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REVIEW

Advancing the Understanding and Treatment of Cancer Cachexia: Mechanisms, Therapeutic Approaches, and Future Opportunities

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Abstract: Cancer cachexia (CC) is a prevalent metabolic disorder in patients with advanced cancer, characterized by persistent skeletal muscle mass loss and irreversible body weight reduction, which significantly diminishes quality of living, therapeutic effectiveness. At present, the specific pathogenesis of CC is only defined as skeletal muscle loss induced by signaling pathways. In the clinical treatment of tumor cachexia, it has been clearly defined that there are multiple methods available for treating this disease, including nutritional therapy and exercise, but all of them have very little therapeutic effect. Surprisingly, traditional Chinese medicine has achieved initial success in treating malignant tumors, and the combined treatment of traditional Chinese and Western medicine has yielded remarkable results. Therefore, it is an urgent need to elucidate the more specific pathogenesis of CC to develop effective treatment approaches, which enhance patients' nutritional health status as well as their overall quality of life and survival ratings. This article aims to review the pathogenesis of CC along with clinical treatment strategies and drug utilization.

Keywords: cancer, cachexia, mechanism, treatment, nutrition, Traditional Chinese medicine

Introduction

Cancer cachexia (CC) is a severe metabolic disorder commonly observed in advanced cancer patients, characterized by persistent loss of skeletal muscle mass and unresponsive weight loss to conventional nutritional interventions.[1,2] Father more, patients with weight degrading may experience fatigue, anorexia, nausea, vomiting, and progressive organ failure.[3] Numerous studies have demonstrated that the involvement of various systems such as immune system, skeletal muscle, adipose tissue, digestive system and central nervous system in the development of cachexia.[4–8] The process of energy consumption is illustrated in Figure 1. The incidence of cachexia among cancer patients ranges from 40% to 60%.[9] Different types of tumors exhibit varying trends in cachexia occurrence. Cachexia is strongly associated with pancreatic cancer, esophageal cancer, gastric cancer, lung cancer, liver cancer and colorectal cancer which account for half of global cancer-related deaths.[10] Mortality rates for cancer patients with cachexia can reach up to 80%. Among them all pancreatic ductal adenocarcinoma has the highest incidence rate at approximately 70%.[10–12] It has been estimated that in 2013, 15.8 subjects per 10000of the total population in European Union suffered from CC.[13] CC significantly impacts patient's quality of life while also leading to poor treatment response and increasing surgical complications. Clinical chemotherapy drugs fail to alleviate its symptoms making it one of the major contributors towards mortality among advanced stage-cancer patients.[14] At present, the known pathogenesis of CC includes muscle atrophy, reduced muscle synthesis, increased muscle catabolic, increased fat degradation, increased fat breakdown, Browning of white fat and inflammatory factors caused by the regulation of multiple signaling pathways. However, our current knowledge mainly comes from animal models. Although the number of human studies exploring the biological mechanisms of muscle

