# microRNAs as potential therapeutic targets for muscle wasting during cancer cachexia

Anthony J Sannicandro[1], Brian McDonagh[1], Katarzyna Goljanek-Whysall[1,2]

1 – Discipline of Physiology, School of Medicine, National University of Ireland, Galway, Ireland

2- Institute of Ageing and Chronic Disease, University of Liverpool, UK

Corresponding author:

Katarzyna Goljanek-Whysall:

Kasia.whysall@nuiglaway; 0035391494299

k.whysall@liverpool.ac.uk

**Abstract:**

**Purpose of the review:** Muscle wasting in cancer cachexia remains an unmet clinical need due to lack of effective therapies associated with the complexity of the disease. Here, we discuss microRNAs, robust regulators of the expression of multiple genes, only recently characterised in cancer cachexia in humans and their therapeutic potential for muscle wasting.

**Recent findings:** Changes in microRNAs in muscle of cancer patients have been demonstrated for the first time and these are associated with networks dysregulated during muscle wasting. These data, together with studies in animal models, indicate that microRNAs are attractive candidate therapeutics for maintaining muscle mass, both during and following cancer treatment and improving patient outcomes.

**Summary:** Cancer cachexia is a complex metabolic condition associated with muscle wasting. Maintenance of muscle mass in cancer patients can improve their response to therapy and prognosis. microRNAs, which can act as oncogenes or tumour suppressors, are also dysregulated in muscle of cachexia patients. Studies in animal models of muscle wasting have demonstrated that microRNAs regulate muscle mass and strength. With more microRNA-based therapeutics in clinical trials and first RNA drugs approved, microRNAs present an attractive novel therapeutic avenue for maintaining muscle homeostasis in cachexia patients to improve their prognosis.

**Keywords:** microRNA, cancer, cachexia, muscle, myomiRs

## Introduction

Skeletal muscle is the most abundant tissue in the body composing 35-50% of total body mass. While a lot of attention has been focused on skeletal muscle wasting as a primary disorder, for example during ageing (sarcopenia) or myopathies; muscle atrophy is also a common co-morbidity associated with cancer (1). Cancer cachexia is a complex metabolic syndrome, with research suggesting prevalence between 15% (e.g. breast cancer), 50% to 80% (e.g. colorectal, lung, pancreatic) of cancer patients, with large variations in weight and muscle loss depending on stage of disease and cancer location (2). In severe cases, cachectic patients may lose up to 75% of their muscle mass (3). Low muscle mass is associated with poor prognosis, restoring muscle mass and function in cancer patients could not only improve their recovery following successful treatment but is also likely to improve the success of the therapy itself (4,5). Currently, there are few therapies for muscle wasting, with most approaches focusing on dietary and exercise-based interventions in addition to several pharmaceutical approaches available, including hormone therapy, androgen receptor modulators, orexigenics, myostatin inhibitors and anti-inflammatory drugs (6,7). These have shown limited success due to poor clinical trial performance and lack of long-term efficacy studies (8). Regardless of the associated pathophysiological process, there is a critically unmet need for muscle preservation strategies that can recapitulate muscle mass and strength. Small RNA drugs have been recently approved by FDA showing promise for no option diseases (9,10) and research into a class of small non-coding RNAs: microRNAs (**miRs**), has shown that microRNAs may also hold a therapeutic potential.

## microRNAs in muscle wasting during cachexia.

The ability of microRNAs to extensively regulate gene expression has led to an increased interest in these small non-coding RNAs. miRs are a class of small ~22-nt RNAs that regulate gene expression in a post-transcriptional manner by recognising mRNA targets based on complimentary sequences and in most cases leading to mRNA degradation and/or inhibition of translation (11). Since their discovery, over 2500 miRs have been described in humans, estimated to regulate 60% of protein-coding genes (12). Of all the non-coding RNAs, miRs are the most studied, with nearly 12,000 miR-related papers being published in 2019 demonstrating the important roles of miRs in maintaining tissue homeostasis in health and disease (13). An important aspect of miRs is their potential to target the expression of multiple genes simultaneously, which in turn allows one miR to fine-tune multiple components of signalling pathways relevant to complex diseases associated with complex background. Muscle wasting

in cachexia is an example of such a complex disorder with multiple genes and signalling pathways involved in maintaining muscle homoeostasis being dysregulated during cancer cachexia. Some of these pathways include, but are not limited to, TNF and IFN signalling, NF-κB and STAT transcription factors and their target genes, IGF1-AKT-FOXO signalling involved in proteostasis (14). These pathways are regulated on multiple levels, including post-transcriptional regulation of gene expression (15). miRs are attractive regulators of pathways involved in muscle homeostasis that can regulate the expression of multiple genes. To date, many miRs have been described as essential in muscle development, regeneration and maintaining muscle homeostasis (23). The expression of multiple miRs has been shown to be dysregulated during muscle wasting in ageing, myopathies or cachexia (16).

