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Non-coding RNAs in cancer-associated cachexia: clinical implications and future perspectives

Anastasia Kottorou[a], Foteinos-Ioannis Dimitrakopoulos[a], Aspasia Tsezou[b,c,*]

[a] Molecular Oncology Laboratory, Division of Oncology, Medical School, University of Patras, 26504, Rio, Greece
[b] Laboratory of Biology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Biopolis, 41500, Larissa, Greece
[c] Laboratory of Cytogenetics and Molecular Genetics, Faculty of Medicine, School of Health Sciences, University of Thessaly, Biopolis, 41500, Larissa, Greece

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ABSTRACT

Cachexia is a multifactorial syndrome characterized by skeletal muscle loss, with or without adipose atrophy, irreversible through nutritional support, in the context of systemic inflammation and metabolic disorders. It is mediated by inflammatory reaction and affects almost 50% of all cancer patients, due to prominent systemic inflammation associated with the disease. The comprehension of the molecular mechanisms that are implicated in cancer cachexia sheds light on its pathogenesis and lays the foundations for the discovery of new therapeutic targets and biomarkers. Recently, ncRNAs, like microRNAs as well as lncRNAs and circRNAs seem to regulate pathways that are implicated in cancer cachexia pathogenesis, as it has been observed in animal models and in cancer cachexia patients, highlighting their therapeutic potential. Moreover, increasing evidence highlights the involvement of circulating and exosomal ncRNAs in the activation and maintenance of systemic inflammation in cancer and cancer-associated cachexia. In that context, the present review focuses on the clinical significance of ncRNAs in cancer-associated cachexia.

1. Introduction

Cachexia is a devastating multifactorial syndrome defined as skeletal muscle loss with or without adipose tissue loss, in the context of chronic systemic inflammation and metabolic disorders, and it is not reversed by nutritional support [1]. Cachexia results from the activity of cytokines, such as tumor necrosis factor alpha (TNFα), interleukin 1 (IL-1), IL-6 and interferon gamma (IFN-γ), which modify the metabolism of macronutrients, reducing protein synthesis, increasing protein degradation, enhancing lipolysis, intensifying the production of acute phase proteins in liver, increasing gluconeogenesis and inducing insulin resistance [2,3]. Sequentially, these alterations result in anorexia accompanied by muscle and fat loss [1].

According to 2011 Delphi International Consensus "cancer cachexia is defined as a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment" [4]. Cancer cachexia is classified to three stages, depending on the severity of the disease: precachexia, which is characterized by weight loss ≤5%, anorexia and metabolic change, cachexia, in which weight loss >5% or body mass index (BMI) <20 and weight loss >2% or sarcopenia and weight loss >2% is observed, and refractory cachexia, which is characterized by low performance score and variable degrees of cachexia, procatabolic and not responsive cancer disease to treatment and very short (<3 months) expected survival [4]. The impact of cachexia on quality of life and survival becomes worse in cachexia and refractory cachexia, while less is the impact of precachexia on prognosis [5].

Cachexia can sometimes present together with sarcopenia and it can be hard to distinguish due to the lack of consensus regarding clinical definition, diagnostic criteria and classification of the syndrome, although in cancer patients cachexia and sarcopenia are two distinct muscle-wasting conditions [6]. Sarcopenia is defined as a progressive and generalized skeletal muscle disorder, which is characterized by muscle loss and function and results in adverse effects such as falls, impaired functions, weakening and mortality [7]. Sarcopenia is usually correlated with thinness, but can sometimes co-exist with obesity (BMI 30.0 kg/m2), which makes muscle mass quantification difficult and can lead to underestimation of the disease, leading to disability or death [8]. Moreover, skeletal muscle depletion is prognostic for cancer patients' survival, independently of BMI [9]. Cachexia should be distinguished from sarcopenia or simple muscle wasting or atrophy, as it is a multifactorial syndrome and different mechanisms underlie the etiology of muscle atrophy in sarcopenia and cachexia. The age-related reduction in

* Corresponding author.
E-mail address: atsezou@med.uth.gr (A. Tsezou).

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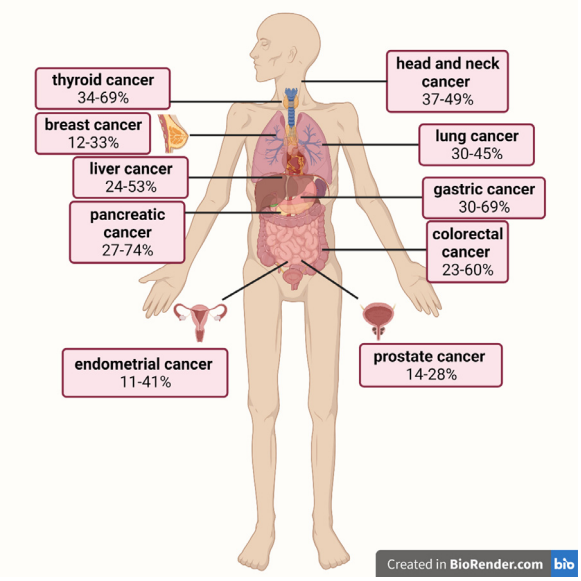

Fig. 1. Prevalence of cancer cachexia in different cancer types. Based on data from the systematic review by Anker et al. [11] (Created with BioRender.com).

endocrine signaling and low calories intake affect muscle loss in sarcopenia, while muscle atrophy in cachexia is caused mainly by inflammation and oxidative stress and leads to muscle and fat loss [6].

It has been documented that loss of 30% of the body weight is significantly associated with mortality of cancer patients [10]. As cachexia is mediated by inflammatory response, it affects almost 50% of all cancer patients, due to the prominent cancer-associated systemic inflammation. However, its incidence differs depending on cancer localization, with patients with solid tumors and especially gastric, pancreatic, lung, colorectal and head and neck cancer to present higher rates [5,11] (Fig. 1). Recently, Freire et al. revealed a tumor-specific cachexia-inducing factors profile, which shows that different solid tumors have different expression profile of secreted genes-inducers of cachexia, explaining why specific cancer types are more likely to develop cachexia [12]. Almost one third of cancer patients will lose >5% of their body weight after cancer diagnosis, while up to 80% of them with advanced disease will be diagnosed with cachexia [10,13,14]. Moreover, pretreatment weight loss in cancer patients significantly reduces overall survival, even in early disease stage [15].