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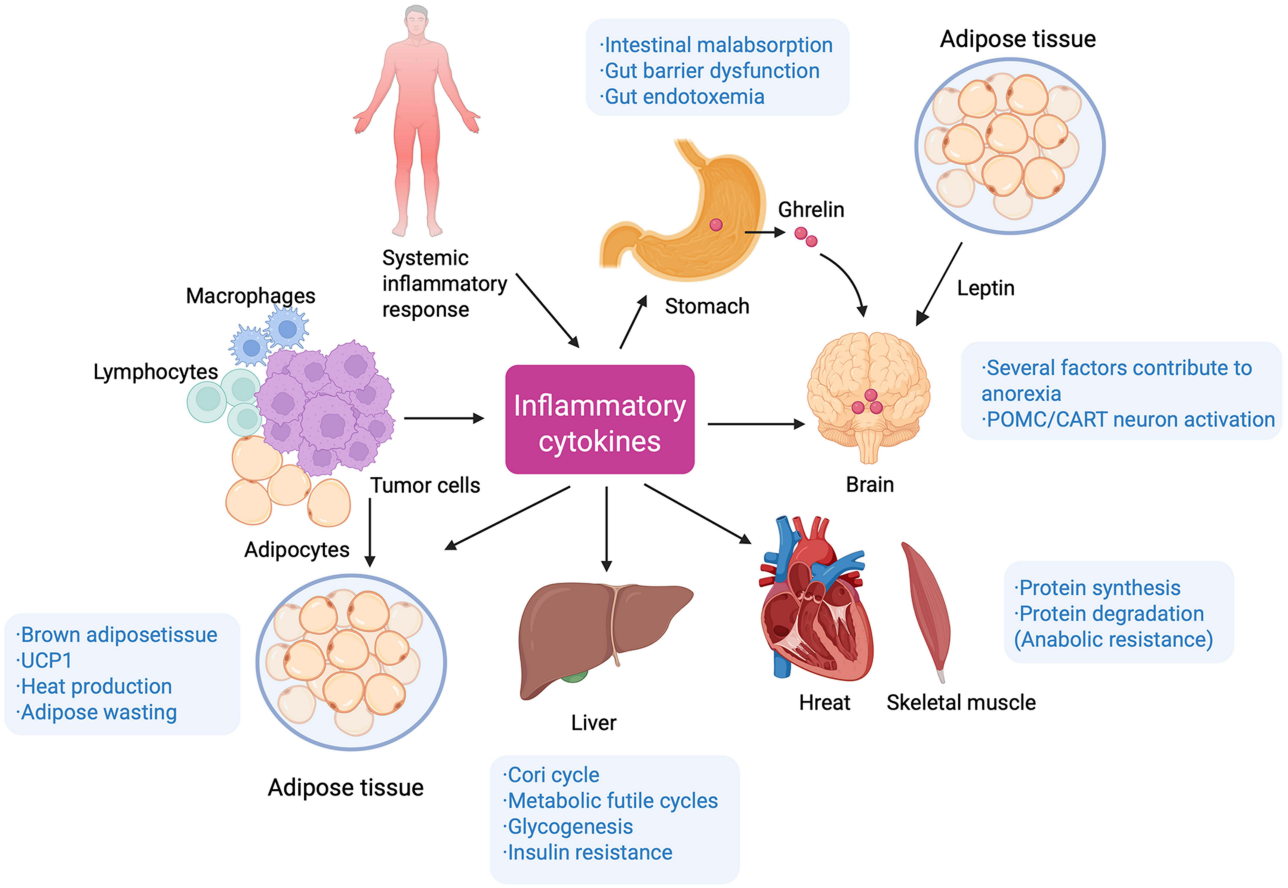

Figure 1 Various organs are involved in the development of CC. The relationship between CC and adipose tissue, liver, brain and other organs is shown in the figure, in which inflammatory cytokines play a major role and connect various organs. Both systemic inflammatory responses and tumor cells can promote the secretion of inflammatory cytokines. These inflammatory factors transmit information to the stomach, causing intestinal malabsorption, intestinal barrier dysfunction and intestinal endotoxemia. The stomach and adipose tissue respectively release polypeptides and leptin, which send signals to the brain and promote the occurrence of anorexia. Inflammatory factors can also directly stimulate adipose tissue to promote the production of brown fat and generate heat. Inflammatory factors carry out the Cori cycle in part of the liver and promote protein synthesis and degradation in the skeletal muscle part of the heart.
Abbreviations: CART, cocaine and amphetamine-regulated transcript; POMC, proopiomelanocortin; UCP1, Uncoupling protein1.

atrophy is increasing, human research remains scarce. In addition, there is a lack of scientific and reasonable evaluation methods and specific drugs for the clinical diagnosis and treatment of CC.Nutritional support therapy is the main treatment for patients with advanced CC, but certain limitations and limited efficacy. Therefore, it is urgent to effectively develop cachexia therapy to enhance the quality of life of patients, improving the nutritional status and combining the treatment of cachexia with anti-tumor therapy to lift the survival rate of patients. In conclusion, CC is a disease that should not be overlooked, and more research on the pathogenesis and treatment of CC is definitely necessary.

CC is very likely to be confused with diseases such as sarcopenia and anorexia. CC is not the same as malnutrition or sarcopenia. Patients with malnutrition can absorb nutrients through meals, while those with sarcopenia have no inflammatory manifestations in their blood pictures. Patients with CC have difficulty absorbing nutrients through "eating", but even so, they still have more inflammatory blood pictures (low central granulocytes and lymphocytes, and elevated white blood cells) than patients with sarcopenia. At present, the diagnostic criteria of CC is generally the international expert consensus in 2011.[15] According to the consensus, the progress of CC can be divided into three stages (Figure 2). Stage one: In the early stage of CC, patients only have slight weight loss, which is less than or equal to 5%, and the main manifestations are anorexia and metabolic changes; Stage two: CC stage, when the main characteristics are weight loss greater than 5% and systemic inflammation, at this stage patients ordinarily have reduced food intake; The last stage is the refractory stage of CC, also known as the ineffective end-stage of anticancer treatment. During this period, the degree of cachexia is different, mainly catabolic, and the survival time is usually less than 3 months.[16]

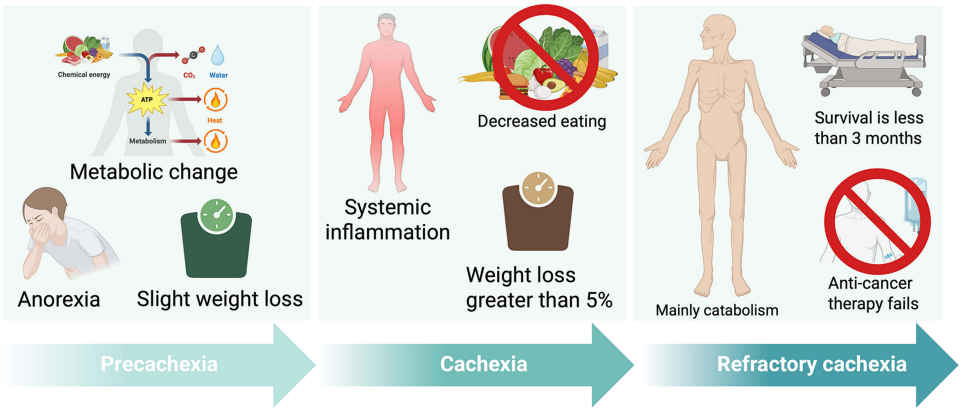

Figure 2 The developmental stage of CC. With the development of CC, the weight of patient decreases, food intaking degrades, and survival time diminishes gradually.In the early stage of cachexia, the body undergoes a series of metabolic changes, and there is a certain possibility of anorexia and weight loss. During the cachexia stage, the body will develop systemic inflammation. At this time, the patient's food intake decreases and their weight drops by greater than 5%. During the refractory cachexia stage, patients have failed multiple times with anti-cancer drugs, and at this point, their survival period is less than three months.

However, based on the current clinical data, not all patients with CC will undergo this stage, which varies greatly depending on the type, location and size of tumors. Additionally, the clinical manifestations of CC are also different, which can be manifested as "recessive cachexia", which is no fat loss.[17]

Here, we conduct a comprehensive analysis of the preclinical diagnosis of CC, the molecular mechanisms of muscle mass reduction related to CC involved in clinical research, and the treatment methods in clinical practice. It also discusses in detail the challenges that humans need to face in the future regarding this disease of CC and points out a direction for future research.

Comprehensive Assessment and Individualized Treatment Strategies for CC

CC is a complex syndrome that requires comprehensive evaluation of each patient's status to optimize treatment decisions. Assessment of CC encompasses evaluating nutritional status, body composition, quality of life, and relevant biomarkers. Clinical evaluation comprises assessing weight loss to determine the clinical stage of cachexia. Body composition analysis encompasses total or regional fat, muscle tissue, and lean tissue using methods such as anthropometry, dual-energy X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), computed tomography (CT), and magnetic resonance imaging (MRI). DXA offers whole-body and local fat and muscle tissue measurements,[18] while BIA estimates body fat and lean tissue through electrical impedance measurement but with less accuracy than DXA.[19] CT and MRI precisely quantify muscle and fat volume but require specialized equipment. CT is regarded as the gold standard due to its high accuracy in distinguishing individual components.[20,21] Laboratory tests for CC encompass blood biochemical markers such as albumin, prealbumin, transferrin reflecting protein levels. Metabolomics studies have disclosed metabolic characteristics of CC leading to the development of diagnostic models by detecting metabolites to identify high-risk groups.[1,22] Inflammatory markers like c-reactive protein (CRP), tumor necrosis factor alpha (TNF-alpha), interleukin 6 (IL-6) can evaluate systemic inflammation. Hormone levels including insulin-like growth factor (IGF-1) and cortisol can be assessed for metabolic abnormalities.[23,24] Muscle function tests involve measuring grip strength using a dynamometer as an indicator of muscle function; walking speed is utilized to evaluate lower limb muscle strength; activities ability questionnaires such as Karnofsky score or ECOG score assess daily life activity's ability level. Nutritional assessment tools include Subjective Global Assessment (SGA),[25] which is suitable for assessing weight change, dietary intake, gastrointestinal symptoms, functional status; Mini Nutritional Assessment (MNA).[26] SGA is a comprehensive questionnaire devised to evaluate changes in weight, dietary intake, gastrointestinal symptoms, and functional status. MNA is particularly appropriate for screening and assessing the nutritional status of elderly patients. Other screening tools include malnutrition screening tools and nutritional risk screening, but only SGA is appropriate for cancer patients.[27] Indirect calorimetry can be utilized for metabolic assessment of patients to measure Resting Energy Expenditure (REE) and assess energy metabolism. Given the array of detection methods available, it is of paramount

importance to carefully select and evaluate the most suitable method based on the patient's condition to comprehensively assess their overall state and optimize treatment strategies.