Changes in miR levels in muscle of cachectic patients or in mouse models of cancer cachexia (17–19) have been recently reported. Narashiman and colleagues demonstrated upregulation of 8 miRs in muscle of cachexia patients with either pancreatic or colorectal cancer (n=22) as compared to muscle of cancer patients with no cachexia (n=20) (19). More recently, Worp *et al.* demonstrated changes in miR expression in the muscle of patients with lung cancer (cachectic n=15, non-cachectic n=11) (17). This is highly relevant as up to 60% of lung cancer patients experience cachexia (17). Limited overlap between the set of miRs differentially expressed in the two studies is likely due to different cancers studied, however both demonstrated that miRs altered in muscle during cachexia are associated with similar pathways, e.g. cell cycle regulation (17,19). A recent meta-analysis of available datasets on miRs in cachexia demonstrated miR:mRNA networks potentially associated with muscle wasting during cachexia, indicating some of the key genes involved in muscle wasting in cachexia are associated with mitochondrial dynamics, such as Bnip 3 involved in mitophagy, Polrmt involved in mitochondrial transcription or Ucp3 involved in energy balance (14). This meta-analysis also revealed the potential role of miR-181 in regulating muscle wasting (14). Our group and others have previously demonstrated the role of miR-181 in regulating mitochondrial dynamics and muscle wasting during ageing (20,21).

**Conserved miR:target interactions between humans and animal models**

We have compared the published datasets to determine which miRs are altered in muscle of cancer patients, as well as in muscle of mouse models of cachexia (Table 1). Based on the published data, 7 miRs were consistently dysregulated during cancer cachexia in humans and in the mouse Lewis Lung Carcinoma (LLC)-induced model of cachexia. These miRs have an established role in cancer and predicted or established role in muscle homeostasis. We used

network analyses based on predicted target genes of these 7 miRs using metaboanalyst (omicsnet: www. https://www.omicsnet.ca/) (Fig. 1). We investigated miR:gene interactions, as well as interactions between the genes. Many genes were targets of more than one of the 7 miRs and several genes formed hubs of interactions with each other, as well as with the miRs, highlighted in Fig.1. Several predicted miR targets are involved in multiple interactions with other genes including known oncogenes, tumour suppressors and genes involved in cancer metastasis, for example p53, Rab5a (a member of RAS oncogene family which promotes cancer invasion (22)), Grb2 (cell cycle and angiogenesis regulator (23)), Bhlhe40 (controls metastasis (24)), Bmi-1 (a member of the polycomb group family, oncogene (25)), Taok1 (inflammation regulator (26)) or P53. Among the miRs downregulated in muscle of cancer patients and mouse models is miR-26 (Table 1, Figure 1). miR-26 has been shown to induce mitochondrial apoptosis mediated by p53 (27) and its function in muscle has been previously described (28). Interestingly, Cul3 associated with the global antioxidant transcription factor Nrf2 pathway. Nrf2 and oxidative homeostasis were among the predicted targets of miRs dysregulated in cachexia. Nrf2 pathway is important for muscle homeostasis and key to cellular sensitivity to carcinogenic stimuli and chemotherapeutic drugs (29). miR-144, downregulated in cachexia, is predicted to target Nrf2. Nrf2 is also associated with regulation of mitochondrial dynamics (30). The only effective to a degree intervention for muscle wasting, exercise, has been associated with changes in mitochondrial plasticity, further confirming the importance of healthy mitochondria for maintaining muscle mass and function (31). Exercise-induced adaptations include a shift towards more oxidative capacities, typically seen in advanced-trained athletes. Contrastingly, muscle wasting, atrophy, and disease are associated with changes in mitochondrial fusion: fission ratio (31). Disrupted mitochondrial dynamics and an altered redox environment resulting in altered signaling and adaptive responses have been postulated as a major determinant of muscle wasting (31,32). Altered mitochondria function can lead to impaired respiration, aberrant mitochondrial autophagy (mitophagy) and chronically elevated reactive oxygen species (ROS) (31). miR-based approaches could provide a way of fine-tuning key regulatory pathways such as mitochondrial dynamics and redox balance through controlling expression of multiple genes associated with antioxidant activity or mitochondria, and ultimately restore muscle homeostasis.

The existing data indicates that several miRs may be important in maintaining muscle mass. However, functional studies of miRs at the pre-clinical level are required to determine the therapeutic potential of miRs for the treatment of muscle wasting in cachexia. Currently available clinical trial data and recently approved RNA drugs provide promise for the future

use of miR therapies either as stand-alone or adjuvants to current treatments and interventions available for cancer cachexia.

## microRNAs as therapeutics

The advantage of miR-based approaches in disorders with multifactorial background as compared to gene therapies is their potential to regulate the expression levels of multiple genes simultaneously. miRs have a similar mechanism of action to small interfering RNA (siRNA)-based RNA therapeutics: Nusinersen for the treatment of spinal muscular atrophy (33), and Patisiran for the treatment of hereditary transthyretin-mediated amyloidosis, which work through binding and subsequently degrading the mRNA (9,33). While miR-mediated targeting of multiple genes has been postulated to potentially yield off-target effects, it has been suggested to be similar to more traditional therapies targeting single genes, thus not excluding miRs from being potent future therapeutic agents (33). No miR drugs are currently in clinics, there are several ongoing phase 1 and 2 clinical trials (e.g. Clinical trial numbers: NCT02508090, NCT03603431, NCT03373786) investigating miR-based approaches for cancers, cardiovascular diseases and brain diseases (13). The development of miR-based drugs shows promise as a stand-alone or an adjuvant to current therapies for difficult to treat diseases of multiple organ systems.

However, for miR therapies to progress, several issue remain to be resolved. For example, re-expressing a miR can be used to restore miR function in disease using chemically modified miR mimics, however this may also result in uptake by tissues which do not normally express that miR and potential off-target effects (34). Optimal miR doses within physiological levels in order to minimise the potential of off-target effects by delivery of miRs to non-target tissues remain to be established. An alternative approach may be the use of anti-miRs (antagomiRs, miR sponges), antisense oligonucleotides with complementary reverse sequences to the endogenous miR to inhibit miR function. These are thought to have high specificity and affinity and less likely off-target effects (35). However, most miRs reported to change in cancer cachexia are downregulated limiting this approach (Table 1). Another significant challenge that faces the future of miR therapies is effective delivery. Typical modifications of synthetic miRs or their inhibitors include cholesterol conjugation, LNA oligos to facilitate cellular uptake, as well using adeno-associated viral (AAV) constructs. Furthermore, tissue-specific promoters can be used to enhance tissue- and cell-specific delivery of the construct (35). Ultimately, a deeper understanding of delivery, mechanisms of action, long-term efficacy,

pharmacodynamics and pharmacokinetics, as well as safety in humans remains paramount to the continued development and advancement of miRs as valid therapeutic compounds.

## Conjugation of miR therapeutics with current exercise and dietary approaches

While there is promise of miRs as drug candidates, there may be further potential to be used in conjunction with current 'gold standard' approaches, enabling more effective restoration of muscle function at both physical and cellular levels. Current approaches for cancer cachexia include diet and exercise interventions, although the levels of fatigue and appetite loss associated with the disease make these interventions extremely difficult for most patients (36). A critical aspect of these approaches is the reliance on exercise and diet to reverse muscle loss in cachexia. Skeletal muscle responds to mechanical loads (e.g. resistance exercise), which in turn, stimulates the anabolic signalling cascade that increases muscle protein synthesis and promotes muscle growth (16). It has been shown that cancer patients have the potential to gain and stabilise muscle mass, however evidence appears to show that this is further impaired in more advanced stages of cancer and highly dependent on dietary protein intake (37). Moreover, a blunted anabolic response to protein ingestion in ageing has been demonstrated, and it has been suggested that a similar response to protein administration in cachectic patients exists and could be key to muscle loss in cancer (38). Furthermore, anorexia and appetite loss are frequently associated with cachexia (39), making nutritional approaches to combating muscle loss challenging for the patients. Mechanistically, the cachexia is largely associated with chronic systemic inflammation, increases in catabolic activity, such as in the ubiquitin-dependent pathway, as well deactivation of the target of rapamycin (mTOR) pathway. These pathways affect the responses (e.g. insulin signalling) to physical activity and exercise (39,40) and several miRs altered in cachexia have been shown to regulate these pathways, e.g. miR-144 regulates insulin sensitivity (Table 1).

A direct approach at targeting the pathways associated with cachexia *via* miR-based therapeutics could restore the homeostasis of chronically deregulated networks and potentially condition the muscle to a more favourable response to diet and exercise. Therefore, miRs could potentially be used as adjuvants aiming at improving the efficacy of the existing interventions by restoring the balance of molecular signalling within muscle and making the tissue more responsive to the interventions.

## Conclusion

Muscle wasting diseases, such as cancer cachexia, continue to be challenging for patients and clinicians, as no effective treatments for restoring muscle mass or function are available. miRs are robust regulators of gene expression which contribute to regulating muscle homeostasis during disease. As most muscle wasting conditions are multifactorial and complex, and miRs can regulate the expression of many genes simultaneously, miRs hold a therapeutic potential that allows the restoration of dysregulated networks involved in maintaining muscle mass and function. Furthermore, the use of miR-based interventions to restore muscle homeostasis could be considered a conjugated approach to the current clinical practice, with dietary and exercise prescriptions becoming more effective. While several obstacles with respect to formulation, delivery, and safety of miR therapeutics remain, miRs hold great promise of future translational medicine approaches to skeletal muscle health.

**Key points:**

- microRNA profiling has identified microRNAs altered in muscle of cancer cachexia patients and animal models of cancer cachexia.
- several microRNAs dysregulated in muscle during cancer cachexia act as tumour suppressors;
- these microRNAs may have a role in muscle regeneration and/or maintenance of muscle mass based on their studies in non-cachexia models of muscle wasting.
- microRNA-based approaches could be used as stand-alone or adjuvants to the current exercise and diet interventions for cachexia to improve their efficacy.
- further functional studies of microRNAs in models of cancer cachexia are needed to provide proof-of-principle for the use of miRs as therapies for cancer cachexia to improve patient prognosis.

**Figure legends.**

**Table 1.** Summary of up- or downregulated microRNAs and their function in muscle of lung (17) or pancreatic or colorectal (19) cancer patients and muscle of mouse Lewis Lung Carcinoma (LLC)-induced cachexia model; ↓ - downregulated; ↑ - upregulated.

| **microRNA/ miRbase accession** | **Expression in human cancer cachexia (**lung (17) or pancreatic or colorectal (19) | **Expression in mouse LLC-induced model of cachexia** | **Previously described function of miR in skeletal muscle and/or cancer** |
|---|---|---|---|
| miR-451a-5p MIMAT0001631 | ↓ (17) | ↓ (18) | Mitochondrial dynamics (41)<br>Inhibits myogenic differentiation (42)<br>Tumour suppressor (43–45) |
| miR-144-5p MIMAT0004600 | ↓ (17) | ↓ (18) | Tumour suppressor (46)<br>Regulates insulin resistance *via* IRS-1 (47) |
| miR-15-5p MIMAT0000068 | ↓ (17) | ↓ (48) | Control mitochondrial-dependent apoptosis (49)<br>Inhibits cell proliferation (50)<br>Inhibits angiogenesis (51)<br>Induces apoptosis<br>Inhibits myogenesis (52)<br>Induces muscle stem cell quiescence |
| miR-519-3p MIMAT0002869 | ↓ (17) | ↑ (48) | Tumour suppressor (53)<br>Inhibits cell proliferation |
| miR-26-3p MIMAT0004499 | ↓ (17) | ↓ (48) | Tumour suppressor (54)<br>Required for myogenesis (28)<br>Limits muscle wasting (55)<br>induces mitochondrial apoptosis mediated by p53 (27) |
| miR-379-3p (miR-411-3p) | ↓ (17) | ↓ (18) | Reduces proliferation and migration /invasion in cancer cell lines (56) |

| | | | |
|---|---|---|---|
| MIMAT0004690 | | | |
| miR-199-3p<br>MIMAT0000232 | ↑ (19) | ↓ (48) | Inhibits cancer cell proliferation (57)<br>Enhance cisplatin sensitivity (58)<br>Tumour suppressor (59)<br>Inhibits myogenesis (60) |

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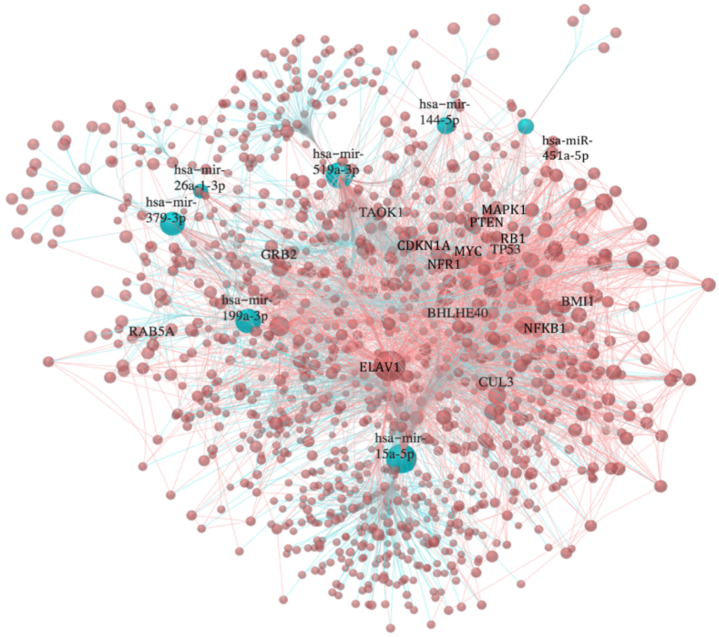


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260 **Figure 1.** microRNA:gene network analysis of interactions of miRs altered in cancer cachexia
261 and their predicted and validated target genes indicating potential therapeutic candidates for
262 muscle wasting during cachexia. microRNAs altered in muscle of cachexia patients and
263 dysregulated in muscle of LLC-induced cachexia (Table 1) were used as input for network
264 analyses. microRNAs and their target genes were analysed for connections (including
265 miR:target and protein:protein interactions criteria) using Metaboanalyst omics net tool (61).
266 Blue hubs indicate microRNAs, red hubs indicate proteins. Proteins which have the highest
267 number of interactions with other proteins and miRs in the network are labelled. Blue lines
268 indicate miR:gene interactions, red lines indicate protein:protein interactions.

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**Conflicts of interest.**

None.

**References**

1. Dunne RF, Loh KP, Williams GR, *et al*. Cachexia and Sarcopenia in Older Adults with Cancer: A Comprehensive Review. Cancers (Basel) [Internet]. 2019 Nov 25;11(12).
2. Ryan AM, Prado CM, Sullivan ES, *et al*. Effects of weight loss and sarcopenia on response to chemotherapy, quality of life, and survival. Nutrition. 2019 Nov 1;67–68.
3. Marinho R, Alcântara PSM, Ottoch JP, *et al*. Role of Exosomal MicroRNAs and myomiRs in the Development of Cancer Cachexia-Associated Muscle Wasting. Front Nutr. 2018 Jan 9;4.
4. Shiroyama T, Nagatomo I, Koyama S, Hirata H, Nishida S, Miyake K, et al. Impact of sarcopenia in patients with advanced non–small cell lung cancer treated with PD-1 inhibitors: A preliminary retrospective study. Sci Rep. 2019 Dec 1;9(1).
5. Pin F, Couch ME, Bonetto A. Preservation of muscle mass as a strategy to reduce the toxic effects of cancer chemotherapy on body composition. Vol. 12, Current Opinion in Supportive and Palliative Care. Lippincott Williams and Wilkins; 2018. p. 420–6.
6. Furrer R, Handschin C. Muscle Wasting Diseases: Novel Targets and Treatments. Annu Rev Pharmacol Toxicol. 2019 Jan 6;59(1):315–39.
7. Morvan F, Rondeau JM, Zou C, Minetti G, Scheufler C, Scharenberg M, et al. Blockade of activin type II receptors with a dual anti-ActRIIA/IIB antibody is critical to promote maximal skeletal muscle hypertrophy. Proc Natl Acad Sci U S A. 2017 Nov 21;114(47):12448–53.
8. Ali S, Garcia JM. Sarcopenia, cachexia and aging: diagnosis, mechanisms and therapeutic options - a mini-review. Gerontology [Internet]. 2014 [cited 2018 Sep

10];60(4):294–305. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24731978

9. Yang J. Patisiran for the treatment of hereditary transthyretin-mediated amyloidosis. Expert Rev Clin Pharmacol [Internet]. 2019 Feb 18 [cited 2019 Nov 19];12(2):95–9. Available from: https://www.tandfonline.com/doi/full/10.1080/17512433.2019.1567326

10. Goodkey K, Aslesh T, Maruyama R, Yokota T. Nusinersen in the Treatment of Spinal Muscular Atrophy. In: Methods in Molecular Biology. Humana Press Inc.; 2018. p. 69–76.

11. Bartel DP. Metazoan MicroRNAs. Vol. 173, Cell. Cell Press; 2018. p. 20–51.

12. Rusanova I, Fernández-Martínez J, Fernández-Ortiz M, Aranda-Martínez P, Escames G, García-García FJ, et al. Involvement of plasma miRNAs, muscle miRNAs and mitochondrial miRNAs in the pathophysiology of frailty. Vol. 124, Experimental Gerontology. Elsevier Inc.; 2019.

13. Bonneau E, Neveu B, Kostantin E, Tsongalis GJ, De Guire V. How close are miRNAs from clinical practice? A perspective on the diagnostic and therapeutic market. EJIFCC [Internet]. 2019 Jun [cited 2019 Nov 18];30(2):114–27. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31263388

14. Freire PP, Fernandez GJ, Cury SS, de Moraes D, Oliveira JS, de Oliveira G, et al. The Pathway to Cancer Cachexia: MicroRNA-Regulated Networks in Muscle Wasting Based on Integrative Meta-Analysis. Int J Mol Sci [Internet]. 2019 Apr 22 [cited 2019 Dec 11];20(8). Available from: http://www.ncbi.nlm.nih.gov/pubmed/31013615

15. Byrne CA, McNeil AT, Koh TJ, Brunskill AF, Fantuzzi G. Expression of genes in the skeletal muscle of individuals with cachexia/sarcopenia: A systematic review. Gualillo O, editor. PLoS One [Internet]. 2019 Sep 9 [cited 2019 Sep 10];14(9):e0222345. Available from: http://dx.plos.org/10.1371/journal.pone.0222345

16. Margolis LM, Rivas DA. Potential Role of MicroRNA in the Anabolic Capacity of Skeletal Muscle with Aging. Vol. 46, Exercise and Sport Sciences Reviews. Lippincott Williams and Wilkins; 2018. p. 86–91.

17. Worp WRPH, Schols AMWJ, Dingemans AC, Op den Kamp CMH, Degens JHRJ, Kelders MCJM, et al. Identification of microRNAs in skeletal muscle associated with lung cancer cachexia. J Cachexia Sarcopenia Muscle [Internet]. 2019 Dec 11 [cited 2019 Dec 16];jcsm.12512. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jcsm.12512

18. Fernandez GJ, Ferreira JH, Vechetti-Júnior IJ, Moraes LN de, Cury SS, Freire PP, et al.

MicroRNA-mRNA Co-sequencing Identifies Transcriptional and Post-transcriptional Regulatory Networks Underlying Muscle Wasting in Cancer Cachexia. 2019 Sep 1;

19. Narasimhan A, Ghosh S, Stretch C, Greiner R, Bathe OF, Baracos V, et al. Small RNAome profiling from human skeletal muscle: novel miRNAs and their targets associated with cancer cachexia. J Cachexia Sarcopenia Muscle [Internet]. 2017 Jun [cited 2018 Nov 7];8(3):405–16. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28058815

20. Goljanek-Whysall K, Soriano-Arroquia A, McCormick R, Chinda C, McDonagh B. miR-181a Regulates p62/SQSTM1, Parkin and Protein DJ-1 Promoting Mitochondrial Dynamics in Skeletal Muscle Ageing. bioRxiv. 2019 Oct 16;805176.

21. Sannicandro AJ, Soriano-Arroquia A, Goljanek-Whysall K. Micro(RNA)-managing muscle wasting. J Appl Physiol. 2019;127(2).

22. Zhang D, Lu C, Ai H. Rab5a is overexpressed in oral cancer and promotes invasion through ERK/MMP signaling. Mol Med Rep. 2017 Oct 1;16(4):4569–76.

23. Hou B, Xu S, Xu Y, Gao Q, Zhang C, Liu L, et al. Grb2 binds to PTEN and regulates its nuclear translocation to maintain the genomic stability in DNA damage response. Cell Death Dis [Internet]. 2019 Aug 18 [cited 2020 Jan 20];10(8):546. Available from: http://www.nature.com/articles/s41419-019-1762-3

24. Sethuraman A, Brown M, Krutilina R, Wu ZH, Seagroves TN, Pfeffer LM, et al. BHLHE40 confers a pro-survival and pro-metastatic phenotype to breast cancer cells by modulating HBEGF secretion. Breast Cancer Res. 2018 Oct 1;20(1).

25. Xu X, Wang Z, Liu N, Zhang P, Liu H, Qi J, et al. The mechanism of BMI1 in regulating cancer stemness maintenance, metastasis, chemo- and radiation resistance. Cancer Transl Med [Internet]. 2018 [cited 2019 Dec 20];4(2):59. Available from: http://www.cancertm.com/text.asp?2018/4/2/59/231378

26. Zhang Z, Tang Z, Ma X, Sun K, Fan L, Fang J, et al. TAOK1 negatively regulates IL-17-mediated signaling and inflammation. Cell Mol Immunol. 2018 Aug 1;15(8):794–802.

27. Gao XM, Zhu Y, Li JH, Wang XY, Zhang XF, Yi CH, et al. MicroRNA-26a induces a mitochondrial apoptosis mediated by p53 through targeting to inhibit Mcl1 in human hepatocellular carcinoma. Onco Targets Ther. 2018 Apr 19;11:2227–39.

28. Dey BK, Gagan J, Yan Z, Dutta A. miR-26a is required for skeletal muscle differentiation and regeneration in mice. Genes Dev. 2012 Oct 1;26(19):2180–91.

29. Xu D, Zhu H, Wang C, Zhu X, Liu G, Chen C, et al. microRNA-455 targets cullin 3 to

activate Nrf2 signaling and protect human osteoblasts from hydrogen peroxide. Oncotarget. 2017;8(35):59225–34.

30. Kitaoka Y, Tamura Y, Takahashi K, Takeda K, Takemasa T, Hatta H. Effects of Nrf2 deficiency on mitochondrial oxidative stress in aged skeletal muscle. Physiol Rep. 2019 Feb 1;7(3).

31. Hood DA, Memme JM, Oliveira AN, Triolo M. Maintenance of Skeletal Muscle Mitochondria in Health, Exercise, and Aging. Annu Rev Physiol [Internet]. 2019 Feb 10 [cited 2019 Nov 25];81(1):19–41. Available from: https://www.annualreviews.org/doi/10.1146/annurev-physiol-020518-114310

32. Barreto R, Mandili G, Witzmann FA, Novelli F, Zimmers TA, Bonetto A. Cancer and chemotherapy contribute to muscle loss by activating common signaling pathways. Front Physiol. 2016 Oct 19;7(OCT).

33. Hanna J, Hossain GS, Kocerha J. The potential for microRNA therapeutics and clinical research. Vol. 10, Frontiers in Genetics. Frontiers Media S.A.; 2019.

34. Rupaimoole R, Slack FJ. MicroRNA therapeutics: towards a new era for the management of cancer and other diseases. Nat Rev Drug Discov [Internet]. 2017 Mar 17 [cited 2019 Oct 20];16(3):203–22. Available from: http://www.nature.com/articles/nrd.2016.246

35. van Rooij E, Kauppinen S. Development of microRNA therapeutics is coming of age. EMBO Mol Med [Internet]. 2014 Jul [cited 2019 Jan 20];6(7):851–64. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24935956

36. Prado CM, Purcell SA, Laviano A. Nutrition interventions to treat low muscle mass in cancer. J Cachexia Sarcopenia Muscle [Internet]. 2020 Jan 8 [cited 2020 Jan 20];jcsm.12525. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jcsm.12525

37. Antoun S, Raynard B. Muscle protein anabolism in advanced cancer patients: response to protein and amino acids support, and to physical activity. Ann Oncol [Internet]. 2018 Feb 1 [cited 2019 Nov 28];29(suppl_2):ii10–7. Available from: https://academic.oup.com/annonc/article/29/suppl_2/ii10/4913823

38. Horstman AMH, Damink SWO, Schols AMWJ, van Loon LJC. Is cancer cachexia attributed to impairments in basal or postprandial muscle protein metabolism? Nutrients. 2016 Aug 16;8(8).

39. Argilés JM, Busquets S, Stemmler B, López-Soriano FJ. Cachexia and sarcopenia: mechanisms and potential targets for intervention. Curr Opin Pharmacol [Internet]. 2015

Jun 1 [cited 2019 May 10];22:100–6. Available from: https://www.sciencedirect.com/science/article/pii/S1471489215000405?via%3Dihub

40. Belloum Y, Rannou-Bekono F, Favier FB. Cancer-induced cardiac cachexia: Pathogenesis and impact of physical activity (Review). Vol. 37, Oncology Reports. Spandidos Publications; 2017. p. 2543–52.

41. Shao Y, Dong LJ, Takahashi Y, Chen J, Liu X, Chen Q, et al. MiRNA-451a regulates RPE function through promoting mitochondrial function in proliferative diabetic retinopathy. Am J Physiol - Endocrinol Metab. 2019 Mar 1;316(3):E443–52.

42. Munk R, Martindale JL, Yang X, Yang JH, Grammatikakis I, Germanio C Di, et al. Loss of miR-451a enhances SPARC production during myogenesis. PLoS One. 2019 Mar 1;14(3).

43. Gao Z, Zhang P, Xie M, Gao H, Yin L, Liu R. miR-144/451 cluster plays an oncogenic role in esophageal cancer by inhibiting cell invasion. Cancer Cell Int [Internet]. 2018 Dec 15 [cited 2019 Dec 19];18(1):184. Available from: https://cancerci.biomedcentral.com/articles/10.1186/s12935-018-0679-8

44. Li L, Gao R, Yu Y, Kaul Z, Wang J, Kalra RS, et al. Tumor suppressor activity of miR-451: Identification of CARF as a new target. Sci Rep. 2018 Dec 1;8(1).

45. Wang G, Yao L, Yang T, Guo L, Gu S, Liu J, et al. MiR-451 suppresses the growth, migration, and invasion of prostate cancer cells by targeting macrophage migration inhibitory factor. Transl Cancer Res. 2019;8(2):647–54.

46. Liu JL, Li J, Xu JJ, Xiao F, Cui PL, Qiao ZG, et al. MiR-144 inhibits tumor growth and metastasis in osteosarcoma via dual-suppressing RhoA/ROCK1 signaling pathway. Mol Pharmacol. 2019 Apr 1;95(4):451–61.

47. Karolina DS, Armugam A, Tavintharan S, Wong MTK, Lim SC, Sum CF, et al. Correction: MicroRNA 144 Impairs Insulin Signaling by Inhibiting the Expression of Insulin Receptor Substrate 1 in Type 2 Diabetes Mellitus. PLoS One. 2011 Sep 2;6(9).

48. Soares RJ, Cagnin S, Chemello F, Silvestrin M, Musaro A, De Pitta C, et al. Involvement of microRNAs in the regulation of muscle wasting during catabolic conditions. J Biol Chem [Internet]. 2014 Aug 8 [cited 2018 Dec 12];289(32):21909–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24891504

49. Patel N, Garikapati KR, Ramaiah MJ, Polavarapu KK, Bhadra U, Bhadra MP. miR-15a/miR-16 induces mitochondrial dependent apoptosis in breast cancer cells by suppressing oncogene BMI1. Life Sci. 2016 Nov 1;164:60–70.

50. Liu T, Xu Z, Ou D, Liu J, Zhang J. The miR-15a/16 gene cluster in human cancer: A

systematic review. J Cell Physiol [Internet]. 2019 May [cited 2019 Dec 19];234(5):5496–506. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30246332

51. Besnier M, Shantikumar S, Anwar M, Dixit P, Chamorro-Jorganes A, Sweaad W, et al. miR-15a/-16 Inhibit Angiogenesis by Targeting the Tie2 Coding Sequence: Therapeutic Potential of a miR-15a/16 Decoy System in Limb Ischemia. Mol Ther Nucleic Acids [Internet]. 2019 Sep 6 [cited 2019 Dec 19];17:49–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31220779

52. Zhao M-J, Xie J, Shu W-J, Wang H-Y, Bi J, Jiang W, et al. MiR-15b and miR-322 inhibit SETD3 expression to repress muscle cell differentiation. Cell Death Dis [Internet]. 2019 [cited 2019 Dec 19];10(3):183. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30796205

53. Abdelmohsen K, Kim MM, Srikantan S, Mercken EM, Brennan SE, Wilson GM, et al. miR-519 suppresses tumor growth by reducing HuR levels. Cell Cycle [Internet]. 2010 Apr 1 [cited 2019 Dec 19];9(7):1354–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20305372

54. Li Y, Sun Z, Liu B, Shan Y, Zhao L, Jia L. Tumor-suppressive miR-26a and miR-26b inhibit cell aggressiveness by regulating FUT4 in colorectal cancer. Cell Death Dis [Internet]. 2017 [cited 2019 Dec 19];8(6):e2892. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28640257

55. Wang B, Zhang A, Wang H, Klein JD, Tan L, Wang Z-M, et al. miR-26a Limits Muscle Wasting and Cardiac Fibrosis through Exosome-Mediated microRNA Transfer in Chronic Kidney Disease. Theranostics [Internet]. 2019 [cited 2019 Dec 19];9(7):1864–77. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31037144

56. O'Brien KP, Khan S, Gilligan KE, Zafar H, Lalor P, Glynn C, et al. Employing mesenchymal stem cells to support tumor-targeted delivery of extracellular vesicle (EV)-encapsulated microRNA-379. Oncogene [Internet]. 2018 [cited 2019 Dec 19];37(16):2137–49. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29367765

57. Phatak P, Burrows WM, Chesnick IE, Tulapurkar ME, Rao JN, Turner DJ, et al. MiR-199a-3p decreases esophageal cancer cell proliferation by targeting p21 activated kinase 4. Oncotarget [Internet]. 2018 Jun 19 [cited 2019 Dec 19];9(47):28391–407. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29983868

58. Cui Y, Wu F, Tian D, Wang T, Lu T, Huang X, et al. miR-199a-3p enhances cisplatin sensitivity of ovarian cancer cells by targeting ITGB8. Oncol Rep [Internet]. 2018 Apr [cited 2019 Dec 19];39(4):1649–57. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/29436681

59. Minna E, Romeo P, De Cecco L, Dugo M, Cassinelli G, Pilotti S, et al. miR-199a-3p displays tumor suppressor functions in papillary thyroid carcinoma. Oncotarget [Internet]. 2014 May 15 [cited 2019 Dec 19];5(9):2513–28. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24810336

60. Jia L, Li Y-F, Wu G-F, Song Z-Y, Lu H-Z, Song C-C, et al. MiRNA-199a-3p regulates C2C12 myoblast differentiation through IGF-1/AKT/mTOR signal pathway. Int J Mol Sci [Internet]. 2013 Dec 27 [cited 2019 Oct 10];15(1):296–308. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24378853

61. Chong J, Soufan O, Li C, Caraus I, Li S, Bourque G, et al. MetaboAnalyst 4.0: Towards more transparent and integrative metabolomics analysis. Nucleic Acids Res. 2018 Jul 2;46(W1):W486–94.