2. Cachexia pathophysiology

Most data on cachexia pathophysiology have been derived from animal models. Clinical data from patients are limited, since cachexia presents in advance stage, when patients' vulnerability does not permit conducting invasive tests. Moreover, cancer cachexia is usually diagnosed in advanced stages, thus the number of patients that can be under observation over time is limited [16].

Reduced food intake, which leads to weight loss is associated with cancer cachexia altering thus the energy balance and normal control of homeostasis. Energy intake is typically lower than energy expended for maintenance of homeostasis [17,18]. Moreover, reduced protein synthesis in muscle of cancer patients that lose weight can be re-activated through nutritional intake. Additionally, tumors compete with organs and tissues for the energy reserves, increasing the energy imbalance even more [19].

Cytokines as well as pro-cachectic factors are mainly implicated in cancer cachexia. Tumor cells, tumor microenvironment and immune cells secrete factors that promote catabolism in tissue-targets, such as pro-inflammatory cytokines [20]. Increased inflammation, which is enhanced by tumors, also participates in catabolic pro-inflammatory factors production. These factors mediate the homeostatic control in Central Nervous System leading to catabolic neuronal effects, as well as in neuroendocrine effects, such as adrenal corticosteroids release and weakness (anorexia, fatigue). These inflammatory, neuronal and behavioral effects directly activate proteolysis and lipolysis in organs-targets and particularly in skeletal muscle, adipose tissue and cardiac muscle [21]. Prostaglandins and particularly prostaglandin E2 are known mediators of tumor-induced bone absorption and paraneoplastic hypercalcemia and have been also documented as mediators of excessive catabolism in skeletal muscle [22]. Among peptidic inflammatory cachexia regulators are included IL-6, IL-1, TNF and IFNγ. These factors bind to their cell receptors leading to activation of specific transcription factors, such as STA3 and NFκ-B, which can induce autophagy and degradation of muscle proteins [23].

In cancer cachexia the interaction of various organs is prominent. It has been documented that Central Nervous System exercises primary control in cachexia pathogenesis through cytokines identification as molecular signals of the disease [24]. Pro-inflammatory cytokines produced by tumor and immune cells interaction can act in the Central Nervous System enhancing the inflammation in hypothalamus, leading to anorexia and skeletal muscle atrophy, while lipolytic factors induce lipolysis of adipose tissue [25–27].

In addition to muscle loss, adipose tissue loss is also responsible for weight loss in cancer patients [28]. Studies have shown that fat loss occurs mostly due to lipolysis, rather than non-reversible adipose cells degeneration due to apoptosis, and that the overall increase of lipolysis in cancer patients is about 50% [29]. Although many explanations have been suggested for tumor-induced lipolysis, as presence of inflammatory cytokines released from macrophages that infiltrate the tumor, induction of triglyceride lipase in fat and loss of activated protein kinase of 5' AMP, the mechanism through which fat loss contributes to skeletal muscle atrophy remains unclear [30–33]. It has also been suggested that white adipose tissue browning as well as vicious biochemical cycles that take place in brown adipose tissue and during which oxidative phosphorylation is not linked to ATP synthesis and only heat is produced, lead to increase and ineffective energy consumption, contributing to cachexia [34–36].

Regarding cardiac muscle atrophy, data derived from animal models with induced cancer cachexia have confirmed it along with cardiac dysfunction [37]. Moreover, data on cardiac atrophy mechanisms derived from animal models are typical of the skeletal muscles' atrophy as well, including inflammation, proteolysis, apoptosis and autophagy [21].

3. Prognostic and predictive role of cachexia

Cachexia, sarcopenia and obesity have been associated with prognosis and effectiveness of therapy in many types of cancer. In non-small cell lung cancer underweight patients bearing EGFR mutations had poor prognosis (time to disease progression and survival) after treatment with tyrosine kinase inhibitors (TKIs) [38]. In a recent meta-analysis, cachexia was related to shorter overall survival of lung cancer patients, both small cell and non-small cell lung cancer [39]. In bladder cancer, cachexia has been associated with increased rate of perioperative complications during radical cystectomy, as well as poor prognosis of patients that had, or not, undergone surgery, while patients with urothelial cancer who had received platinum-based chemotherapy and regained skeletal muscle mass had good prognosis [40,41]. In colorectal cancer, developing cachexia after cancer diagnosis has been associated with poor prognosis (disease-free survival and overall survival) [42]. Similarly, in pancreatic cancer, where cachexia accounts for almost 80% of mortality, cachectic patients that had surgery or palliative therapy had shorter survival compared to non-cachectic patients [43]. In another study in advanced gastric cancer, patients who had palliative chemotherapy and cachexia, as confirmed with computed tomography, had poor prognosis [44].

Furthermore, cachexia has also been associated with cancer prognosis and prediction of response or therapy toxicities as well [45]. Metabolic changes that take place during cachexia result in reduced immunity against cancer, which negatively affects immunotherapy, that is implemented today in many types of cancer. Recent studies in non-small cell lung cancer patients, with cachexia presented before therapy or cachexia developed during therapy with immune checkpoint inhibitors, reported lower response rate, shorter disease-free survival and overall survival [46,47]. Besides, high Body Mass Index has been associated with higher response rates to immune therapy and better prognosis of patients with lung or other types of cancer [48–50]. Additionally, in a very recent systematic review published by Guzman-Prado et al. sarcopenia was linked to increased risk for adverse events in cancer patients treated with immune checkpoint inhibitors [51]. In metastatic renal cancer, treatment with sorafenib can intensify muscle wasting, even in patients with normal or high BMI and has been associated with weakness, fatigue and physical disability [52].

4. Epigenetics and cancer cachexia

Epigenetic mechanisms typically include DNA methylation, histone modifications and non-coding RNAs (ncRNAs) [53]. The role of DNA methylation in cancer has been established in every step of cancer progression, from initial carcinogenesis to metastasis [54,55]. However, few studies have reported the association of DNA methylation and cachexia. In a recent study, He et al. analyzed the blood methylation pattern of sarcopenic and non-sarcopenic women, 65–80 years old, and found that sarcopenic women had higher methylation levels in genomic regions before the transcription initiation site [56]. The methylated regions concerned genes related to muscle function, energy metabolism and cytoskeleton regulation, such as *HSPB1, PBX4, CNKSR3, ORMDL3, MIR10A, ZNF619* and *CRADD* [56]: *HSPB1* promotes the correct folding of other proteins, *PBX4* play critical roles in embryonic development, *CNKSR3* coordinates assembly of a multiprotein epithelial sodium channel (ENaC)-regulatory complex, *ORMDL3* is highly expressed in fat and regulates cytokine production, *ZNF619* is associated with muscular dystrophies and *CRADD* encodes a protein containing a death domain (DD) motif.

DNA methylation seems to play significant role in memory contribution or reprogramming of skeletal muscles in muscle loss. *In vitro* cultured muscle cells seem to remember the initial environment from which they were isolated [57]. Particularly, myoblasts that were treated initially with TNFα continued exhibiting high levels of *myoD* methylation even after 30 cell divisions and cells showed decreased morphological and biochemical differentiation. Since TNFα is chronically increased in cancer cachexia and high levels are associated with muscle loss, its lasting effect on *myoD* seems to play a critical role in muscle loss [57].

Regarding histone modifications, sirtuin 1 (Sirt1) is a NAD-dependent deacetylase of proteins which are key-regulators of cell defense and survival as response to stress, thus contributing to cell regulation. In myoblasts cultures Sirt1 was found increased in stress conditions and contributed to myoblasts death decrease, while after treatment with the antioxidant reservatrol, it regulated skeletal muscle survival and enhanced differentiation [58]. In another study, Byun et al. showed that HDAC11 can suppress myoblasts differentiation through MyoD-dependent regulation of transcription [59]. More specifically, in myoblasts cell line C2C12, HDAC11 expression pattern increased during myoblasts differentiation, while HDAC11 ectopic expression inhibited myoblasts differentiation, while mutated and inactive HDAC11 (H142/143A) did not. Moreover, wild type HDAC11 suppressed MyoD-induced activity of MEF2C and MYOG (Myogenin) and reduced histone acetylation close to E-boxes, MyoD and MEF2C and MYOG promoters, whereas mutated HDAC11 did not [59].

Trichostatin A (TSA), a histone deacetylase inhibitor has been shown to abolish muscle atrophy in a mouse model, through *MuRF1* regulation [60]. Particularly, TSA reduced muscle atrophy, prevented type I and IIα fibers loss and reversed slow fibers transition to fast fibers. Autophagy-lysosomes pathway remained non activated, while MurF1 expression was suppressed, without transcription factor Foxo3 being affected [60].

Among epigenetic mechanisms, non-coding RNAs have emerged as the most prominent ones involved in cancer cachexia.

4.1. Non-coding RNAs and cancer cachexia

The term non-coding RNAs (ncRNAs) describes a large group of transcripts with low or no potential of translation to proteins, considering that only 2% of total transcribed RNAs is translated to proteins [61–63]. The majority of the genomes of mammals is transcribed into ncRNAs, many of which are further processed to alternative splicing and generate smaller molecules, which nevertheless are not translated to proteins [64]. NcRNAs can differ in length, and can be short, such as microRNAs (miRNAs), small interfering RNAs (siRNAs), small nuclear RNAs (snRNAs), piwi-interacting RNAs (piRNAs) and other, or long, such as long ncRNAs (lncRNAs). NcRNAs play a significant role in phenotypic variation, chromatin architecture, transcription, RNA editing, translation, and other functions, thus are implicated in many physiological and pathophysiological processes, mainly via binding to multiple RNA molecules and regulating their expression [64]. Among the different ncRNAs, the most well studied ones are miRNAs, on which, along with lncRNAs, the present review will focus.

Recently, ncRNAs have been associated with cancer cachexia, modifying substantial functions, such as skeletal muscle and adipose tissue turnover. Moreover, it has been demonstrated that circulating ncRNAs can function as potential biomarkers for cancer cachexia risk [65,66].

4.1.1. miRNAs and animal studies in cancer cachexia

MiRNAs are short ncRNAs, 19-24 nt long, that regulate almost 60% of all genes coding proteins [67]. This regulation can occur through miRNAs binding to mRNA and sequential mRNA degradation or suppression of translation. Their role in cancer is well established, as they are implicated in every step of carcinogenesis, due to their involvement in proliferation, apoptosis, migration and invasion [61,68,69].

In an *in vivo* study using wild type and Parp-1$^{-/-}$ and Parp-2$^{-/-}$ (poly ADP-ribose polymerase) mouse models with lung cancer and cachexia an association was demonstrated between Parp-1/2 expression levels and muscle-specific miRNAs [70]. It was shown that miR-1 was downregulated in skeletal muscles, while in cachectic wild type and Parp-2$^{-/-}$ mice miR-133a expression was reduced in diaphragm and gastrocnemius compared to control mice, whereas in Parp-1$^{-/-}$ mice it was reduced only in diaphragm. In cachectic Parp-1$^{-/-}$ and Parp-2$^{-/-}$ mice miR-206 expression was also reduced in diaphragm, as well as in gastrocnemius and diaphragm of wild type cachectic mice. MiR-486 expression was lower in diaphragm and gastrocnemius of wild type and Parp-2$^{-/-}$ cachectic mice, compared to non-cachectic mice, whereas in Parp-1$^{-/-}$ cachectic mice no such difference was observed. Moreover, inhibition of Parp-1 via miR-133a, miR-206 and miR-486 promoted proliferation and differentiation of muscle cells, while inhibition of Parp-2 through miR-206 promoted differentiation of muscle cells in gastrocnemius of cachectic mice with lung cancer. Overall the above results in Parp-1$^{-/-}$ and Parp-2$^{-/-}$ mouse models highlight the association between Parp expression and signaling pathways regulated by miRNAs implicated in cancer cachexia [70].

A study by Lee *et al.* showed that miRNAs analysis of anterior tibialis muscle from 8 week old C57BL/6J mice with Lewis lung carcinoma that developed cachexia revealed 9 miRNAs with differential expression [71]. More specifically, miR-147-3p, miR-299a-3p, miR-1933-3p, miR-511-3p, miR-3473d, miR-223-3p, miR-431-5p, miR-665-3p and miR-205-3p were differentially expressed. These miRNAs are implicated in various functions, including cell signaling and growth, and inflammatory responses and were suggested to be involved in promoting a catabolic muscle state. However, the validation of the functional role

Table 1
Deregulated muscle or adipose tissue ncRNAs in animal models of cancer cachexia and the pathway that are possibly implicated in (strong experimental evidence or predicted), according to miRPathDB v2.0 [75].