Skeletal Muscle Expenditure in CC: From Protein Imbalance to Key Signaling Pathways

CC is the primary cause of death in most cancer patients, which not only reduces the quality of life of patients but also exacerbates the physical pain they endure. The pathogenesis of CC is complicated and still unclear. The better we understand the potential mechanisms of CC, the more we can improve treatment outcomes and quality of life for patients. The pathogenesis of CC is diverse, including muscle atrophy, decreased muscle synthesis, increased muscle breakdown, fat degradation, increased lipolysis, Browning of white fat and inflammatory factors.[2,28] Among them, loss of skeletal muscle is the keys point of CC, which is usually caused by decreased protein synthesis, increased protein degradation or a relative imbalance between the two.[29] The occurrence and development of CC are regulated by multiple signaling pathways (Table 1). For instance, the insulin-like growth factor-1 (IGF-1) signaling pathway that promotes the transcription and translation of mRNA in muscle, and the TGF-β superfamily (TGF-β, Activins, Myostatin) that causes Ca^{2+} imbalance and leads to skeletal muscle contractility dysfunction through the classical SMAD pathway.[30,31] More importantly, among multiple signaling pathways, the key link that causes CC muscle atrophy is the JAK/STAT3 signaling pathway.

JAK/STAT3 Pathway: The Key Regulatory in CC Muscular Atrophy

JAK / STAT3 pathway is a signaling pathway shared by various cytokines. It plays a crucial role in regulating cell growth, differentiation, apoptosis and other processes. It also exerts a regulatory effect the occurrence and development of CC. Relevant studies have indicated that JAK / STAT3 signaling pathway is a key link in causing muscle atrophy in CC. JAK (Janus kinase) plays an essential part in the JAK/STAT3 pathway. JAK is a kind of kinase protein of intracellular non-receptor tyrosine kinase family, which is activated after binding to the receptor on the cell membrane and transmitted through the JAK signaling and activators of transcription (STAT) signaling pathway. JAK/STAT signaling pathway is involved in transmitting extracellular polypeptide signals to target gene promoters in the nucleus. This pathway is initiated by cytokine ligand binding to cell surface receptors, which triggers JAK activation, and activated JAK phosphorylates key tyrosine residues on the receptor. Subsequently, activated JAK recruits specific stats to form dimers through its SH2 domain (SRC homology 2, SH2).[32] With the assistance of importin, this dimer enters the nucleus and binds to specific DNA targets, thereby regulating a series of physiological and pathological processes such as cell growth, differentiation, proliferation and apoptosis.[33] In the protein family of stats, the protein and gene expression of STAT3 are crucial for causing muscle atrophy in CC. The activation of JAK/STAT3 pathway will trigger inflammatory response. Clinical experimental observation revealed that some inflammatory factors can stimulate JAK/STAT3 signaling pathway to cause STAT3 overexpression, such as influential of chronic inflammation can lead to CC probably. Thus, JAK or STAT3 inhibitors can effectively decelerate the process of muscle atrophy.[34] The key to maintain the normal dynamic balance of skeletal muscle lies in the fact that when there is exogenous or endogenous stimulation, its mass and metabolic function will change, which is since skeletal muscle is a highly plastic tissue. The dynamic balance of skeletal muscle is affected by exogenous or endogenous stimuli, which alter its mass and metabolic function. Anabolic balance is regulated

Table 1 Signaling Pathways Related to the Development of CC

Signal Pathway	Mechanism	Cytokines	Literature Review
JAK/STAT3	Skeletal muscle atrophy	IL-6/IL6ST	[31]
NF-κB/TNF-α	Reduced muscle synthesis	NLRP3/IL1β	[32]
SIRT1/FoxO1	Skeletal muscle atrophy	GPR39	[33]
PI3K/AKT	Skeletal muscle atrophy	IGF-1/IGFR	[10]
NF-κB	Skeletal muscle atrophy	TNF/TNFR, TWEA	[10]
SMAD	Skeletal muscle atrophy	TGF-β/TGFBR2	[29, 30]
WAT lipolysis	Increased fat grading	Increased fat grading	[34, 35]
WAT browns	UCP1	Inflammatory factor	[34, 35]

by growth factors, as nutrient utilization and physical activity; Catabolic balance mainly promotes protein degradation through the activation of ubiquitin proteasome system (UPS) and autophagosome lysosome pathway, resulting in the loss of skeletal muscle mass.[35,36] In the related research of CC, JAK/STAT3 signaling pathway was found to regulate the ubiquitin proteasome pathway and autophagy pathway. These two pathways lead to massive loss of skeletal muscle by degrading proteins in the body, thereby contributing to the process of causing muscle atrophy in CC.[37]

JAK/STAT3 Activation: Linking to Muscle Atrophy via Ubiquitin Proteasome System

UPS is one of the systems primarily accountable for protein degradation in cells. It participates in more than 80% of protein degradation in cells. It includes ubiquitin ligase, ubiquitin, proteasome and other components. In UPS, ubiquitin ligases covalently bind ubiquitin molecules to target proteins to form ubiquitinated proteins. E1 is the first member of ubiquitin ligases, which supervises activating ubiquitin molecules, it is ubiquitin binds to ATP and transfers to itself. This is the first and critical step in the process of ubiquitin modification. E2 is the second member of the ubiquitin ligase complex, which receives ubiquitin transferred from E1 and transfers it to target proteins. E3, the third member of the ubiquitin ligase complex, is a crucial regulator in the ubiquitination process. E3 catalyzes the covalent attachment of ubiquitin to target proteins and realizes the ubiquitination of target proteins by forming isopeptide bonds with specific lysine residues of target proteins. The process of ubiquitin connecting to target proteins is the rate determining step of USP, while muscle atrophy gene (MAFbx/Atrogin-1) and muscle ring finger 1 (MuRF1) are E3 enzymes that promote muscle degradation.[38,39] These members jointly participate in the process of ubiquitination, ensuring that ubiquitin can be correctly connected to the target protein, so that the target protein can be recognized and degraded by the proteasome (Figure 3). In addition, there are other pathways involved in E3 ubiquitin ligases, such as HECT-type E3 ligases, in particular members of the neural precursor cell expressed

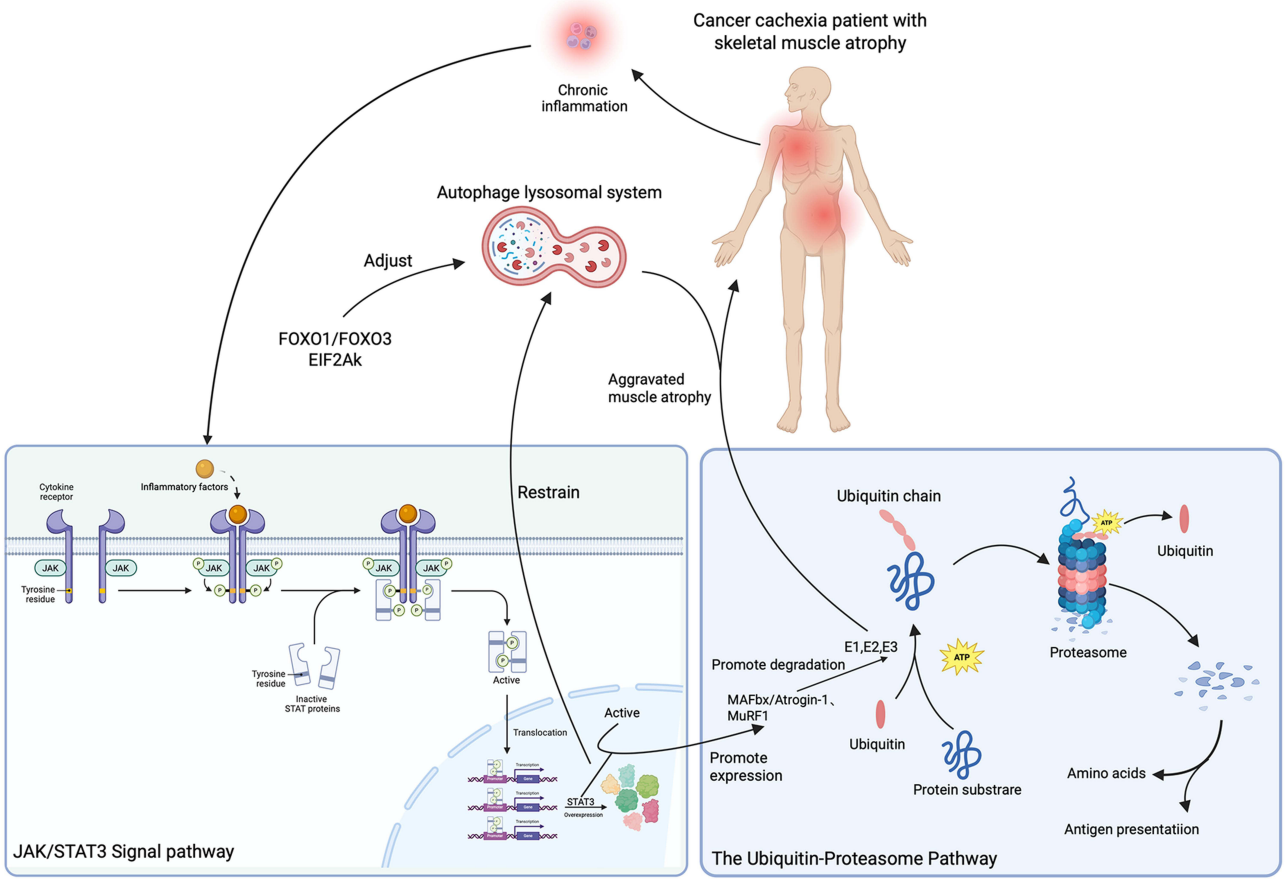

Figure 3 The JAK/STAT3 pathway regulates muscle atrophy. JAK/STAT3 signaling pathway has a regulatory effect on the ubiquitin proteasome pathway and autophagy pathway, causes skeletal muscle atrophy by regulating both pathways.

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developmentally downregulated protein 4 (NEDD4) including NEDD4-1, NEDD4-L, SMURFs, WWPs, and ITCH, play critical roles in dysregulation or dysfunction of autophagy in cancer cells.[40]

In a study that analyzed the role of STAT3 in regulating the secretion of exosomes from C26 colon cancer cells in mice and its contribution to the development of CC, it was found that subcutaneously inoculating C26 colon cancer cells with knockout or overexpression of STAT3 in mice respectively, discovered that STAT3 knockout improved the CC of mice, and the content of serum IL-6 and exosomes decreased. While STAT3 overexpression presented the opposite situation, the CC of mice further exacerbated and the content of serum IL-6 and exosomes further increased, which described STAT3 knockout could significantly inhibit the secretion of exosomes from C26 cells and relieve the muscle atrophy and the ability of lipolysis.[41] A study on the atrophy of gastrocnemius muscle and C2C12 myoblasts in C26 mice showed that by inhibiting the activity of STAT3, it can effectively slow down the muscle consumption of C26 in mice and the atrophy of C2C12 myotubes induced by IL-6. This mechanism of action may be due to the decreased expression of MAFbx/Atrogin-1 and MuRF-1 after inhibition of STAT3, thereby effectively maintaining muscle mass.[42] The above studies indicated that STAT3 mediated UPS is responsible for in the muscle protein degradation.

JAK/STAT3 Activation: Linking to Muscle Atrophy via Autophagy Lysosome System

Autophagy is an important physiological process regulated by cells themselves. During the process, the fusion of autophagosomes and lysosomes gives rise to auto phagolysosomes, which are utilized to maintain the stability of the intracellular environment and remove damaged organelles or protein aggregates.[43] Autophagy encompasses four steps. The first step is the induction stage. In this stage, when cells are under pressure or stress, specific signaling pathways will be activated to promote the initiation of autophagy. Among them, the key signaling pathways include mTOR signaling pathway and AMPK signaling pathway. The second step is membrane formation. In the process of autophagy at this time, a double-layer membrane structure wrapping damaged or old organelles will initially form, which is called autophagosome. The third step is fusion and degradation. Currently, autophagosomes are subsequently fused with lysosomes to form auto phagolysosomes, in which enzymes degrade the contents of membrane capsules, such as proteins, organelles. And it also can release useful metabolites. The fourth step is the reuse of metabolites. After degradation, the generated metabolites can be reused in new cellular metabolic processes to maintain cell survival and function. In the physiological state of human body, autophagy maintains intracellular homeostasis at a slow pace to meet the needs of normal cell metabolism and organelle renewal. However, under various stress conditions, autophagy has dual effects on the maintenance of muscle mass. Long term inhibition of autophagy may lead to muscle weakness and atrophy, while excessive activation of autophagy may accelerate the hydrolysis of skeletal muscle proteins, resulting in muscle atrophy.[44,45] The role of STAT3 in the regulation of autophagy is complex and diverse. It can not only inhibit the occurrence of autophagy but also affect the progress of autophagy by regulating gene expression or participating in the regulation of other signaling pathways.[46–49] Among which, EIF2AK gene can promote autophagy by phosphorylating EIF2A; FoxO1 and FoxO3 genes can promote autophagy by transcriptionally activating a series of autophagy related genes. Another researcher found that the related autophagy genes LC3B and p62/SQSTM1 were overexpressed in the muscles of patients with esophageal CC, indicating that autophagy lysosomes may participate in the development of muscle atrophy in human CC through activating the proteolytic system.[50,51]

PGC-1α/FoxO1 Pathway: Dual Mechanisms to Combat CC Muscle Atrophy

PGC-1α is a peroxisome proliferator receptor γ Coactivators, which participates in the bioactivity of skeletal muscle and adipose tissue, can activate transcription factors to initiate mitochondrial biogenesis, maintain mitochondrial function, increase mitochondrial mass and activity, improve muscle function, and delay muscle atrophy.[52–54] The manifestation of CC is systemic inflammation and involuntary weight loss, and muscle atrophy is the most significant and fundamental factor contributing to weight loss. FoxO1, a member of the fork head transcription factor family, which can interfere with skeletal muscle mitochondrial function to play a normal role.[55] PGC-1α is not only an upstream regulator of muscle atrophy biomarker molecules, but also a regulator of FoxO1 signal transduction. PGC-1α can resist muscle atrophy by inhibiting FoxO to block the transcription of muscle ring finger gene 1 (MuRF1), E3 ligase mediated ubiquitin ligase, and inhibiting the FoxO induced expression of atrophy factors atrogin1 and MuRF1.[56]

The Role of the IGF-1/PI3K/Akt/mTOR Signaling Pathway in Promoting Muscle Protein Synthesis

The loss of skeletal muscle mass, a critical factor in CC is typically caused by decreased protein synthesis, enhanced degradation, or a relative imbalance between the formers.[57] Insulin-like growth factor-1 (IGF-1) signal transduction pathway is one of the prime mechanisms to induce protein synthesis. Alterations in the rate of protein synthesis involve changes in the rate of mRNA transcription and translation, and IGF-1 can promote the transcription and translation of mRNA in muscle. IGF-1 activates insulin receptor substrate-1 (IRS-1) /PI3K/AKT signaling, which is an important mechanism of muscle hypertrophy. Akt induces protein synthesis by counteracting the inhibition of mTOR.[15]

Diversified and Comprehensive Intervention Strategies for Refractory CC

CC is refractory, early diagnosis and intervention are indispensable.[58] The etiology of CC is diverse, including anorexia, skeletal muscle depletion, metabolic changes in liver or adipose tissue, and systemic inflammation. Therefore, besides drug treatment, multiple types of intervention are requisite. At present, drug therapy is the main method extensively employed in clinical practice, and other methods include nutritional support therapy, exercise, and psychological counseling and others.[59]

Frontiers in Drug Therapy for CC: Diverse Strategies From Appetite Stimulation to Targeting Mechanisms

Currently, several experimental studies have examined drugs related to the prevention of muscle and fat mass loss, including leucine and fish oil, Rosiglitazone (Insulin sensitizer), Activin receptor type 2 blocker, bortezomib (NF-κB inhibitor) and vitamin D supplements.[60–63] Ghrelin is an endogenous peptide predominantly secreted by the stomach. Once bound to its receptor, it can stimulate a variety of pathways to positively regulate the body weight, muscle mass, appetite and body metabolism of patients. Ghrelin has been verified to exert anti-inflammatory effects and inhibit the secretion of pro-inflammatory factors in patients with CC, and it can also improve food intake, gastrointestinal motility, taste regulation and glucose metabolism, which is anticipated to play an important role in the treatment of CC.[58,64] In patients with cachexia experiencing decreased appetite and weight loss, short-term administration of progesterone analogues such as megestrol and corticosteroids like dexamethasone or fluroxymedone can be contemplated. Numerous clinical trials have demonstrated that progestins can effectively increase appetite in these patients, such as medroxyprogesterone (MP), megestrol (MA). Its mechanism of action is related to glucocorticoids, and progesterone can stimulate neuropeptide Y(NPY) in the central nervous system to promote appetite.[65] Glucocorticoids can inhibit prostaglandin activity and productions of IL-1 and TNF production, and may have a transient effect on anorexia, but it does not significantly improve weight loss. Its side effects include increasing blood glucose, muscle atrophy and osteoporosis. It is currently recommended only for patients with advanced CC. In addition, the impact of olanzapine on chemotherapy-induced anorexia was assessed in a double-blind, placebo-controlled randomized controlled trial (RCT) involving 124 adults (median age, 55 years) with locally advanced or metastatic gastric, hepatobiliary, or lung cancer.[66] The findings demonstrated enhanced appetite in patients receiving olanzapine. However, it is noteworthy that two treated patients experienced grade 3 experimental drug toxicity reactions. This suggests that olanzapine may also have potential in managing CC. However, its effect on tumor-associated anorexia and body composition remains unclear at present.[67] It was found in a two-stage randomized, double-blind, 12-week trial among patients with CC and elevated GDF-15 levels, the inhibition of GDF-15 with ponsegromab resulted in increased weight gain and overall activity level and reduced cachexia symptoms, findings that confirmed the role of GDF-15 as a driver of cachexia.[68] However, there is no consistent clinical data to prove that it can increase the muscle mass of patients. Androgens are expected to make a big difference in the treatment of CC in the future. Other drugs including lipid drugs such as ω-3 atty acids and corticosteroids can also improve appetite and quality of life,[69] but cortisol drugs may cause muscle atrophy and are limited in use.[70] Plant extract gingerol can improve anorexia, gastrointestinal motility disorders, skeletal muscle and atrophy. Formoterol, β2-adrenergic agonist has antagonistic effects on protein and muscle degradation and can improve muscle atrophy in cachexia. The glycoprotein hormone erythropoietin can reduce the production of IL-6 and improve the patient's

metabolism and exercise capacity. Cardiac drugs ACE inhibitors and β-blockers can also play a role in the treatment of cachexia. ACE receptor inhibitors can inhibit the production of TNF-α to reduce the wasting of muscle mass, while β-blockers can preserve body weight and improve the quality of life of patients.[10]

Traditional Chinese Medicine Prevention and Treatment of CC: From the Theories of "Vitality" and "Yin Fire" to Modern Pharmacology

The clinical manifestations of CC patients, such as loss of appetite, early satiety, anemia, fatigue, and depression due to involuntary weight loss caused by skeletal muscle, adipose tissue, belong to the category of "asthenia" in traditional Chinese medicine. A variety of tumors are more prone to be associated with CC in the later stage, of which gastrointestinal tumor is the most common tumor in the world, and the combined CC is called advanced gastrointestinal CC.[71] At present, the curative effect of Western medicine in the treatment of advanced gastrointestinal CC is not satisfactory. Traditional Chinese medicine has demonstrated good curative effect in improving the clinical symptoms and quality of life of patients with advanced gastrointestinal CC. According to its symptoms, it is consistent with the "lack of form" in traditional Chinese medicine, indicating that the body is weak; The deficiency of the internal organs matches the "deficiency of essence" in traditional Chinese medicine, which can refer to the deficiency of kidney essence, bone dystrophy. It is manifested as obvious weight loss, intestinal flora disturbance,[72] systemic excessive inflammatory response[73] and will eventually form complex and intractable metabolic disorder syndrome. The essence of CC is caused by the imbalance between the material base provided by human life activities and the material that promotes energy production. According to traditional Chinese medicine, vitality is the material base provided for human life activities. Fire can promote energy production, the process of body material and energy metabolism out of control caused by the imbalance between vitality and fire. This is why "fire and vitality do not stand side by side". Deficiency of vitality is the root of internal friction of CC, and vitality comes from the normal function of spleen and kidney;[74,75] The absence of Yin fire is the key to the progression of CC, and the deficiency of vitality leads to the hyperactivity of Yin fire. According to the medication law of Tonifying Qi, elevating Yang and drain fire in *the Treatise on Spleen and Stomach* written by D.Li,tonifying middle school, Promoting Yang and removing dampness can be taken as the basic treatment principles, among which the representative prescriptions are Bu-zhong-yi-qi-tang, Sheng-yang-san-huo-tang, Sheng-yang-chu-shi-tang.[74] Among them, the relieving effect of Bu-zhong-yi-qi-tang on disease-related fatigue and anti-cancer effect may be related to the activation of the immune system. It may increase the infiltration of tumor lymphocytes, reduce the expression of PD-1 in peripheral blood, reduce the infiltration of PD-1 and PD-L1 in tumors, regulate peripheral immunity, and prevent tumor immune escape.[76] A recent study has shown that Bu-zhong-yi-qi-tang can effectively improve the inflammation and oxidative stress of the spinal cord and gastrocnemius muscle in a mouse model of amyotrophic lateral sclerosis (ALS), improve its motor function and prolong its survival period. It has been confirmed that Bu-zhong-yi-qi-tang can regulate the immune responses of muscles and neurons to delay the progression of Musculo neurological diseases.[77] In addition, