MicroRNAs: Novel players in the diagnosis and treatment of cancer cachexia (Review)

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Abstract. Cachexia denotes a complex metabolic syndrome featuring severe loss of weight, fatigue and anorexia. In total, 50-80% of patients suffering from advanced cancer are diagnosed with cancer cachexia, which contributes to 40% of cancer-associated mortalities. MicroRNAs (miRNAs) are non-coding RNAs capable of regulating gene expression. Dysregulated miRNA expression has been observed in muscle tissue, adipose tissue and blood samples from patients with cancer cachexia compared with that of samples from patients with cancer without cachexia or healthy controls. In addition, miRNAs promote and maintain the malignant state of systemic inflammation, while inflammation contributes to cancer cachexia. The present review discusses the role of miRNAs in the progression of cancer cachexia, and assess their diagnostic value and potential therapeutic value.

Contents

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1. Introduction

Cachexia is a complex syndrome featuring loss of weight that results from reduced skeletal muscle mass (1). This syndrome usually appears in the late stages of severe illnesses, including cancer, kidney disease, human immunodeficiency virus, congestive heart failure and chronic obstructive pulmonary disease (2,3). Patients with cachexia are insensitive to treatment, have a low quality of life and have a high mortality rate (4).

Cancer cachexia affects 50% of patients with cancer and causes ~40% of cancer-associated mortalities (5). The incidence of cancer cachexia changes with the stage and type of cancer (6). According to a previous cohort study on patients with advanced tumors, those with pancreatic cancer are at the greatest risk of developing cancer cachexia (~70%), followed by colorectal, gastroesophageal, and head and neck cancer (~45%) (7), while patients with breast and prostate cancer are at the lowest risk of developing cachexia (20-30%) (7). In addition, cancer cachexia may result in inefficient chemotherapy, increased treatment interruptions or decreased survival rates (8).

The diagnostic standard of cachexia is loss of weight >5% or >2% among patients who have a body mass index (BMI) less than 20 kg/m^2 (9). In addition, neuroendocrine changes occur in patients with cancer cachexia, leading to early satiety and food aversion (10). The Warburg effect is the catabolism of glucose to lactate to obtain adenosine triphosphate (11). Lactate is converted to glucose in the liver at a cost of energy. When glucose is released into the bloodstream, cancer cells may use it again for glycolysis. The Cori cycle is a fruitless glucose-lactate shuttle that increases energy expenditure and hepatic gluconeogenesis (12). As a result, catabolic metabolism in fat and skeletal muscle provides additional glucose precursors for gluconeogenesis. In cachexia, the Warburg effect in myocytes contributes to muscle mass reduction (13). Reduced food absorption and excessive metabolism eventually lead to a negative energy balance and mass loss, particularly skeletal muscle mass loss (5). Decreased skeletal muscle mass and muscle function are found to negatively influence the life quality among patients with cancer cachexia and have recently been widely referred to as 'sarcopenia' (14,15). Cancer

cachexia may subsequently progress to refractory cachexia, and interventions at such stage are unlikely to be successful.

Currently, there are limited options for the treatment of cancer cachexia. There are two therapeutic concepts: i) non-pharmacological options, which are focused on nutrition and exercise interventions (3,16); and ii) chemotherapy, including the usage of hormone therapy (e.g. gonadotropins), myostatin inhibitors and anti-inflammatory drugs (17). However, the effectiveness of these treatments remains unclear, as clinical outcomes and long-term efficacy reports are insufficient (18). Therefore, novel early diagnostic biomarkers and therapeutic targets for cancer cachexia are needed (19).

Several microRNAs (miRNAs or miRs), such as let-7d-3p and miR-345-5p, were found to be markedly dysregulated among patients with cachexia (6,20). Furthermore, several miRNAs have been found to have a regulatory effect on inflammatory pathways, and on the degradation and synthesis of proteins in skeletal muscle, which makes miRNAs potential novel therapeutic candidates in cancer cachexia therapy (21,22). The present review summarizes miRNAs differentially expressed in specimens derived from patients with cancer cachexia, including muscle, adipose tissue and blood. In addition, the present review proposes that miRNAs may be considered as potential diagnostic markers or therapeutic targets for cancer cachexia.

2. miRNAs in the development of cancer and cancer cachexia

miRNAs are short RNAs that can regulate the expression of ~60% of protein-encoding genes of human mRNAs (23). miRNAs were firstly identified in 1993, and additional types of miRNAs have been identified and studied since then (24). The miRBase database contains published miRNA sequences, and the up-to-date version of this database contains >2,570 mature miRNAs from humans (25). The majority of miRNAs can be transcribed by RNA polymerase (pol) II or pol III in the nucleus to produce primary precursor miRNAs (pri-miRNAs) (60-100 nt) (Fig. 1) (26). The Drosha/DiGeorge critical region 8 ribonuclease complex divides pri-miRNAs to generate precursor pre-miRNAs, which are later exported to the cytoplasm via the exportin-5 complex (27). The Dicer/TAR-RNA binding protein complex subsequently divides pre-miRNAs to produce mature double-stranded miRNAs (28). To become functional, double-stranded miRNAs are then disassembled to produce passenger and guide strands. The passenger strand is degraded, while the guide strand is loaded onto the RNA-induced silencing complex (29,30). The primary function of miRNAs is to inhibit the translation of target mRNAs.

miRNA expression profiling shows that changes in miRNA expression are associated with various illnesses, including primary muscle diseases, dexamethasone-induced atrophy, diabetes and wasting diseases (such as cancer cachexia) (31,32). In addition, various aspects of metabolic changes and inflammatory responses are also regulated by miRNAs (33-35). Hypermetabolism and systemic inflammation are typical symptoms of cancer cachexia (36). Therefore, miRNAs possibly impact cancer cachexia pathogenesis.

Cancer cells may produce inflammatory cytokines and cause local and systemic inflammation in the host (37,38). Previous studies have demonstrated that the tumor itself may be capable of secreting exosomes containing miRNAs (39-42), which can increase the synthesis of circulating inflammatory factors (39). The levels of circulating inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin 1 (IL-1) and IL-6, can be also altered in patients with cachexia (43,44). miRNAs can be transported via exosomes, which can be secreted into the serum, cerebrospinal fluid, urine and saliva (45). Exosomes from adipose tissue in the tumor microenvironment may also promote the development of systemic inflammation (46,47).

miR-182-5p, miR-183-5p, miR-21-5p, the miR-200 family, miR-7-5p, miR-125b-5p, miR-96-5p, miR-139-5p, miR-99a-5p, miR-497-5p and miR-486-5p have been found to be altered in breast cancer (BC) (48). A total of 26 differentially expressed miRNAs were found to interact with frequently deregulated genes known to be involved in colorectal cancer pathways (49). The majority of these miRNAs could predict the prognosis of patients with colorectal cancer in stages II and III (49). It has been demonstrated that miRNAs can be used for the early detection of oral cancer (50). A total of 9 differentially expressed miRNAs (miR-486-1, miR-486-2, miR-153, miR-210, miR-9-1, miR-9-2, miR-9-3, miR-577 and miR-4732) have been identified, which could be used as lung adenocarcinoma diagnostic biomarkers (51).

In addition, miRNAs may have a prognostic value for patients treated with a combination of interventions, including diet and physical activity (48). Differentially expressed extracellular vesicle (EV) miRNAs resulting from the Mediterranean diet may be engaged in pathways associated with cardiometabolic risk factors in overweight BC survivors (52). In addition, environmental factors such as pesticides may modify miRNA expression and the DNA methylation status (53). Alteration of miRNA expression profiles upon exposure to naturally occurring asbestiform fibers is a diagnostic indicator of mesothelial neoplastic transformation (54). In patients with colon cancer, vascular endothelial growth factor (VEGF) may be an independent predictor of weight loss (55). VEGF promotes the proliferation, migration and tube formation of endothelial cells (ECs), and has become a primary target of anti-angiogenic therapy (56-59). Furthermore, VEGF is linked to systemic inflammation and malnutrition, supporting the possible involvement of VEGF in cancer cachexia pathogenesis (55). VEGF is required for tumor angiogenesis, and inhibition of VEGF inhibits angiogenesis and tumor growth (57,60-62). miRNAs promote angiogenesis by facilitating the proliferation and migration of ECs (63). The hypoxia inducible factor-1α/VEGF signaling pathways regulated by miR-210, miR-21 and miR-126 play a role in colon cancer initiation (64). Overexpression of miR-638 could inhibit angiogenesis and tumor growth in hepatocellular carcinoma by suppressing VEGF signaling (65). miRNAs produced from tumor cells, such as miR-23a, miR-494 and miR-210, were reported to be packaged into EVs and transported to recipient ECs (66). These miRNAs promote angiogenesis by facilitating the proliferation and migration of ECs (63).

3. miRNAs in muscular atrophy

Patients with cancer cachexia can lose ≤75% of their skeletal muscle mass, which may lead to poor prognosis and higher

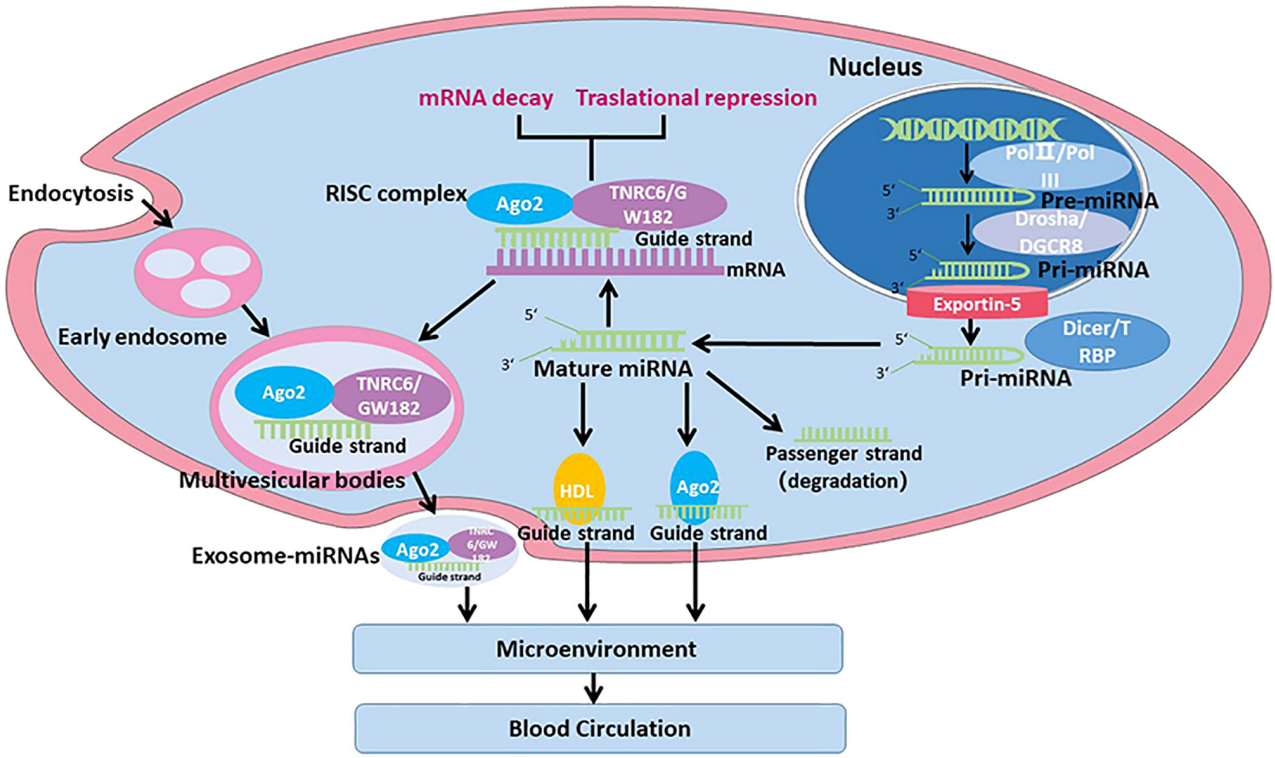

Figure 1. microRNA (miRNA) biogenesis and release in tumor cells. miRNAs are transcribed by RNA polymerase II (pol II) or polymerase III (pol III) in the nucleus to generate primary miRNAs (pri-miRNAs). Pri-miRNAs are separated with Drosha/DiGeorge Critical Region 8 (DGCR8) complex to generate pre-miRNAs, which will be exported to cytoplasm via exportin-5 complex. The Dicer/TAR-RNA binding protein (TRBP) complex further separates the pre-miRNAs to generate mature double-stranded miRNAs. Afterward, the passenger strand for mature miRNA undergoes degradation, and the guide strand is loaded into the RNA-induced silencing complex (RISC) for regulating target gene expression.

mortality associated with cancer (67). Muscle protein degradation in cancer cachexia is mediated mainly by the ubiquitin proteasome system, induced by activation of E3 ligands (68). The Fork head box O (FoxO) signaling pathway is involved in this process by inducing the transcription of E3 ubiquitin ligases, of which there are three members in skeletal muscle: FoxO3, FoxO1 and FoxO4 (68). Inhibition of FoxO transcriptional activity attenuates muscle fiber atrophy during cachexia (69). miRNA-486 reduces FoxO1 protein expression and enhances FoxO1 phosphorylation to inhibit E3 ubiquitin ligase (70). miR-21 associates with and activates Toll-like receptor 7, which induces apoptosis in muscle cells via the c-Jun N-terminal kinase pathway, leading to atrophy (18).

Dysregulated expression of miRNAs (such as myomiRNAs, a subset of miRNAs with high expression in skeletal muscle) is associated with muscle atrophy, which is a hallmark of cancer cachexia (71-74). The expression profile of miRNAs in rectus abdominis muscle samples was evaluated among patients with cancer who exhibited or not a cachexia syndrome (6). In that study, 8 miRNAs were upregulated among patients with cancer cachexia, including let-7d-3p, miR-423-5p, miR-345-5p, miR-532-5p, miR-3184-3p, miR-1296-5p, miR-423-3p and miR-199a-3p (6). Pathway analysis indicated that the target miRNAs were enriched in the adipogenesis, myogenesis, inflammation and innate immune response pathways (6). In another study, the expression levels of 754 miRNAs in broad fascia biopsies of 8 healthy individuals and 8 patients with non-small cell lung cancer who exhibited cachexia were investigated (75). The expression of 28 miRNAs was significantly changed, with 23 miRNAs being downregulated and 5 upregulated (75). In addition, the genes of TNF, transforming growth factor-β, IL-6 and insulin are among the 158 putative target genes identified using miRTarBase (75). A total of 9 miRNAs were found to be differentially expressed in muscles of a cancer cachexia mouse model (20). miRNA-mRNA co-sequencing revealed activation of the atrophy-related transcription factors STAT3, NF-κB and FoxO, thus exposing transcriptional and post-transcriptional regulatory networks involved in muscle wasting (76).

4. miRNAs in adipose tissue depletion

The hallmarks of cancer cachexia are muscle loss, browning of white adipose tissue (WAT) and lipolysis (77,78). Increased levels of circulating inflammatory cytokines can also induce lipolysis and proteolysis in adipose tissue and muscle, respectively, as well as downregulate protein synthesis, which causes a reduction in skeletal muscle mass and adipose tissue in patients with cancer cachexia (21). WAT can promote the circulation of inflammatory cytokines as well as regulate inflammatory processes in immune cells and tissues by secreting miRNA-containing exosomes (79-81). miR-483-5p, miR-744, miR-23a and miR-99b were found to be downregulated in the abdomen subcutaneous adipose tissue of patients with gastrointestinal cancer and cachexia in contrast to those of patients without cachexia syndrome, while the expression of miR-378 was upregulated (82). miRNAs in blood may serve as non-invasive biomarkers of cancer malignancy, and miRNAs can remain highly stable in blood.

Table I. miRNAs in specimens of patients with cancer cachexia or cancer.

miRNAs	Specimens	(Refs.)
let-7d-3p, miR-345-5p, miR-423-5p, miR-532-5p, miR-1296-5p, miR-3184-3p, miR-423-3p, miR-199a-3p	Muscles from cachectic patients with pancreatic and colorectal cancer	(6)
miR-450a-5p, miR-424-5p, miR-450b-5p, miR-424-3p, miR-335-3p, miR-103-3p, miR-483-5p, mir-409-3p, miR-15b-5p, miR-370-3p, miR-20a-3p, miR-451a, miR-517c-3p, miR-144-5p, miR-766-3p, miR-1255b, miR-517a-3p, miR-512-3p, miR-522-3p, miR-520g-3p, miR-483-3p, miR-519a-3p, miR-26a-2-3p, miR-485-3p, miR-379-5p, miR-518b, miR-520h, miR-656-3p	Muscles from cachectic patients with non-small cell lung cancer	(75)
miR-483-5p, miR-23a, miR-744, miR-99b, miR-378	Abdominal subcutaneous tissues/primary human dipocytes from cachectic patients with gastrointestinal cancers	(82)
miR-1	Serum from cachectic patients with advanced hepatocellular carcinoma	(95)
miR-21	Serum from cachectic patients with colorectal cancer	(88)
miR-130a	Plasma from cachectic patients with head and neck cancer	(96)
miR-203	Serum from patients with colorectal cancer	(87)
miR-468	Serum from patients with breast cancer	(97)

5. Circulating miRNAs in cancer cachexia

miRNAs also present in serum, saliva, plasma, urine, and cerebrospinal fluid (83,84). The psoas muscle mass index (PMI) provides a simple approach to describing skeletal muscle volume in the body (85,86). A study on miR-203 in the blood of patients with colorectal cancer demonstrated that patients with low PMI had higher levels of miR-203 than those with high PMI (87). Furthermore, overexpression of miR-203 in serum is an independent predictor of sarcopenia (87). Similarly, previous studies have shown that the level of miR-21 increased in the blood of patients with colorectal cancer who developed cancer cachexia compared with that of patients who did not develop cancer cachexia (88).

Exosomes are the most common type of EVs, which are small membrane-bound vesicles between 30 and 150 nm in diameter (89). The presence of miRNA-rich circulating exosomes may promote the development and maintenance of systemic chronic inflammation in patients with cancer cachexia (21,89). Furthermore, a previous study reported the upregulation of miR-155 in exosomes of BC cells (4T1), which can target peroxisome proliferator-activated receptor-γ in adipocytes, and promote adipocyte metabolism and browning differentiation (90). In conclusion, tumor-derived exosomal miRNAs may induce cancer cachexia, and therefore exosomal miRNAs are considered potential early diagnostic markers of cancer cachexia (90-94).

6. Discussion and perspectives

Dysregulation of specific miRNAs, such as let-7d-3p, miR-345-5p, miR-532-5p, miR-378, miR-92a-3p, miR-21, is involved in the development of cachexia. Cachexia may induce the differential expression of miRNAs but it has not been validated. Dysregulated expression of miRNAs was observed in muscle tissue, adipose tissue and blood specimens from patients with cancer cachexia in contrast to the findings in patients who did not exhibit cancer cachexia or in healthy controls (Table I) (6,75,82,87,88,95-97). However, miRNAs directly obtained from adipose or muscle tissue biopsies are not applicable as diagnostic markers of cancer cachexia (84). Thus, the diagnostic value of miRNAs for cancer cachexia should be restricted to circulating miRNAs. miRNAs with high stability in body fluids can be potentially used as non-invasive markers (98,99). miRNAs from plasma/serum have been reported as biomarkers for the early diagnosis of different types of tumor, including gastric cancer (100), BC (101) and pancreatic cancer (102). Therefore, it can be proposed that circulating miRNAs in the blood can be used as biomarkers to differentiate patients at risk of developing cancer cachexia. For example, circulating miRNAs such as miR-21 may serve as markers for diagnosing cancer cachexia among patients likely to develop colorectal cancer (88). However, the application of using circulating miRNAs in patients with cancer as biomarkers for diagnosis needs to be validated in future clinical trials.

Multiple characteristics of miRNAs make them potential targets for new treatments of cancer cachexia. Firstly, miRNAs regulate the translation of mRNAs belonging to multiple genes and signaling pathways that are dysregulated in cancer cachexia, such as TNF, IFN signaling, STAT and NF-κB transcription factors and associated target genes (15,103-105). Secondly, miRNAs have been used to promote muscle development and maintain muscle homeostasis (106). The expression of multiple

miRNAs has been found to be dysregulated in muscle wasting of cachexia (107). Thirdly, treatment of cancer cachexia with miRNAs can induce reversible and specific changes in gene regulation without affecting the DNA (108). miRNAs can be used as knockdown complementary mRNA targets (103). In knockdown therapy, complement-specific miRNA drugs compete with their mRNA targets for translation. Fourthly, EVs can prevent miRNAs from being degraded in transfer and expedite their uptake via target cells (109,110). Finally, miRNAs can be efficiently stabilized or concentrated using novel processing methods (103,111). However, no miRNA drugs have been clinically used to date, although there are several ongoing clinical trials on phases 1 and 2 (112). For example, a phase I clinical study that applied miR-16 mimics for the treatment of non-small cell lung cancer or mesothelioma was accomplished, and may be followed up by a phase II study (113). miRNAs have also been adopted for targeting serum amyloid 1 and 2, which are lipoproteins usually generated in response to inflammatory cytokines, and were shown to successfully relieve muscle atrophy in a pre-clinical mouse model (114). miRNA mimics already used in clinical studies for cancer therapy, such as miR-16, can be investigated in animal models of cancer cachexia to evaluate whether they can improve weight loss and alleviate cancer cachexia symptoms. The implications of miRNAs in the pathogenesis of cancer cachexia make them attractive therapeutic targets. In addition, miRNA-based therapies for cancer cachexia target specific pathways that have the potential to restore homeostasis in chronically dysfunctional networks and enable positive muscle responses to exercise and diet.

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Availability of data and materials

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Authors' contributions

ZL conceived and designed the review. XL, LD and QL wrote the first draft of the manuscript in light of the literature data. Data authentication is not applicable. All authors contributed to the article and approved the submitted version for publication.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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