Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Translational Medicine of Aging 4 (2020) 81–85

Contents lists available at ScienceDirect

Translational Medicine of Aging

journal homepage: www.keaipublishing.com/TMA

Aging Science Talks: The role of miR-181a in age-related loss of muscle mass and function

Maria Borja-Gonzalez [a, 1], Jose C. Casas-Martinez [a, 1], Brian McDonagh [a], Katarzyna Goljanek-Whysall [a, b, *]

[a] School of Medicine, Physiology, National University of Ireland Galway, Galway, H91 W5P7, Ireland
[b] Institute of Aging and Chronic Disease & The Medical Research Council Versus Arthritis Centre for Integrated Research Into Musculoskeletal Aging, CIMA, University of Liverpool, Liverpool, L7 8TJ, UK

ARTICLE INFO

Article history:
Received 5 June 2020
Accepted 3 July 2020
Available online 8 July 2020

Keywords:
microRNA
miR-181a
Muscle
Sarcopenia
Aging
Mitochondria

The outbreak of COVID-19 was declared a Public Health Emergency of International Concern in January 2020, scientists all over the world found new ways of progressing scientific research and maintaining or even expanding collaboration in a virtual setting. “Aging Science Talks” were one of the most successful initiatives that engaged scientists all over the world working in the field of aging and highly relevant in the context of the pandemic.

Aging is the biggest risk factor for developing chronic disorders such as heart disease, type 2 diabetes, chronic obstructive pulmonary disease (COPD), stroke, neurodegenerative diseases, chronic kidney diseases (CKDs) and cancer [1,2]. Aging is a complex process with detrimental effects on cell and tissue homeostasis which ultimately effects organ function [3]. Several mechanistic pathways have been associated with aging, such as an increase in inflammation, oxidative stress, DNA mutations, mitochondrial dysfunction, accumulation of senescence cells and disrupted proteostasis [4–6]. Although life expectancy has increased, this has not been accompanied by an increase in health span, which can subsequently result in a greater strain on healthcare systems [7]. The susceptibility of the aged individual suffering chronic disorders has been recently highlighted due to the Coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Emerging data show that older people and those with certain underlying medical conditions, such as obesity or diabetes, are particularly affected by SARS-CoV-2 [8–11]. Aging and COVID-19 are associated with changes in systemic inflammation and dysregulation of the immune system function [8] and it has been suggested that COVID-19 survivors, especially those requiring mechanical assisted ventilation will suffer from frailty [12]. Early studies have shown the existence of musculoskeletal deterioration in patients with COVID-19, although long-term follow-up studies are needed [13].

Frailty is largely associated with sarcopenia, aging-related loss of muscle mass and function, characterised by a progressive and degenerative loss of skeletal muscle mass, quality, and strength during aging [14]. Sarcopenia affects 5–13% of 60–70 year olds and up to 50% of people over 80 [15]. Currently, diet and exercise remain the only effective interventions, that aim to maintain muscle mass and force, however no therapeutic has been established to successfully treat sarcopenia [16,17]. The molecular mechanisms

* Corresponding author. School of Medicine, Physiology, National University of Ireland Galway, Galway H91 W5P7, Ireland.
E-mail addresses: k.whysall@liverpool.ac.uk, kasia.whysall@nuigalway.ie (K. Goljanek-Whysall).
[1] These authors contributed equally to this manuscript.

https://doi.org/10.1016/j.tma.2020.07.001

underlying sarcopenia are multifactorial [18–20]. Nevertheless, the transcriptome and proteome changes, as well as epigenetic changes in skeletal muscle during aging have been identified [21] [–] [25].

The role of microRNAs (miRNAs, miRs) as epigenetic modifiers in regulating loss of muscle mass and function has become increasingly recognised (reviewed in Ref. [17]). miRs are short, non-coding RNAs which regulate the expression of approximately 2/3 human genes [26]. miRs bind to their targets, usually within the 3′UTR region of mRNAs, *via* sequence complementarity. This results in gene expression regulation at the post-transcriptional level, through the degradation of the target mRNA(s) and/or translational block, ultimately resulting in decreased protein levels [26].

In skeletal muscle, miRs have been demonstrated to control multiple biological processes, including development, regeneration, and aging (reviewed in Ref. [27,28]). A number of miRs are involved in the regulation of muscle protein synthesis, that target regulators involved maintaining the balance between muscle atrophy and hypertrophy, and including regeneration of skeletal muscle [29–32]. Early studies in humans demonstrated differential expression of miRs in skeletal muscle during aging [24,33]. We and others have demonstrated the role of miRs in aging-associated processes in skeletal muscle, such as satellite cell senescence and inflammation [30,34,35].

Bioinformatic analyses of non-coding RNAs and transcripts in human and rodent muscle during aging have identified miR-181a as a potentially key regulator of muscle mass and function during aging [25,36]. The miR-181 family of miRs includes four miRs in humans and rodents: miR-181a, b, c and d. miR-181a and b are clustered together at two genomic loci on chromosomes 1 and 9 and miR-181c and d are clustered on chromosome 19 in humans. Interestingly, the two miR-181 clusters producing two members of miR-181 family each, have been shown to have divergent roles in myocardial function [37]. The miR-181 family is predicted to regulate over 1000 genes [38]. Unsurprisingly, the miR-181 family has been shown to regulate multiple genes in many tissues, including genes associated with mitochondrial dynamics [37,39–48].

In skeletal muscle, miR-181a appears to be the predominant miR-181 family member in skeletal muscle affected by aging and has been suggested as biomarker of muscular health [36,46]. miR-181 has also been demonstrated to be upregulated in muscle during exercise and predicted to regulate transcription factors and co-activators involved in the adaptive response of muscle to exercise [49]. Based on computer simulation models, miR-181a was predicted to regulate muscle atrophy and hypertrophy through its target genes: HOXA11 by inhibiting MYOD, and SIRT1, through regulating FoxO3 signalling [50] (Fig. 1). Indeed, we and others confirmed these as miR-181a direct targets [25,50]. More recently, miR-181 family of miRs gained more attention due to their regulation of processes associated with mitochondrial dynamics and directly targets PARK2 and p62/SQSTM1 [44,46,51] (see Fig. 1).

Mitochondrial dysfunction is one of the hallmarks of aging [5]. During aging, skeletal muscle is characterised by a loss of mitochondrial content [52] and disrupted mitochondrial turnover, particularly in sedentary individuals [46,53–56]. A number of studies to date suggest that miR-181a may be a global regulator of mitochondrial dynamics, redox homeostasis and potentially energy balance of the whole organism [34,39,44,46,51].

For example, post-stroke treatment with antagomiR-181a has been shown to reduce infarction size through regulating BCL-2 expression and NF-KB activation [57]. The regulation of Bcl-1 by miR-181 has also been demonstrated in astrocytes [40]. In this study, reduction of miR-181 levels and concomitant upregulation of BCL-2 led to a controlled increase in oxidative stress and antioxidant defence. Furthermore, inhibition of miR-181a was reported to protect the brain from stroke *via* regulation of GRP78 and miR-181a/b downregulation has been proposed to protect retinal neurons from cell death through regulating mitochondrial homeostasis [44,58].

The role of miR-181 in regulating the response to oxidative stress has also been studied in the context of myocardial function [37]. miR-181c levels were shown to negatively correlate to those of COX1, whereas miR-181a/b were suggested to regulate the levels of PTEN [37]. The authors proposed that decreased levels of miR-181c resulted in COX1 upregulation and dysfunction of complex IV and increased ROS production *in vitro* [59].

It therefore appears that miR-181 may play a critical role in regulating redox homeostasis and potentially mitochondrial dynamics in nervous and cardiac cells, with studies suggesting that inhibition of miR-181 may prevent cell death and improve antioxidant response *via* targeting BCL-1, BCL-2, GRP78 and PTEN. Interestingly, in other tissues miR-181 has been demonstrated to be a positive regulator of metabolism, mitochondrial function and redox homeostasis [60].

miR-181 has been proposed to function as the primary metabolic rheostat in immune cells trough targeting of PTEN and PI3K signaling [61]. Loss of miR-181a1/b1 in thymocytes was demonstrated to result in major metabolic reprogramming: a dysregulated expression of key components of the glycolytic, pentose phosphate and nucleotide biosynthetic pathways and miR-181a1/b1-deficient cells failed to reach the biosynthetic potential of proliferating thymocytes [62]. This led to suboptimal glucose uptake, reduced glycolytic rates, and impaired metabolic fitness in miR-181-deficient cells [62].

Moreover, mice lacking multiple miR-181 alleles display immune phenotypes in B-cell development and T-cell homeostatic proliferation [63]. Interestingly, miR-181a1/b1; miR-181a2/b2 double knockout mice show reduced survival when compared to littermates and a significant reduction in body size [62]. Furthermore, no data on triple knock-out mice exists, which may suggest that complete deficiency of the miR-181 family is lethal [61].

Consistently, the role of miR-181 as a positive regulator of metabolism though regulation of PTEN, overexpression of the miR-181a/b1 cluster was also demonstrated to enhance osteogenesis through protein synthesis and mitochondrial metabolism [51]. Moreover, oxygen consumption rate and ATP-linked respiration were increased by miR-181a/b1 through its regulation of the PTEN/PI3K signalling [51]. In the context of cancer, miR-181a has been shown to have pro- but also anti-oncogenic role [39,41,64–66]. In $CD8^+$ T cells, interferon-γ is regulated by miR-181a during differentiation [67].

In our study, using miR gain- and loss-of-function approaches, we have demonstrated that miR-181 regulates skeletal muscle size and function during aging through regulating mitochondrial dynamics [46]. Specifically, we demonstrated that miR-181a prevents the accumulation of Park2, DJ-1 and p62 in muscle during aging. This accumulation could be associated with disrupted mitochondrial turnover observed during aging [46]. Using the mitoQC reporter construct for the investigation of mitophagic flux [68], we demonstrated that miR-181a overexpression promotes mitophagy. The increased mitophagic flux may be associated with activation of alternative pathways than Pink/Parkin pathway, such as receptor-mediated mitophagy *via* BNIP3. Mitochondrial turnover is regulated by a number of different pathways and the exact regulatory mechanisms have not yet been fully determined [69,70]. Interestingly, we also observed a parallel increase in markers of mitochondrial biogenesis, e.g. increased PGC1a expression, following miR-181a overexpression in skeletal muscle [46]. A coupling of mitochondrial biogenesis and mitophagy has been previously observed in *C. elegans* and proposed to be mediated via NRF2

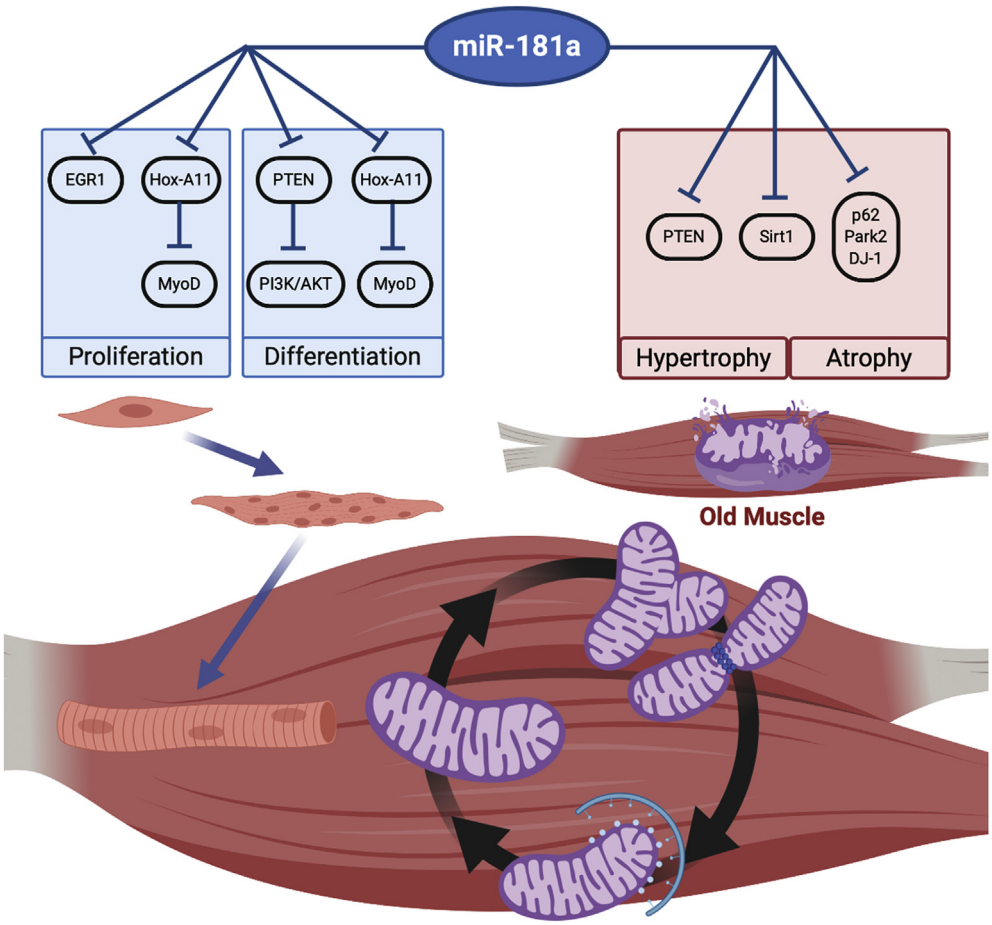

Fig. 1. The role of miR-181a in skeletal muscle aging.

pathway [71]. Ultimately the overexpression of miR-181a resulted in increased mitochondrial content and increased myofibre size and muscle force in skeletal muscle from old mice [46]. Interestingly, the positive effects of miR-181 on mitochondrial function have been demonstrated in other tissues such as chondrocytes [72].

Whilst most data agree on the importance of miR-181 in regulation of mitochondrial dynamics, redox homeostasis and energy balance, it appears that the role of miR-181a could be context-dependent as has been reported for other miRs [30,73]. Different members of miR-181 family were shown to have divergent function in myocardial function [37,38,42,43]. miR-181 family members are ubiquitously expressed and the dose dependent reduction in organism size and viability following reduction of levels of the miR-181 family members suggests the critical role of this miR family in metabolic fitness and proliferation [61]. Moreover, miR-181 target genes such as Parkin or PTEN are conserved among species and it has been suggested that this family of miRNAs has evolved to provide anabolic robustness during development [61]. This may also suggest the important role of miR-181 family in a multitude of disorders associated with changes in mitochondrial dynamics and oxidative stress, such as sarcopenia or aging.

The potential of miRs as novel therapeutics for various disorders has been proposed due to their implication in regulating multiple pathways and involvement in many disease states including aging and sarcopenia [25,27,35]. Despite multiple miR-based therapies being in clinical trials, no miR-based drug has been yet approved for use [74–79]. Since the recent approval of the first RNA drug for disease (2018) with no other treatment options, an interest in RNA therapeutics has increased. Onpattro (patisiran) infusion has been used to treat peripheral nerve disease (polyneuropathy) caused by hereditary transthyretin-mediated amyloidosis (hATTR) in adult patients [80]. As miRs regulate the expression of multiple genes simultaneously, they are attractive therapeutic targets for disorders with a complex molecular background, such as sarcopenia. miRs are small, charged, and water-soluble molecules and can be injected intravascularly or subcutaneously [81]. Moreover, synthetic miRs and their inhibitors can be efficiently delivered, into muscle without a systemic immune response [74,82]. Furthermore, various miR-based therapies are undergoing clinical trials, miR mimics and inhibitors (antagomiRs, antimiRs) [74]. Some of the remaining issues that remain to be resolved before miRs can enter the drug market are potential off-target effects and tissue-specific delivery. These would be of significance when designing a miR-based therapeutic for muscle disorders, as delivery would likely be via IV injection which could result in systemic expression. Nevertheless, miR-based approaches have shown efficacy in diseases such as cancer, hepatitis C and heart abnormalities [75,83]. Emerging data for miRs as therapeutic is encouraging and with emerging technologies, miR-based approaches may provide functional interventions for preventing aging- and disease-related loss of muscle mass and strength.

Declaration of competing interest

The authors declare no conflict of interest.

