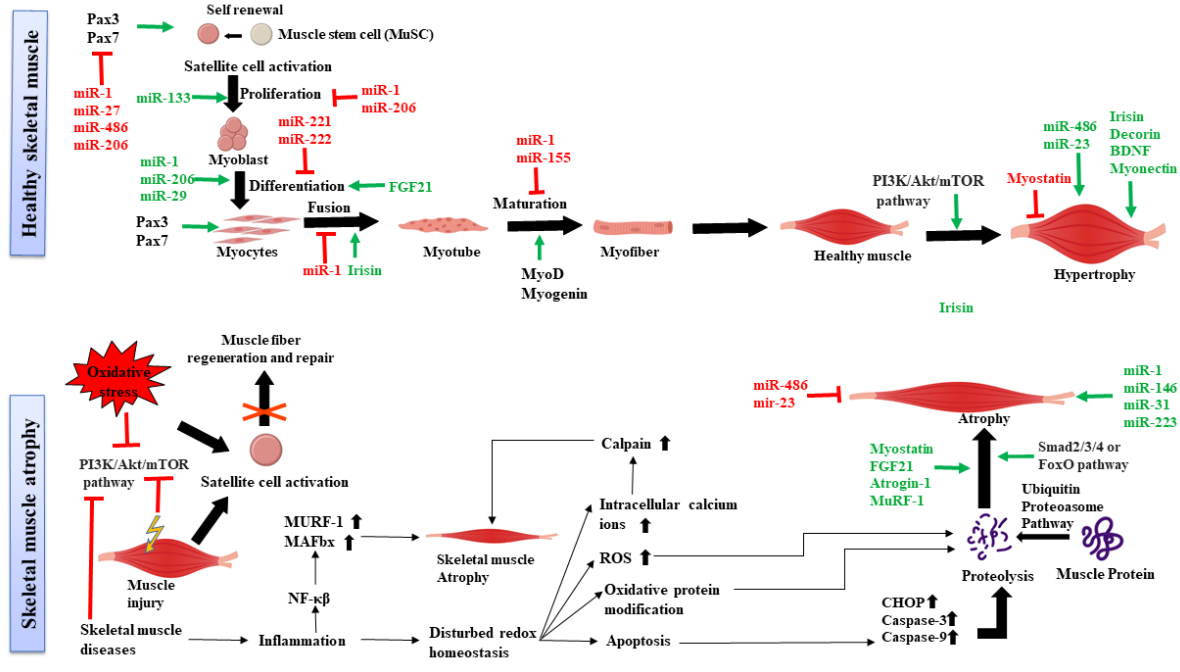

Figure 1. Role of miRNA and myokines in regulating key pathways in skeletal muscle.

have been exploited to block myostatin either by directly binding to myostatin itself or by indirectly binding to its receptor complex [10]. Myostatin inhibition induces skeletal muscle hypertrophy, improves the muscle strength, and increases the mass and the cross-sectional area of muscle fibers [11]. Our findings on healthy Indian participants revealed that myostatin level was significantly increased and irisin level was significantly decreased during chronic exposure as compared to sea level participants, indicating a shift in muscle homeostasis and increased muscle degradation in hypobaric hypoxia (HH) environments [12]. After 2-week exposure to HH, there was significant decline in body mass, BMI, fat free mass, decreased irisin and increased myostatin serum concentrations in high-altitude male climbers [13]. Therefore, understanding the signaling pathways/mechanisms regulating muscle growth, regeneration as well as repair is very essential to develop novel strategies to ameliorate skeletal muscle atrophy.

Another key mediator which governs skeletal muscle development and repair are miRNAs, the small non-coding (approximately 18–25 nucleotides) RNAs. Recent research in miRNA indicates their role as biomarkers and therapeutic targets in skeletal muscle diseases [14]. The most studied myomiRs (miR-1, miR-206, miR-133) and a subset of non-muscle-specific miRNAs (miR-29 family, miR-320 miR-23a/b clusters, miR-486-5p) are differentially expressed during developmental stages, differentiation, proliferation, repair, and pathological diseases such as muscular dystrophy, cancer cachexia, sarcopenia [15–17]. Myokines and miRNA also have a crucial role in high-altitude induced skeletal muscle loss [18–20]. Thus, recent evidence highlights a complex and bidirectional interplay between skeletal muscle myokines and miRNAs. This article explores the novel strategy of myokines and miRNA to develop therapeutics for various skeletal muscle-related diseases.

Recently, miRNA therapeutics such as miRNA mimics (agomiRs) and molecules targeting/inhibiting the miRNAs (antimiRs or antagomiRs) have shown promising results in targeting the key proteins regulating skeletal muscle diseases. The antagomiR-based inhibition of miR-1/miR-206 resulted in decreased expression of PAX3 (target gene), loss of myogenin expression and delayed myogenesis [21]. Also, the expression of miR-127 and miR-22-3p gets upregulated and downregulated respectively to promote myoblast proliferation *in vitro*. The repeated intramuscular administration of miR-127 mimic (agomiR-127) and antagomiR-22-3p upregulated mTOR expression to promote protein synthesis *in vivo* [22].

Hence, this therapeutic strategy offers completely new possibilities for gene modification, cell therapy, and drug development for the treatment of diseases.

In Silico Analysis of miRNAs (miR-1 and miR-320) and Myokines Interaction in *Homo sapiens* and *Rattus norvegicus*

In this article, miRNAs (miR-1 and miR-320) that play major role in maintaining skeletal muscle homeostasis have been shortlisted. Using miRDB 6.0, miRWalk 2.0, miRTarBase 10.0, and TargetScan 8.0 version databases, gene targets of miR-1 and miR-320 were searched till February 2026 and retrieved in *Homo sapiens* and *Rattus norvegicus* (**Table 1**). Using Literature survey, known myokine genes were screened. Out of total number of gene targets, myokines have been screened for hsa-miR-1, rno-miR-1, hsa-miR-320 and rno-miR-320 as shown in **Tables 2** and **3**. Schematic workflow for the identification and screening of myokine-targeting miRNAs is shown in **Figure 2**. After thorough scrutiny, 20 myokines for hsa-miR-1, 16 myokines for rno-miR-1, 33 myokines for hsa-miR-320 and 29 myokines for rno-miR-320 were found as target genes of their respective regulating miRNAs (**Table 3**). The interactions were imported into Cytoscape 3.10.2 version software for regulatory network construction to identify highly regulated myokines by miR-1 and miR-320 (**Figure 3**). This crosstalk of miRNAs (miR-1 and miR-320) and myokines would in turn help to decipher novel therapeutic targets for skeletal muscle diseases.

Using *in silico* tools, we observed FNDC5 (irisin, a positive regulator of skeletal muscle mass) as target gene for hsa-miR-1 and hsa-miR-320; and MSTN (myostatin, a negative regulator of skeletal muscle mass) as target gene for hsa-miR-1 and rno-miR-320, which might have regulatory mechanisms to uplift or suppress compromised muscle maintenance. The miRNAs regulating crucial myokines, irisin and myostatin, might play dynamic role in maintaining skeletal

Table 1. Total number of genes as targets for miRNAs (miR-1 and miR-320) in *Homo sapiens* and *Rattus norvegicus* using miRDB, miRWalk, miRTarBase, and TargetScan databases.

Databases	Total no. of genes retrieved for hsa-miR-1	Total no. of genes retrieved for rno-miR-1	Total no. of genes retrieved for hsa-miR-320	Total no. of genes retrieved for rno-miR-320
miRDB	1,410	1,143	1,466	611
miRWalk	1,237	671	11,547	8,226
miRTarBase	966	22	919	7
TargetScan	4,025	3,570	5,268	4,418

Table 2. Screening of miRNAs (miR-1 and miR-320) targeting number of myokines in *Homo sapiens* and *Rattus norvegicus* using miRDB, miRTarBase, miRWalk and TargetScan databases.

Databases	Total no. of myokines as target genes for hsa-miR-1	Total no. of myokines as target genes for rno-miR-1	Total no. of myokines as target genes for hsa-miR-320	Total no. of myokines as target genes for rno-miR-320
miRDB, miRWalk, miRTarBase, TargetScan	20	16	33	29

Table 3. Representation of miRNA and myokine interaction in a tabular form: miR-1 and miR-320 with its targeting myokines in *Homo sapiens* and *Rattus norvegicus* as retrieved from miRDB, miRTarBase, miRWalk and TargetScan databases.

miRNA	Myokines (Target genes)	miRNA	Myokines (Target genes)
hsa-miR-1	BDNF	rno-miR-1	Bdnf
hsa-miR-1	BMP7	rno-miR-1	Cxcl12
hsa-miR-1	DCN	rno-miR-1	Fndc3a
hsa-miR-1	FNDC3A	rno-miR-1	Hsp90aa1
hsa-miR-1	FSTL1	rno-miR-1	Hsp90b1
hsa-miR-1	HSP90AB1	rno-miR-1	Hspa1a
hsa-miR-1	HSP90B1	rno-miR-1	Hspa4
hsa-miR-1	HSPA1A	rno-miR-1	Igf1
hsa-miR-1	HSPA2	rno-miR-1	Metrnl
hsa-miR-1	HSPA4	rno-miR-1	Nampt
hsa-miR-1	IGF1	rno-miR-1	Sesn3
hsa-miR-1	IL10	rno-miR-1	Sparcl1
hsa-miR-1	IL6	rno-miR-1	Tgfa
hsa-miR-1	MMP2	rno-miR-1	Tgfb2
hsa-miR-1	MSTN	rno-miR-1	Tgfb3
hsa-miR-1	NAMPT	rno-miR-1	Vegfa
hsa-miR-1	SESN3		
hsa-miR-1	TGFB3		
hsa-miR-1	VEGFA		
hsa-miR-1	VEGFC		
miRNA	**Myokines (Target genes)**	**miRNA**	**Myokines (Target genes)**
hsa-miR-320	BDNF	rno-miR-320	Apln
hsa-miR-320	BMP10	rno-miR-320	Bdnf
hsa-miR-320	BMP2	rno-miR-320	Bmp6
hsa-miR-320	BMP6	rno-miR-320	Bmp7
hsa-miR-320	BMP 7	rno-miR-320	Chi3l1
hsa-miR-320	CHI3L1	rno-miR-320	Ctsb
hsa-miR-320	CTSB	rno-miR-320	Cx3cl1
hsa-miR-320	CX3CL1	rno-miR-320	Cx3cl10
hsa-miR-320	CXCL10	rno-miR-320	Cxcl12
hsa-miR-320	CXCL12	rno-miR-320	Dcn
hsa-miR-320	FGF1	rno-miR-320	Fgf2
hsa-miR-320	FGF3	rno-miR-320	Fstl1
hsa-miR-320	FGFBP1	rno-miR-320	Hspa4
hsa-miR-320	FNDC3A	rno-miR-320	Igf1
hsa-miR-320	FNDC5	rno-miR-320	Il15
hsa-miR-320	FSTL1	rno-miR-320	Il1rn
hsa-miR-320	FSTL3	rno-miR-320	Il6

miRNA	Myokines (Target genes)	miRNA	Myokines (Target genes)
hsa-miR-320	HSP90AB1	rno-miR-320	Lif
hsa-miR-320	HSP90B1	rno-miR-320	Metrnl
hsa-miR-320	HSPA4	rno-miR-320	Mstn
hsa-miR-320	IGF1	rno-miR-320	Nampt
hsa-miR-320	IL10	rno-miR-320	Sesn1
hsa-miR-320	IL4	rno-miR-320	Sesn2
hsa-miR-320	IL6	rno-miR-320	Sesn3
hsa-miR-320	LIF	rno-miR-320	Sparc
hsa-miR-320	NAMPT	rno-miR-320	Tgfb2
hsa-miR-320	SESN1	rno-miR-320	Vegfa
hsa-miR-320	SESN2	rno-miR-320	Vegfc
hsa-miR-320	SESN3	rno-miR-320	Vegfd
hsa-miR-320	SPARC		
hsa-miR-320	TGFB2		
hsa-miR-320	TGFB3		
hsa-miR-320	VEGBF		

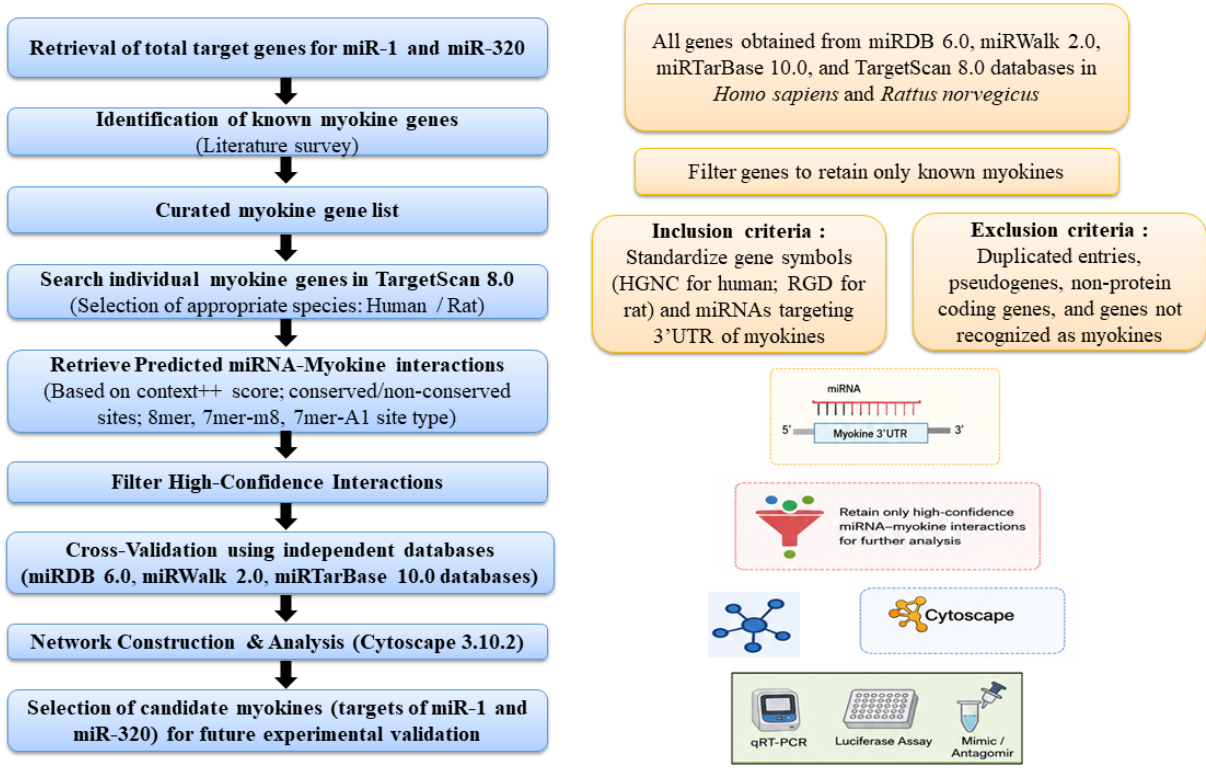

Figure 2. Bioinformatics workflow for the identification and screening of myokine-targeting miRNAs.

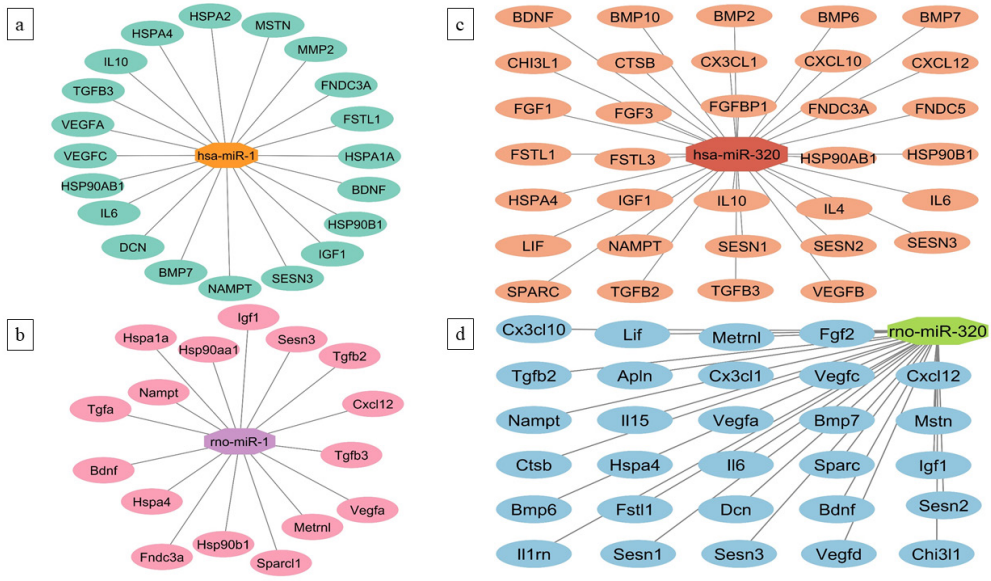

Figure 3. Crosstalk of miRNAs (miR-1 and miR-320) and myokines to decipher novel therapeutic targets for skeletal muscle diseases using Cytoscape 3.10.2 version software. (**a**) Visualization of hsa-miR-1 and 20 myokines network. (**b**) Representation of rno-miR-1 and 16 myokines network. (**c**) Visualization of hsa-miR-320 and 33 myokines network. (**d**) Representation of rno-miR-320 and 29 myokines using Cytoscape v.3.10.2.

muscle homeostasis. Further, experimental validation is required to decode the significant role of these candidate myokines (targets of miR-1 and miR-320) using quantitative real-time PCR (qRT-PCR), luciferase reporter assays, and gain-/loss-of-function experiments employing miRNA mimics or antagomiRs.

Further, our earlier studies have experimentally validated miRNA-myokine interactions under normal physiological conditions as well as stress environments. We observed significantly increased expressions of miR-1, miR-320, myostatin, IL-6, IL-15, and decreased expressions of irisin, apelin, decorin, osteocrin, Meteorin-like myokines under HH [18,19]. The altered expressions of miRNAs and myokines under HH negatively affected muscle adaptive responses, modulated myogenesis, metabolic signaling and upregulated protein degradation contributing to muscle loss.

Despite extensive knowledge of miRNA function, the gene-mediated regulation of miRNA expression or precise gene-level mechanisms governing miRNA transcription and maturation under tissue-specific and stress-induced conditions remain insufficiently studied. A deeper understanding of miRNA-myokine interactions might offer promising opportunities for therapeutic interventions and biomarker development. This attempt might unravel various ways to discover novel therapeutics against skeletal muscle diseases, and to counteract metabolic dysfunction, inflammation, skeletal muscle atrophy and impaired muscle degeneration.

Novel Therapeutics: miRNA-targeting Myokines

Although the myokines and miRNA are novel candidates for therapeutics, another important aspect of research is, miRNA-myokine interaction and regulation. Can a miRNA target myokine? Can a myokine regulate the expression of a particular miRNA?

This hypothetical idea can unravel a new paradigm in skeletal muscle research with relevant experimental validation (**Figure 4**). Myokines and miRNAs act as potent modulators of metabolism, muscle homeostasis, regeneration, skeletal muscle remodeling, inflammation, and inter-organ communication. This myokine-miRNA network may be associated with various molecular responses that promote or alter metabolic flexibility and reinforce or suppress pathological signaling to govern systemic health. Despite the recognized role of miRNAs (or myomiRs) and myokines in skeletal muscle homeostasis, the gene-level and epigenetic mechanisms regulating their expressions under hypoxia and atrophy-associated conditions remain largely unresolved. Several bioinformatic approaches help in screening the targets regulated by miRNAs, predict the miRNA-mRNA binding sites, affinity, detect the true miRNA-mRNA interactions, and determine miRNA-based gene regulatory effects. This may bridge a gap between computational tools and experimental validation to understand the precise function of miRNAs.

Also, *in silico* human and rat miRNA–myokine interaction networks reveal that several miRNAs target the same myokines across both species, while some miRNAs exhibit species-specific targeting patterns. These differences likely arise from a combination of genuine biological divergence, disparities in database annotation and coverage, and the inherent limitations of computational target prediction algorithms. At the same time, human miRNA databases are generally more comprehensive and experimentally validated than those for rat, leading to differences in the number and confidence of reported interactions. Nevertheless, the identification of conserved miRNA–myokine interactions across species is particularly valuable, as these are more likely to represent fundamental regulatory mechanisms preserved through evolution. Such conserved interactions provide stronger candidates for biomarker discovery and therapeutic intervention than species-specific predictions. Based on earlier reported preclinical studies, irisin and myostatin regulating miRNAs have been listed in **Table 4**.

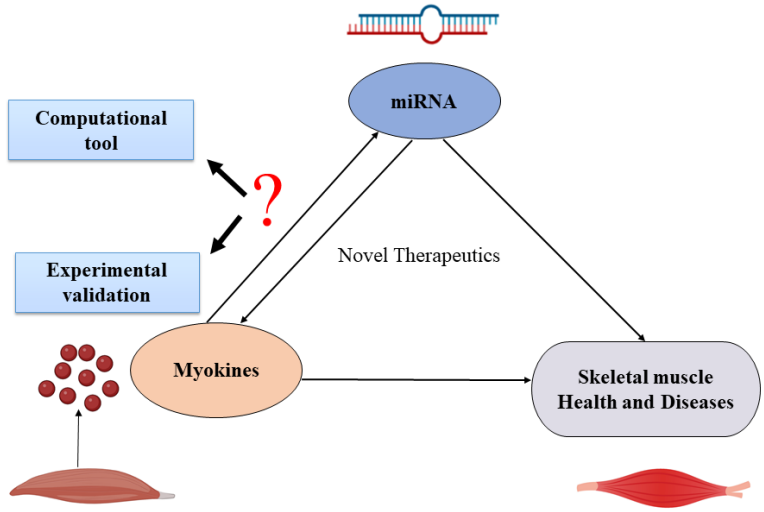

Figure 4. Crosstalk of miRNA and myokines to decipher novel therapeutic targets for skeletal muscle diseases.

Table 4. Irisin and myostatin regulating miRNAs based on preclinical studies.

Myokine	Targeting miRNA	Source of study	Experimental outcome	References
Irisin (FNDC5)	miR-214-3p	Osteosarcoma cells	Inhibition of FNDC5 expression in serum and tissue of osteosarcoma patients	[24]
FNDC5	miR-665-3p	Mice	Downregulate FNDC5 to inactivate AMPKα pathway to facilitate oxidative stress, inflammation and NAFLD progression	[25]
FNDC5	miR-150	Diabetic mice	Pyroptosis in diabetic bone tissue	[26]
FNDC5	miR-758, miR-668	3T3-L1 cells; Male C57BL/6J mice	Modulates CDK5 and leptin pathway	[27]
Irisin	miR-199a	A549 cells; Acute lung injury mouse model	Irisin treatment downregulates miR-199a to maintain lung weight, reduce inflammation and alleviate lung injury	[28]
FNDC5	miR-135a-5p	Human BM-MSCs	miR-135a-5p triggers FNDC5/Irisin to induce osteogenic differentiation	[29]
FNDC5	miR-337-3p	Serum from GDM patients; HTR-8/SVneo and BeWo cells, Trophoblast	FNDC5 downregulates miR-337-3p to increase cell viability and suppress apoptosis	[30]
Irisin	miR-34a	DCM rats	Inhibition of miR-34a shows anti-myocardial fibrotic effect by promoting irisin secretion	[31]
FNDC5	miR-34a-5p	C2C12; Mice	Hypoxia reduced Fndc5 and increased miR-34a-5p to mediate proteostasis	[32]
Myostatin (Mstn)	miR-34a	Mouse C2C12 myoblasts; SVF cells from WAT of Mice	Mstn and miR-34a downregulates Fndc5 to inhibit browning of WAT	[33]
Myostatin	miR-1, miR-133a, miR-133b, miR-206	Mice	Repression of skeletal muscle mass	[34]
Myostatin	miR-1, miR-133a/b, miR-206	C2C12 cells	Myostatin downregulates myomiRs prior to/during myotube formation	[35]
Myostatin (MSTN)	miR-27b-3p	HEK293T cells, DF-1 cells, Chicken primary myoblast (CPM)	Both miR-27b-3p and MSTN inhibit the proliferation and differentiation of CPMs	[36]
Myostatin	miR-486	C2C12 cells; C57BL/6 mice	Overexpression of miR-486 inhibits Mstn, induces myotube hypertrophy *in vitro* and increases skeletal muscle size *in vivo*	[37]
Myostatin (MSTN)	miR-27a/b	C2C12 cells	Direct inhibition of myostatin by miR-27a and miR-27b	[38]

Translational Challenges

We have comprehensively reviewed the role of myokines in redox homeostasis, muscle proteostasis and mitochondrial dynamics affecting the skeletal muscle health and function [23]. Irisin and myostatin represent two complementary therapeutic targets for miRNA-based intervention in skeletal muscle disorders. Irisin, a cleaved product of the FNDC5 gene, promotes mitochondrial biogenesis, myogenesis, angiogenesis, and oxidative metabolism, making it an attractive target for treating sarcopenia, cachexia, muscular dystrophy, obesity, and metabolic diseases. Several miRNAs, including miR-214-3p, miR-665-3p, miR-150, miR-758, miR-668, miR-199a, miR-135a-5p, miR-337-3p, miR-34a, have been reported to suppress FNDC5/irisin expression; therefore, inhibition of these miRNAs using antagomiRs may restore irisin levels and improve muscle regeneration and metabolic function [24–32]. In contrast, myostatin is a potent negative regulator of skeletal muscle growth, and therapeutic inhibition of myostatin signaling has emerged as a promising strategy for preventing muscle wasting. miRNAs such as miR-1, miR-133a/b, miR-206, miR-27a/b, miR-486, directly or indirectly suppress myostatin expression or its downstream signaling, thereby enhancing muscle hypertrophy, satellite cell activation, and protein synthesis [33–38]. Targeting miRNA-regulating myokines or myokine-regulating miRNAs has emerged as a promising therapeutic strategy for skeletal muscle disorders; however, several translational challenges must translation depends on overcoming challenges related to tissue-specific delivery, improving the safety and efficiency of viral and non-viral delivery systems, minimizing off-target effects, toxicity, and identifying miRNAs with high specificity for beneficial myokine regulatory networks. Advances in muscle-targeted lipid nanoparticles, engineered viral vectors, multi-omics technologies, and precision medicine approaches are expected to facilitate the development of safer and more effective miRNA-based therapies for skeletal muscle atrophy, sarcopenia, cachexia, and other muscle-related disorders. These pleiotropic effects highlight the need for comprehensive transcriptomic, proteomic, pharmacokinetics, immune activation, and toxicological studies to evaluate safety before clinical application. Most miRNA-based approaches remain in the preclinical stage while several myostatin-targeting biologics (monoclonal antibodies and ActRII receptor inhibitors) have advanced into Phase I-III clinical trials for conditions such as obesity, spinal muscular dystrophy, sarcopenia, and muscle-wasting disorders. This highlights the role of myostatin as the most clinically advanced myokine target. Current status on development of irisin- and myostatin-based therapies has been summarized in **Table 5**.

Table 5. Current status on development of irisin- and myostatin-based therapies.

Target (Myokine)	Therapeutic approach	Example	Diseases	Clinical Phase	Current Status	References
Irisin (FNDC5)	Recombinant irisin protein	Experimental	Obesity, insulin resistance, type 2 diabetes, osteoporosis, sarcopenia	Preclinical	No registered human clinical trials	[6,39–43]
Irisin (FNDC5)	miRNA modulation (anti-miR-696)	Experimental	Skeletal muscle atrophy	Preclinical	C2C12 myoblasts	[44]
Myostatin (MSTN)	miRNA mimics (miR-27a/miR-27b)	Experimental	CKD-induced muscle atrophy	Preclinical	In vitro/in vivo model; no human trials	[45–47]
Myostatin (MSTN)	Monoclonal antibody	Stamulumab (MYO-029)	Muscular dystrophy	Phase I/II	Trial completed; development discontinued due to limited efficacy	[48]
Myostatin (MSTN)	Monoclonal antibody	Apitegromab	Spinal muscular atrophy (SMA)	Phase III	Ongoing pivotal clinical trial	[49,50]
Myostatin (MSTN)	ActRII receptor antibody	Bimagrumab	Obesity, Type 2 diabetes, Sarcopenic obesity	Phase II	Completed; showed fat loss with lean mass preservation	[51]
Myostatin (MSTN)	ActRII receptor antibody	Bimagrumab plus semaglutide, alone or in combination	Obesity	Phase II	Substantial decreased body weight	[52]
Myostatin (MSTN)	Monoclonal antibody	Trevogrumab (REGN1033) alone, or in combination with semaglutide	Obesity, Sarcopenia, metabolic diseases, Type 2 diabetes	Phase II	Ongoing	[53]
Myostatin (MSTN)	Monoclonal antibody	Taldefgrobep alfa	Obesity, Spinal muscular atrophy (SMA), Duchenne Muscular dystrophy (DMD)	Phase II (obesity); Phase III (SMA); Phase II/III (DMD)	Active clinical development	[54,55]
Myostatin (MSTN)	Follistatin-based therapeutic	ACE-083	Facioscapulohumeral muscular dystrophy (FSHD); Charcot-Marie-Tooth disease (CMT) type 1	Phase II	Ongoing	[56–58]

Future Perspectives

As myokines are key players in myogenesis and myodegradation, miRNAs which regulate these myokines are very crucial for developing therapeutics. Hence, miRNA and myokine interaction is a pivotal research area to be exploited. The field of miRNA-based therapeutics still faces key challenges in establishing specificity and sensitivity towards their intended targets. Further, optimal dosing, stability, off-target effects and targeted delivery with minimal toxicity are also crucial concerns to be addressed. Future research should focus on integrating artificial intelligence (AI)-assisted target prediction of miRNA with multi-omics approaches to improve the discovery of clinically relevant miRNA–myokine regulatory networks. Advanced machine learning and deep learning algorithms can integrate RNA secondary structure, binding affinity of myokines and miRNAs, sequence characteristics, evolutionary conservation, and experimentally validated interactions to prioritize high-confidence miRNA–myokine pairs while minimizing false-positive predictions. Therefore, understanding the pivotal role of miRNA–myokine network in skeletal muscle is essential for identifying novel therapeutic targets for chronic diseases such as sarcopenia, cachexia, and muscular dystrophy to reduce global health burden and better quality of life.

Conflict of Interest

The authors declare no conflicts of interest.

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