ncRNA	Pathway possibly implicated in	Expression	Tissue	Reference
hsa-miR-1 hsa-miR-133a hsa-miR-206	Genes targeted by miRNAs in adipocytes Potassium channel complex Generic Transcription Pathway	Decreased	Diaphragm and gastrocnemius from cachectic mice with lung cancer	[70]
hsa-miR-486	Somatroph axis (GH) and its relationship to dietary restriction and aging	Decreased	Skeletal muscles from mice with breast cancer	[73]
mmu-miR-147-3p mmu-miR-205-5p mmu-miR-511-3p	Hippo signaling pathway Axon guidance phospholipase C-activating G protein-coupled receptor signaling pathway	Increased	Tibialis anterior from cachectic mice with Lewis lung carcinoma	[71]
mmu-miR-223-3p mmu-miR-299a-3p mmu-miR-1933-3p	Focal adhesion Axon guidance Peptide GPCRs			
mmu-miR-3473d mmu-miR-431-5p mmu-miR-665-3p	FoxO signaling pathway Ascorbate and aldarate metabolism Insulin signaling pathway	Decreased		
CAAlnc1	Regulates the expression of C/EBP-α and PPAR-γ	Increased	Liver and brown adipose tissue from cachectic mice with cancer	[74]

of the above miRNAs needs to be established in mature skeletal muscle [71].

Integrated microRNAs-mRNAs omics analyses have become an additional tool in comprehension of transcriptional and post-transcriptional regulatory networks implicated in muscle loss in cancer cachexia. In a recent study by Fernandez et al. mRNA and miRNAs expression profiles of anterior tibialis muscle from mice with Lewis lung carcinoma and cachexia were analyzed [72]. The analysis revealed 1,008 mRNAs and 18 microRNAs with differential expression between cachectic and control mice. Despite the heterogeneity in mRNA expression profile, genes that were uniformly regulated in cachectic mice and were implicated in extracellular matrix, proteolysis, and inflammatory response were identified. Further analysis of transcription factors' binding sites revealed activation of transcription factors associated with atrophy, such as NF-κB, Stat3, AP-1, and FoxO. The mRNA-miRNA expression profile integration showed a post-transcriptional regulation by miRNAs suggesting a key role of extracellular matrix remodeling in muscle atrophy in cachexia [72].

In Table 1 are presented deregulated muscle or adipose ncRNAs in animal models of cancer cachexia.

4.1.2. MiRNAs in cancer cachexia patients

MyomiRs represent a set of miRNAs, with high expression levels in skeletal muscles. Among them are included miR-1, miR-133a, miR-133b, miR-206, miR-208, miR-208b, miR-486, and miR-499. MyomiRs are transcriptionally controlled by myogenic regulatory factors and regulate skeletal muscle growth and muscle development and maintenance [76]. Since myomiRs are strongly regulated during resistance exercise, it has been suggested that they could be used as biomarkers for cachectic patients follow-up, in order to avoid detrimental exercise, or as companion biomarkers for drugs that mimic exercise, such as trimetazidine [77].

Narasimhan et al. in an interesting study analyzed miRNAs from rectus abdominis muscle biopsies from cachectic and non-cachectic cancer patients using next generation sequencing [78]. They revealed 8 miRNAs which were upregulated in cancer cachexia patients and were implicated in muscle metabolism, myogenesis and inflammation, namely, hsa-let-7d-3p, hsa-miR-345-5p, hsa-miR-423-5p, hsa-miR-532-5p, hsa-miR-1296-5p, hsa-miR-3184-3p, hsa-miR-423-3p and hsa-miR-199a-3p [78]. The authors demonstrated that let-7d-3p promotes downregulation of transferrin receptor pathway affecting muscle cells proliferation and myogenic differentiation, while miR-345-5p downregulates *NOV* and *COL1A1* and consequently upregulates *CYR61; NOV* and *CYR61* are implicated in insulin-like growth factor 1, Akt and mTOR pathways, reducing the ability for protein synthesis. In the same study, it was shown that miR-423-5p and miR-3184-3p downregulate *SQLE* and *FADS2*, which are involved in lipids biosynthesis, while miR-423-5p can also regulate leptin and other genes involved in energy balance and downregulates *DLK1*, which is implicated in muscle hypertrophy. Furthermore, it was shown that miR-423-3p promotes calcium signaling impairment, affecting *CAMK2A* and that miR-3184-3p is implicated in Wnt/β-catenin signaling, attenuating myogenic differentiation and that it can regulate *BMPR1B* and *GREM1*, affecting TGF-β and BMP signaling. In addition, it was demonstrated that miR-532-5p targets *SULF1* which is related to BMP signaling affecting somits development, *RPS6KA6*, which contributes to CNTF (ciliary neurotrophic factor) activities and *NPY1R,* which is implicated in appetite regulation. Overall Narasimhan *et al.* suggested that different miRNAs play a critical role in modulation of the pathways involved in muscle atrophy in cachectic cancer patients.

A recent meta-analysis regarding miRNA–mRNA interaction networks associated with muscle loss in cancer cachexia revealed 52 differentially expressed genes in muscle tissue from patients and rodent models of cancer cachexia [79]. Protein-protein interaction network in muscle wasting in cancer cachexia highlighted most interaction components being transcriptional factors and proteins associated with the apoptotic process, metabolism and inflammatory response. Moreover, the study predicted new miRNA–mRNA interactions, which can contribute to muscle loss during cancer cachexia, like miR-27a/Foxo1, miR-27a/Mef2c, miR-27b/Cxcl12, miR-27b/Mef2c, miR-140/Cxcl12, miR-199a/Cav1 and miR-199a/Junb [79].

The post-transcriptional pathway which includes HuR-RNA binding protein seems also to play a critical role for cancer cachexia initiation and especially in muscle loss [80]. HuR can change its function from muscle fibers formation inducer to muscle loss inducer by binding initially to the 3'UTR of *STAT3* mRNA, in a region close to a complementary to miR-330. HuR binding inhibits miR-330 binding to *STAT3* mRNA and consequently its translation inhibition. The negative interaction of HuR with miR-330 implies a mechanism through which muscle fibers can modulate STAT3 expression in order to define their future in response to stress [80].

In a very recent study van de Worp et al. analyzed the expression levels of 754 miRNAs in vastus lateralis biopsies from 8 cachectic patients with non-small cell lung cancer and 8 healthy individuals and validated the results in 15 cachectic patients with non-small cell lung cancer, 11 non- cachectic patients with non-small cell lung cancer and 22 healthy individuals [81]. They demonstrated that 28 miRNAs exhibited differential expression, 5 were upregulated and 23 downregulated. Further analysis of the miRNAs revealed 158 potential target genes, which

Table 2
Deregulated muscle or adipose tissue ncRNAs in cancer cachexia patients and the pathway that are possibly implicated in (strong experimental evidence), according to miRPathDB v2.0 [75].

ncRNA	Pathway possibly implicated in	Expression	Tissue	Reference
hsa-miR-3184-3p hsa-miR- 423-5p hsa-let-7d-3p hsa-miR-1296-5p hsa-miR-345-5p hsa-miR-532-5p hsa-miR-423-3p hsa-miR-199a-3p	Photodynamic therapy-induced HIF-1 survival signaling Carbohydrate metabolic process mRNA Processing Protein-containing complex Cancer, Intestinal immune network for IgA production Lung fibrosis Chromosomal and microsatellite instability in colorectal cancer Focal Adhesion	Increased	Muscles from cachectic patients with colorectal or pancreatic cancer	[78]
hsa-miR-424-5p hsa-miR-424-3p hsa-miR-450a hsa-miR-451a hsa-miR-144-5p	Cell cycle Transcriptional regulation by RUNX1 Herpes simplex infection Hepatitis B Androgen receptor signaling pathway	Increased Decreased	Vastus lateralis from cachectic patients with non-small cell lung cancer	[81]
hsa-miR-483-5p hsa-miR-23a hsa-miR-744 hsa-miR-99b hsa-miR-378	Envelope proteins and their potential roles in EDMD physiopathology Muscle myosin complex LncRNA involvement in canonical Wnt signaling and colorectal cancer Somatroph axis (GH) and its relationship to dietary restriction and aging Determination of heart left/right asymmetry	Decreased Increased	Abdominal subcutaneous tissue from cachectic patients with gastrointestinal cancer	[83]
VLDLR-AS1	Response to chemotherapy	Increased	Adipose tissue from cachectic patients with gastrointestinal cancer	[84]
MALAT1	Transcriptional regulator for genes genes involved in cancer metastasis and cell migration	Decreased	Subcutaneous white adipose tissue from cachectic patients with cancer	[85]

were involved in 22 pathways associated with muscle regenerative or degenerative processes, such as IL-6, TGF-β, TNFα, insulin and Akt. More specifically, miR-424-5p, miR-424-3p and miR-450a-5p had higher expression levels in the muscles of cachectic patients, whereas miR-144-5p and miR-451a had lower expression levels, compared to healthy ones. In non-cachectic patients only miR-424-3p was significantly upregulated compared to controls. Moreover, although the number of the patients was small, the combination of miR-450-5p and miR-451a expression had prognostic value for patients' survival [81].

In addition to muscle atrophy, lipolysis and fat browning are also prominent features of cancer cachexia, in which miRNAs are implicated (Table 2, Fig. 2) [82]. In gastrointestinal cancer, when abdominal subcutaneous tissue from cachectic and non-cachectic patients was compared, downregulation of miR-483-5p, miR-23a, miR-744 and miR-99b and upregulation of miR-378 was observed in cachectic patients, which was positively related to catecholamines-induced lipolysis [83]. In *in vitro* experiments, where human adipocytes from healthy donors were cultured, inhibition of miR-378 led to impaired lipolysis induced from norepinephrine and downregulation of genes with key role in lipolysis, such as *LIPE, PNPLA2* and *PLIN1* [83].

In Table 2 are presented deregulated muscle or adipose ncRNAs in cancer cachexia patients.

4.1.3. Circulating miRNAs in cancer cachexia patients

Additionally to their intracellular localization, miRNAs can be secreted actively by the cell, or released through cell membrane as a reaction to various stimuli, leading in their circulation in blood or other biological fluids [86]. This gets particular value for muscle loss, as very few blood biomarkers have been associated with muscle mass, such as myostatin and arginine [87–89].

Circulating miRNAs can serve as potential biomarkers, not only for muscle loss, but also muscle regeneration, effectiveness of therapy and early detection of cachexia as well (Table 3, Fig. 2). It has been reported that patients with head and neck cancer and low miR-130a plasma levels have high TNF-α plasma levels and increased risk for cachexia [90]. Additionally, miR-130a expression can separate cachectic from mildly malnourished patients, with sensitivity and specificity values of 76.4% and

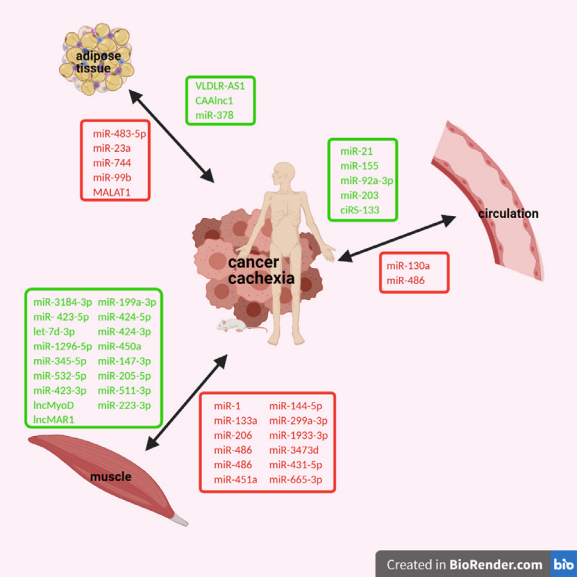

Fig. 2. Deregulated ncRNAs in muscle or adipose tissue or in circulation of patients or animal models with cancer cachexia. Downregulated ncRNAs are colored in red and upregulated ncRNAs are colored in green. (Created with BioRender.com).

80.8%, respectively. When low miR-130a levels were combined high TNF-α levels, sensitivity and specificity values increased to 83.3% and 91.7%, respectively. In patients with weight loss >5% nutritional evaluation was improved when miR-130a levels were used, resulting in sensitivity and specificity 88.6% and 94.3%, respectively, suggesting that miR-130a is a potential biomarker for cachexia prediction, as well as improvement of cachexia diagnosis in patients with head and neck cancer [90].

Okugawa *et al* showed that colorectal cancer patients with low psoas muscle index had high serum miR-21 levels making miR-21 a useful pa-

Table 3
Deregulated circulating ncRNAs in cancer cachexia and the pathway that are possibly implicated in (strong experimental evidence), according to miRPathDB v2.0 [75].

ncRNA	Pathway possibly implicated in	Expression	Circulation	Reference
hsa-miR-21	Cancer, regulation of catalytic activity	Increased	Lung or pancreatic cancer-derived exosomes Serum from cachectic patients with colorectal cancer	[113] [91]
hsa-miR-155	Chromosome, nuclear lumen	Increased	Breast cancer-derived exosomes	[109]
hsa-miR-92a-3p	Activation of BIM and translocation to mitochondria	Increased	Chronic myeloid leukemia-derived exosomes	[111]
hsa-miR-130a	Negative regulation of blood vessel endothelial cell migration	Decreased	Plasma from cachectic patients with head and neck cancer	[90]
hsa-miR-203	Hepatitis B, Pancreatic cancer, Androgen receptor signaling pathway	Increased	Serum from patients with colorectal cancer	[92]
hsa-miR-486	Role of phospholipids in phagocytosis	Decreased	Serum from patients with breast cancer	[73]
ciRS-133	Circular RNA sponge for miR-133	Increased	Gastric cancer-derived exosomes	[65]

rameter for the clinician to decide the nutritional strategy for these patients [91]. Later, the same group showed that patients with low psoas muscle index had high miR-203 serum levels, whereas intramuscular fat was not associated with serum or tissue miR-203 levels [92]. Moreover, high miR-203 levels were shown to be an independent prognostic factor for myopenia for colorectal cancer patients [92]. In *in vitro* experiments, human skeletal muscle cells after transfection with miR-203 mimics became less proliferative and more apoptotic, indicating a possible prognostic value of serum miR-203 in myopenia, and a novel therapeutic target for inhibition of myopenia in colorectal cancer [92].

MiR-486, a muscle-enriched miRNA, has been found downregulated in the circulation of breast cancer patients and animal models compared to healthy controls [73]. In breast cancer mice, miR-486 levels were low in muscles, whereas miR-486 target genes, such as *PTEN* and *FOXO1A* were increased and the signaling was attenuated through the PI3K/AKT pathway. MyoD expression, which is a transcription factor that regulates miR-486 expression, was shown to be low in skeletal muscles as well. Moreover, when supernatant medium from breast cancer cells cultures was added to C2C12 myoblasts cultures, miR-486 levels were decreased, while PTEN and FOXO1A levels increased. Further analysis of the medium revealed TNFα and 4 more cytokines as mediators of miR-486 expression in myoblasts, implicating TNFα-dependent miRNA circuitry in muscle differentiation and survival pathways in cancer. [73].

MyomiRs have also been found to be released in circulation by rhabdomyosarcoma, a malignant tumor arising from skeletal muscles, leading to high serum levels of miR-1, miR-133a, miR-133b, and miR-206 [93]. Changes in circulating myomiRs have been demonstrated in different types of cancer. For instance, in gastric cancer patients, an increase in miR-1 in circulation has been reported, while in non-small cell lung cancer, melanoma, astrocytoma and osteosarcoma, lower levels of circulating myomiRs have been observed [94–97]. MiR-1, miR-133a, miR-133b and miR-206 which are tumor-suppressive miRNAs are mostly downregulated in several types of cancers, while, expression of serum miR-1, miR-20a, miR-27a, miR-34 and miR-423- 5p could be used to detect gastric cancer [94,98]. In lung cancer, a risk-score signature consisted of miR-486, miR-30d, miR-1 and miR-499 serum levels could differentiate patients in two groups, in long and short survival groups [96]. Additionally, low serum miR-133b miR-206 expression had negative prognostic value for both overall survival and disease-free survival in osteosarcoma patients [99].

4.1.4. Exosomal miRNAs in cancer cachexia

Paracrine and endocrine effects of miRNAs have been associated with expansion of systemic inflammation, development of metastasis and activation of muscle loss-promoting pathways [100]. Alternatively, miRNAs can be transferred in circulation by enclosure into exosomes [101]. Exosomes are small membrane vesicles of 30–100 nm which can effectively transfer proteins, RNA, cytokines and other molecules, with great stability avoiding their degradation in circulation [102–104].

One of the main mechanisms involved in cancer cachexia initiation is white adipose tissue induction of circulating inflammatory cytokines [31]. It has been documented that white adipose tissue can secrete exosomes containing miRNAs, which regulate inflammatory processes in tissues and immune cells [105,106]. Moreover, adipose tissue exosomes can trigger and regulate tumor growth, progression and aggressiveness [105]. Similarly, various studies have shown than tumor-derived exosomes contain miRNAs which play a role in inflammation activation in cancer [107,108]. These cancer exosomes induce production and release of proinflammatory cytokines, promoting cancer cells' survival through their interaction with mesenchymal stem cells [107]. Moreover, tumor-derived exosomes can induce tumor progression, modifying the tumor microenvironment and promoting metastasis [107,108].

Tumor-derived exosomes can induce cancer cachexia as Wu et al. showed recently [109]. More specifically, when adipocytes were cultured in presence of 4T1 breast cancer cells, they exhibited upregulation of UCP1 (uncoupling protein 1) and downregulation of PPARγ (peroxisome proliferator activated receptor gamma) and phosphorylated (P)-PPARγ, which are implicated in fat accumulation, as well as downregulation of phosphorylated ERK1/2 (extracellular signal-regulated kinase) and upregulation of phosphorylated p38 [109]. Furthermore, after co-culturing muscle cells with breast cancer cells, muscle cells lost myosin heavy chain and had increased death rate, myotubes atrophied, UCP3 levels increased, P-p38 was upregulated, while P-ERK1/2, PPARγ and P-PPARγ were downregulated, suggesting that tumor-derived exosomes contain miRNAs which promote catabolism in adipocytes and muscle fibers [109]. Moreover, miR-155 was upregulated in tumor-derived exosomes and PPARγ targeting in adipocytes promoted remodeling of adipocytes metabolism and browning. It is noteworthy that cancer cells that were co-cultured with adipocytes or myocytes displayed increased invasiveness via epithelial-mesenchymal transition, while tumor-derived exosomes increased catabolism and metabolites release in adipocytes and myocytes [110].

In agreement with the above study, injection of leukemia exosomes to mice led to weight and fat loss [111]. Moreover, mesenchymal stem cells of adipose tissue could receive chronic myeloid leukemia cells (K562) exosomes and subsequently suppress adipogenicity [111]. In K562 cells as well as in K562-derived exosomes upregulation of miR-92a-3p was observed, which could suppress adipogenicity through downregulation of *Cebpa* (*CCAAT enhancer binding protein alpha*), suggesting a key role of exosomal microRNAs, in cancer cachexia mediation.

Furthermore, exosomal miRNAs have been documented to contribute to initiation, as well as maintenance of cancer cachexia-associated inflammation [100,112]. Overexpression of miR-21 in lung

or pancreatic cells-derived microvesicles induced apoptosis in skeletal muscle cells [113]. Myoblasts isolated from TLR7$^{-/-}$ (toll-like receptor 7) mice and cultured with supernatant medium from Lewis carcinoma cells or serum from cachectic patients with pancreatic cancer exhibited reduced cell death rate [113]. Moreover, exogenous addition of miR-21 in myoblasts from TLR7$^{+/+}$ increased cell death rate, while in proliferating myoblasts after transfection with miR-21, JNK and c-Jun were upregulated, suggesting that miR-21 promotes cell death through activation of TLR7 signaling downstream of JNK [113].

In summary, these findings highlight the role of exosomal miRNAs in initiation and maintenance of inflammation in cancer cachexia. Systemic inflammation affects negatively muscle metabolism, regulating signaling pathways involved in muscle proteins synthesis and degradation, contributing to muscle loss, which characterizes cancer cachexia [100,114,115].

In Table 3 are presented deregulated circulating ncRNAs in cancer cachexia.

4.1.5. Long non-coding RNAs in animal models of cancer cachexia

LncRNAs (long non-coding RNAs) are transcripts longer than 200 RNAs with no potential of translation [116]. It is well established that lncRNAs are implicated in many cell functions; they can regulate and remodel chromatin, they can regulate transcription and nuclear bodies, they are implicated in mRNA cycle, translation and post-translational modifications [116]. LncRNAs exert their regulatory effects mainly through interacting with miRNAs [116,117]. They are implicated in various diseases including cancer and cachexia, while few studies implicate lncRNAs in cancer cachexia [74,84,118,119]. LncRNAs play a significant role in myoblast differentiation and muscle development, mainly through regulating cell cycle inhibitors and myogenic factors, thus it is not surprising that lncRNAs are dysregulated in muscle regeneration and various muscular diseases, such as atrophy and hypertrophy, muscular dystrophy etc [120].

LncIRS1 (insulin receptor substrate 1) is a lncRNA that was recently revealed to act as an endogenous competitive RNA in mouse skeletal muscles where it is upregulated [121]. LncIRS1 was shown to regulate myoblasts proliferation and differentiation *in vitro* and *in vivo* and muscle mass and sectional area of fibers *in vivo* [121]. LncIRS1 can act as miR-15 family sponge regulating IRS1 expression. When overexpressed it activates the IGF1-PI3K/Akt signaling pathway increasing skeletal muscle proliferation and muscle mass and modulates the expression of important atrophy genes, while its suppression results to decreased IGF1 levels and weight loss in mice. All above point to a potential therapeutic role of lncIRS1 for treating muscle atrophy [121–123].

LncRNA MAR1 (muscle anabolic regulator 1), another lncRNA associated with cachexia, is upregulated in mice skeletal muscles and has been positively associated with muscular differentiation and growth, *in vitro* and *in vivo,* through interacting with miR-487b, which regulates Wnt5a (Wnt family member 5A) and promotes muscular differentiation and regeneration [124]. When overexpressed, it attenuated muscle atrophy, while muscle strength and mass was retained, making it a possible candidate as therapeutic target for muscle atrophy associated with cancer cachexia, for example being overexpressed and delivered using adeno-associated virus particles (AAV) [124].

LncRNAs have also been involved in adipose tissue loss of cachectic mice. In particular, Shen et al. analyzed the transcriptome of white adipose tissue from cachectic vs non-cachectic mice that had been injected with colon adenocarcinoma (C26) cells and identified a functional CAAlnc1 (cachexia-related anti-adipogenesis lncRNA 1) which suppressed adipogenesis through interaction with HuR (necessary protein for adipogenesis) leading to fat loss [74].

4.1.6. LncRNAs in cancer cachexia patients

In a study conducted by Liu et al. adipose tissue from cachectic and non-cachectic patients with gastrointestinal cancer was analyzed and VLDLR-AS1 (VLDLR Antisense RNA 1) was related to cachexia and fat loss [84]. Further analysis and prediction models suggested that VLDLR-AS1 regulated GOLGA3 (golgin A3), DUSP14 (dual specificity phosphatase 14) and UCHL1 (ubiquitin C-terminal hydrolase L1) through interaction with miR-600 and ZNF219 (zinc finger protein 219), as well as RNF141 (ring finger protein 141) and CALU (calumenin) through binding to miR-1224-3p. However, the mechanism through which VLDLR-AS regulates fat loss in cancer cachexia has not been established [84].

Since deregulated myogenesis is associated with cachexia, Gong *et al.* suggested that lncMyoD, a lncRNA which is activated during myoblasts differentiation directly by MyoD (myogenic differentiation 1), is also possibly associated to cachexia [125]. When it is active lncMyoD binds to IMP2 (IGF2-mRNA-binding protein 2) and negatively regulates the IMP2-mediated translation of critical for proliferation genes, such as *N-Ras* (neuroblastoma ras oncogene) and *c-Myc* (myelocytomatosis oncogene) [125]. LncMyoD suppression has been reported to inhibit muscular differentiation and cell cycle exit, pointing to its potential association with cachexia [125].

Very recently, Han et al. suggested that lncRNA MALAT1 (metastasis associated lung adenocarcinoma transcript 1) can regulate *PPAR-γ* expression at the transcriptional level and it is associated with adipose loss in cancer-associated cachexia. MALAT1 expression in the subcutaneous white adipose tissue of cancer-associated cachexia patients was low and was prognostic of low fat mass index and poor clinical outcome of the patients [85].

4.1.7. circRNAs in cancer cachexia

Circular RNAs (circRNAs) are generated when specific exons are circularized through covalent bonds [126]. It has been documented that circRNAs can act as miRNAs sponge, since they contain many binding sites for miRNAs and seem to play significant role in various diseases [127,128].

Regarding the role of circRNAs in cancer cachexia, there is only one study in gastric cancer, which reports that ciRS-133 (circRNA Hsa_circ_0010522) expression was positively associated with brown fat mass and body adipose percentage [65]. *In vivo* studies revealed that ciRS-133 interacts with miR-133. Exosomes derived from gastric cancer cell line (SGC7091) had high expression of ciRS-133, and when added to 3T3L1 culture medium resulted to PRDM16 (PR-domain containing 16) and UCP1 upregulation. On the other hand, miR-133 overexpression downregulated PRDM16 and UCP1, whereas suppression of miR-133 reversed this effect [65]. Injection of SGC7901 cells with overexpression of ciRS-133 in mice led to increase of ciRS-133 expression in cancer tissue, of serum exosomes and inguinal adipose tissue. Moreover, the mice presented with reduced inguinal adipose tissue mass and browning, suggesting that ciRS-133 worsens cancer cachexia, probably through fat browning [65].

5. NcRNAs in cancer-associated cachexia: clinical implications and future perspectives

Detection of cachexia in early stages (precachexia or cachexia) is vital for prevention of refractory cachexia, relief of symptoms and improvement of quality of life and prognosis. Circulating miRNAs, such as miR-21 can aid to this direction as an indication to the clinicians for the nutritional strategy they should suggest to high risk colorectal cancer patients [91]. MyomiRs and other miRNAs that are released in circulation by various tumors (ie miR-450-5p and miR-451a) and have prognostic value for patients' survival can also be used for identification of high risk patients with urgent need for treatment [81,93]. Other circulating miRNAs, such as miR-130a, can separate cachectic from mildly malnourished head and neck cancer patients, which is also crucial for effective treatment and delay of refractory cachexia [90]. Moreover, miRNAs such as myomiRs that are regulated during resistance exercise, have been suggested to be used as companion biomarkers for drugs that mimic exercise, such as trimetazidine [77].

As long as several pathways are implicated in cancer cachexia, therapeutic approaches modifying multiple targets would be ideal. Such a therapeutic approach for cancer cachexia is provided via epigenetic therapy, which can cause reversible changes in gene regulation, without affecting DNA sequence [129].

When considering treatment of multifactorial background, miRNAs have an advantage over gene therapy, as they can regulate the expression of multiple genes at the same time. In the context of a new therapeutic strategy, miRNAs can be used either as knockdown therapy or as replacement therapy, as they bind with high specificity on their complementary mRNA target leading to translational suppression. In the case of knockdown therapy, antagomiRs consist of specific oligomers which are complementary to specific miRNAs and they compete with mRNA targets in order to bind to the miRNAs. In the replacement therapy, miRNA mimics interfere with the mRNA target, functioning as endogenous miRNA [130].

Currently, siRNAs which have similar mechanism of action to that of miRNAs, are used for the treatment of spinal muscular atrophy and hereditary transthyretin -mediated amyloidosis (Nusinersen and Patisiran, respectively) [131,132]. In cancer therapy, miRNAs may be used as knockdown or replacement therapy, when targeting miRNAs which function as oncogenes or tumor suppressor genes, respectively.

Two types of carriers are usually used for miRNAs transfer, viral and non-viral vectors [133]. However, the efforts for the development of viral vectors for miRNAs transfer have failed, mainly due to the immune response trigger, leading the researchers towards non-viral alternatives [134]. Although results from preclinical studies were promising, translational clinical studies results using miRNAs replacement therapy have proved rather disappointing. A phase I clinical study which implied miR-34 replacement therapy in cancer patients failed to pass to phase II, due to its toxic side effects (NCT01829971, NCT02862145) [135]. On the other hand, a phase I clinical study using miR-16 mimics in mesothelioma or non-small cell lung cancer patients has been successfully completed and despite some complications, it is expected to continue to phase II (NCT02369198) [136].

One of the main challenges in miRNA replacement therapy is the effectiveness and accuracy of miRNAs in target cells. An ideal transfer system should protect miRNAs from degradation, transfer them and facilitate their intake form the target cells, while they should not trigger immune response [137–139]. Extracellular vesicles satisfy those criteria and preclinical studies with extracellular vesicles transferring nucleic acids have shown promising results in tumors [140,141]. MiRNAs or antagomiRs can be integrated in extracellular vesicles and be used as therapeutic agents in the clinical setting [142]. A phase I clinical study is ongoing which evaluates the effectiveness and side effects of exosomes carrying *IGFR1* antisense oligodeoxynucleotides (NCT02507583). In another ongoing clinical study, mesenchymal exosomes carrying a small siRNA which targets mutant KRAS is used in pancreatic cancer patients (NCT03608631). These clinical studies, as well as many more, highlight the possible use of extracellular vesicles as short-RNAs carriers which can modulate gene expression and proliferation of different tumors. Although the results from preclinical studies are promising, many obstacles need to be overcome before miRNAs are applied for therapeutic purposes in the clinical setting.

MiRNAs-based approaches are not used in cancer cachexia treatment yet, although the implication of miRNAs in cancer-associated cachexia pathogenesis makes them an attractive therapeutic target. In a preclinical mouse model, a miRNA was used to target serum amyloid 1 and 2 (SAA), which are typical apolipoproteins induced in response to inflammatory cytokines and promote muscular atrophy. In C26 colon adenocarcinoma mice injected with AAV–miRNA targeting SAA1/2, serum levels of SAA1/2 were 4 times reduced, although no difference was observed in cachexia progression [143]. Further liver-specific RNA and proteomic analysis revealed a high level of overlapping and their exploration can pave the way to novel treatment strategies [143]. However, from bench to bedside a translational failure is often observed, with most of the successful preclinical studies turning sour in clinical studies with human patients, thus impeding drug discovery. The main reason for this translational failure lies in species differences as well as other external and internal validity issues [144]. Nevertheless, animal models and preclinical studies still remain the cornerstone for understanding the molecular mechanisms underlying cancer cachexia and have to be interpreted critically [145].

MiRNAs-based therapeutic approaches for cancer cachexia targeting specific pathways could potentially restore homeostasis of chronically deregulated networks and predispose muscles to positive response to therapy including exercise and diet. Therefore, miRNAs could be used additionally to increase the effectiveness of already existing therapies [146]. Animal models are essential for validation of candidate drugs for cancer cachexia treatment before being applied in clinical trials and more studies should be focused to this direction.

6. Conclusion

The comprehension of the molecular mechanisms that are implicated in cancer cachexia is significant not only for understanding the pathophysiology of the disease, but for novel therapeutic targets and biomarkers identification as well. NcRNAs, such as microRNAs, regulate the signaling pathways implicating in cancer cachexia pathophysiology making them attractive therapeutic targets and promising biomarkers for cancer cachexia diagnosis, prognosis and follow up.

Declaration of Competing Interest

The authors declare no competing interests.

Author contributions

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