References

[1] J.R. Ruiz, et al., Association between Muscular Strength and Mortality in Men: Prospective Cohort Study, " *BMJ*, 2008.
[2] N. Kubben, T. Misteli, Shared molecular and cellular mechanisms of premature aging and aging-associated diseases, Nat. Rev. Mol. Cell Biol. 18 (10) (2017) 595–609.
[3] R. Fernando, C. Drescher, K. Nowotny, T. Grune, J.P. Castro, Impaired proteostasis during skeletal muscle aging, Free Radic. Biol. Med. 132 (September 2018) 58–66, 2019.
[4] D. Gallagher, et al., Weight stability masks sarcopenia in elderly men and women, Am. J. Physiol. Endocrinol. Metab. 279 (2 42–2) (2000) 366–375.
[5] C. López-Otín, M.A. Blasco, L. Partridge, M. Serrano, G. Kroemer, The Hallmarks of Aging, Cell 153 (6) (2013) 1194–1217.
[6] M. Fernandes, et al., Systematic analysis of the gerontome reveals links between aging and age-related diseases, Hum. Mol. Genet. 25 (21) (2016) 4804–4818.
[7] J.M. Aburto, F. Villavicencio, U. Basellini, S. Kjærgaard, J.W. Vaupel, Dynamics of life expectancy and life span equality, Proc. Natl. Acad. Sci. U.S.A. 117 (10) (2020) 5250–5259.
[8] J. Nikolich-Zugich, K.S. Knox, C.T. Rios, B. Natt, D. Bhattacharya, M.J. Fain, SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes, GeroScience 19 (2020).
[9] K. Liu, Y. Chen, R. Lin, K. Han, Clinical features of COVID-19 in elderly patients: a comparison with young and middle-aged patients, J. Infect. 80 (6) (2020) 14–18.
[10] A.L. Mueller, M.S. Mcnamara, D.A. Sinclair, Why Does COVID-19 Disproportionately Affect the Elderly? Preprints 12 (2020) 9959–9981.
[11] F.E. Lithander, et al., COVID-19 in Older People: A Rapid Clinical Review, " *Age Aging*, 2020.
[12] C.H. Nickel, M. Rueegg, H. Pargger, R. Bingisser, Age, comorbidity, frailty status: effects on disposition and resource allocation during the COVID-19 pandemic, " *Swiss Med. Wkly.*, 2020.
[13] N.P. Disser, et al., Musculoskeletal consequences of COVID-19, J. Bone Jt. Surgery, Inc. 1 (2020) 1–8.
[14] L. Larsson, et al., Sarcopenia: aging-related loss of muscle mass and function, Physiol. Rev. 99 (1) (2019) 427–511.
[15] G. Abellan Van Kan, Epidemiology and consequences of sarcopenia, J. Nutr. Health Aging 13 (8) (2009) 708–712.
[16] J.E. Morley, Treatment of sarcopenia: the road to the future, J. Cachexia, Sarcopenia and Muscle 9 (7) (2018) 1196–1199.
[17] A.J. Sannicandro, B. McDonagh, K. Goljanek-Whysall, MicroRNAs as potential therapeutic targets for muscle wasting during cancer cachexia, Curr. Opin. Clin. Nutr. Metab. Care 23 (3) (2020) 157–163.
[18] K. Goljanek-Whysall, L.A. Iwanejko, A. Vasilaki, V. Pekovic-Vaughan, B. McDonagh, "Aging in Relation to Skeletal Muscle Dysfunction: Redox Homoeostasis to Regulation of Gene Expression," *Mammalian Genome*, 2016.
[19] L. Larsson, et al., Sarcopenia: aging-related loss of muscle mass and function, Physiol. Rev. 99 (1) (2019) 427–511.
[20] J.G. Ryall, J.D. Schertzer, G.S. Lynch, Cellular and Molecular Mechanisms Underlying Age-Related Skeletal Muscle Wasting and Weakness, Biogerontology 9 (4) (2008) 213–228.
[21] M. Murgia, et al., Single muscle fiber proteomics reveals fiber-type-specific features of human muscle aging, Cell Rep. 19 (11) (2017) 2396–2409.
[22] P.G. Giresi, et al., Identification of a Molecular Signature of Sarcopenia, *Physiol. Genomics*, 2005.
[23] M.J. Drummond, J.J. McCarthy, C.S. Fry, K.A. Esser, B.B. Rasmussen, Aging differentially affects human skeletal muscle microRNA expression at rest and after an anabolic stimulus of resistance exercise and essential amino acids, Am. J. Physiol. Endocrinol. Metab. 295 (6) (2008) E1333–E1340.
[24] M.J. Drummond, et al., Aging and microRNA Expression in Human Skeletal Muscle: A Microarray and Bioinformatics Analysis, " *Physiol. Genomics*, 2011.
[25] A. Soriano-Arroquia, L. House, L. Tregilgas, E. Canty-Laird, K. Goljanek-Whysall, The Functional Consequences of Age-Related Changes in microRNA Expression in Skeletal Muscle, " *Biogerontology*, 2016.
[26] R.C. Friedman, K.K.H. Farh, C.B. Burge, D.P. Bartel, Most mammalian mRNAs are conserved targets of microRNAs, Genome Res. 19 (1) (2009) 92–105.
[27] D.M. Brown, K. Goljanek-Whysall, MicroRNAs: modulators of the underlying pathophysiology of sarcopenia? Aging Res. Rev. 24 (2015) 263–273.
[28] K. Goljanek-Whysall, D. Sweetman, A.M. Münsterberg, microRNAs in skeletal muscle differentiation and disease, Clin. Sci. 123 (11) (2012) 611–625.
[29] F. Iannone, et al., Expression patterns of muscle-specific miR-133b and miR-206 correlate with nutritional status and sarcopenia, Nutrients 12 (2) (2020) 1–15.
[30] R.J. Soares, et al., Involvement of MicroRNAs in the regulation of muscle wasting during catabolic conditions, J. Biol. Chem. 289 (32) (2014) 21909–21925.
[31] B.K. Dey, J. Gagan, Z. Yan, A. Dutta, miR-26a is required for skeletal muscle differentiation and regeneration in mice, Genes Dev. 26 (19) (2012) 2180–2191.
[32] T.H. Cheung, et al., Maintenance of Muscle Stem-Cell Quiescence by microRNA-489, " *Nature*, 2012.
[33] D.A. Rivas, et al., Diminished skeletal muscle microRNA expression with aging is associated with attenuated muscle plasticity and inhibition of IGF-1 signaling, Faseb. J. 28 (9) (2014) 4133–4147.
[34] A. Soriano-Arroquia, R. Mccormick, A.P. Molloy, A. Mcardle, K. Goljanek-Whysall, Age-related changes in miR-143-3p: igfbp5 interactions affect muscle regeneration, Aging Cell 15 (2) (2016) 361–369.
[35] M. Borja-Gonzalez, J.C. Casas-Martinez, B. McDonagh, K. Goljanek-Whysall, Inflamma-miR-21 negatively regulates myogenesis during aging, Antioxidants 9 (4) (2020) 345.
[36] C.J. Proctor, K. Goljanek-Whysall, Using computer simulation models to investigate the most promising microRNAs to improve muscle regeneration during aging, Sci. Rep. 7 (1) (2017) 1–12.
[37] S. Das, et al., Divergent effects of miR-181 family members on myocardial function through protective cytosolic and detrimental mitochondrial microRNA targets, J. Am. Heart Assoc. 6 (3) (2017) 1–17.
[38] V. Agarwal, G.W. Bell, J.W. Nam, D.P. Bartel, Predicting Effective microRNA Target Sites in Mammalian mRNAs, " *Elife*, 2015.
[39] Y. Liu, et al., Molecular mechanisms of pathogenesis in hepatocellular carcinoma revealed by RNA-sequencing, Mol. Med. Rep. 16 (5) (2017) 6674–6682.
[40] Y.B. Ouyang, Y. Lu, S. Yue, R.G. Giffard, MiR-181 Targets Multiple Bcl-2 Family Members and Influences Apoptosis and Mitochondrial Function in Astrocytes, " *Mitochondrion*, 2012.
[41] L. Yang, Y. Ma, Y. Xin, R. Han, R. Li, X. Hao, Role of the microRNA 181 family in glioma development, Mol. Med. Rep. 17 (1) (2018) 322–329.
[42] R. Ducas, et al., Echocardiography and vascular ultrasound: new developments and future directions, Can. J. Cardiol. 29 (3) (2013) 304–316.
[43] Y. Xu, Y. Zhang, J. Ye, IL-6: a potential role in cardiac metabolic homeostasis, Int. J. Mol. Sci. 19 (9) (2018) 2474–2489.
[44] A. Indrieri, et al., "miR-181a/b downregulation exerts a protective action on mitochondrial disease models, EMBO Mol. Med. 11 (5) (2019) 1–16.
[45] P. Chen, J. Pan, X. Zhang, Z. Shi, X. Yang, The role of microRNA-181a in myocardial fibrosis following myocardial infarction in a rat model, Med. Sci. Mon. Int. Med. J. Exp. Clin. Res. 24 (2018) 4121–4127.
[46] K. Goljanek-whysall, A.S.R. Mccormick, C. Chinda, B. Mcdonagh, miR-181a regulates p62/SQSTM1, parkin, and protein DJ-1 promoting mitochondrial dynamics in skeletal muscle aging, *Aging Cell*, no. January (2020) 1–16.
[47] W. Xie, et al., miR-181a regulates inflammation responses in monocytes and macrophages, PloS One 8 (3) (2013) 1–12.
[48] W. Xie, Z. Li, M. Li, N. Xu, Y. Zhang, MiR-181a and inflammation: MiRNA homeostasis response to inflammatory stimuli in vivo, Biochem. Biophys. Res. Commun. 480 (2) (2013) 647–652.
[49] A. Safdar, A. Abadi, M. Akhtar, B.P. Hettinga, M.A. Tarnopolsky, miRNA in the regulation of skeletal muscle adaptation to acute endurance exercise in C57Bl/6J male mice, PloS One 4 (5) (2009) 1–8.
[50] I. Naguibneva, et al., The microRNA miR-181 targets the homeobox protein Hox-A11 during mammalian myoblast differentiation, Nat. Cell Biol. 8 (3) (2006) 278–284.
[51] H. Zheng, J. Liu, E. Tycksen, R. Nunley, A. McAlinden, MicroRNA-181a/b-1 over-expression enhances osteogenesis by modulating PTEN/PI3K/AKT signaling and mitochondrial metabolism, Bone (Tarrytown) 123 (2019) 92–102.
[52] F. St-Jean-Pelletier, " J. Cachexia, The impact of aging, physical activity, and pre-frailty on skeletal muscle phenotype, mitochondrial content, and intramyocellular lipids in men, Sarcopenia Muscle 8 (2) (2017) 213–228.
[53] D.A. Hood, J.M. Memme, A.N. Oliveira, M. Triolo, Maintenance of skeletal muscle mitochondria in health, exercise, and aging, Annu. Rev. Physiol. 81 (2019) 19–41.
[54] C. Tezze, et al., Age-Associated Loss of OPA1 in Muscle Impacts Muscle Mass, Metabolic Homeostasis, Systemic Inflammation, and Epithelial Senescence, *Cell Metab.*, 2017.
[55] G. Favaro, et al., DRP1-mediated mitochondrial shape controls calcium homeostasis and muscle mass, Nat. Commun. 10 (1) (2019) 1–17.
[56] M. Sandri, et al., Signalling Pathways Regulating Muscle Mass in Aging Skeletal Muscle. The Role of the IGF1-Akt-mTOR-FoxO Pathway, " *Biogerontology*, 2013.
[57] L.J. Xu, Y.B. Ouyang, X. Xiong, C.M. Stary, R.G. Giffard, Post-stroke treatment with miR-181 antagomir reduces injury and improves long-term behavioral recovery in mice after focal cerebral ischemia, Exp. Neurol. 264 (2015) 1–7.
[58] Y.B. Ouyang, et al., MiR-181 regulates GRP78 and influences outcome from cerebral ischemia in vitro and in vivo, Neurobiol. Dis. 45 (1) (2012) 555–563.
[59] S. Das, et al., Nuclear miRNA Regulates the Mitochondrial Genome in the Heart, " *Circ. Res.*, 2012.
[60] M. Cheng, et al., MicroRNA-181a Suppresses Parkin-Mediated Mitophagy and Sensitizes Neuroblastoma Cells to Mitochondrial Uncoupler-Induced Apoptosis, " *Oncotarget*, 2016.
[61] A. Williams, J. Henao-Mejia, C.C.D. Harman, R.A. Flavell, "miR-181 and metabolic regulation in the immune system," *Cold Spring Harb*, Symp. Quant. Biol. 78 (2013) 223–230.
[62] J. Henao-Mejia, et al., The MicroRNA miR-181 Is a Critical Cellular Metabolic Rheostat Essential for NKT Cell Ontogenesis and Lymphocyte Development and Homeostasis, " *Immunity*, 2013.
[63] M. Coffre, S.B. Koralov, miRNAs in B Cell development and lymphomagenesis, Trends Mol. Med. 23 (8) (2017) 721–736.
[64] S.-F. Zhou, S.-M. He, S. Zeng, Z.-W. Zhou, Z. He, Hsa-microRNA-181a is a regulator of a number of cancer genes and a biomarker for endometrial carcinoma in patients: a bioinformatic and clinical study and the therapeutic implication, Drug Des. Dev. Ther. 9 (2015) 1103–1175.

[65] L. Zhang, et al., The miR-181 family promotes cell cycle by targeting CTDSPL, a phosphatase-like tumor suppressor in uveal melanoma, J. Exp. Clin. Canc. Res. 37 (1) (2018) 1–13.
[66] T. Rezaei, et al., microRNA-181 serves as a dual-role regulator in the development of human cancers, Free Radic. Biol. Med. 152 (2020) 432–454.
[67] T. Amado, et al., MicroRNA-181a regulates IFN-γ expression in effector CD8+ T cell differentiation, J. Mol. Med. 98 (2) (2020) 309–320.
[68] G.F.G. Allen, R. Toth, J. James, I.G. Ganley, Loss of iron triggers PINK1/Parkin-independent mitophagy, EMBO Rep. 14 (12) (2013) 1127–1135.
[69] L. Montava-Garriga, I.G. Ganley, Outstanding questions in mitophagy: what we do and do not know, J. Mol. Biol. 432 (1) (2020) 206–230.
[70] K. Palikaras, E. Lionaki, N. Tavernarakis, Mechanisms of mitophagy in cellular homeostasis, physiology and pathology, Nat. Cell Biol. 20 (9) (2018) 1013–1022.
[71] K. Palikaras, E. Lionaki, N. Tavernarakis, Interfacing Mitochondrial Biogenesis and Elimination to Enhance Host Pathogen Defense and Longevity, " *Worm*, 2015.
[72] L. Zheng, et al., Circadian Rhythms Regulate Amelogenesis, " *Bone*, 2013.
[73] F. Erhard, et al., Widespread context dependency of microRNA-mediated regulation, Genome Res. 24 (6) (2014) 906–919.
[74] C. Chakraborty, A.R. Sharma, G. Sharma, C.G.P. Doss, S.S. Lee, Therapeutic miRNA and siRNA: moving from bench to clinic as next generation medicine, Mol. Ther. Nucleic Acids 8 (2017) 132–143.
[75] J. Hanna, G.S. Hossain, J. Kocerha, The potential for microRNA therapeutics and clinical research, Front. Genet. 10 (478) (2019) 1–6.
[76] R.u. Takahashi, M. Prieto-Vila, I. Kohama, T. Ochiya, Development of miRNA-based therapeutic approaches for cancer patients, Canc. Sci. 110 (4) (2019) 1140–1147.
[77] J. Hayes, P.P. Peruzzi, S. Lawler, MicroRNAs in cancer: biomarkers, functions and therapy, Trends Mol. Med. 20 (8) (2014) 460–469.
[78] R. Rupaimoole, F.J. Slack, MicroRNA therapeutics: towards a new era for the management of cancer and other diseases, Nat. Rev. Drug Discov. 16 (3) (2017) 203–222.
[79] N. Hosseinahli, M. Aghapour, P.H.G. Duijf, B. Baradaran, Treating cancer with microRNA replacement therapy: a literature review, J. Cell. Physiol. 233 (8) (2018) 5574–5588.
[80] S.M. Hoy, Patisiran: First Global Approval, " *Drugs*, 2018.
[81] B. Simonson, S. Das, MicroRNA therapeutics: the next magic bullet? Mini Rev. Med. Chem. 15 (6) (2015) 467–474.
[82] G. Biglino, M. Caputo, C. Rajakaruna, G. Angelini, E. van Rooij, C. Emanueli, Modulating microRNAs in cardiac surgery patients: novel therapeutic opportunities? Pharmacol. Therapeut. 170 (2017) 192–204.
[83] C.M. Curtin, I.M. Castaño, F.J. O'Brien, Scaffold-based microRNA therapies in regenerative medicine and cancer, Adv. Healthcare Mater. 7 (1) (2018) 1–22.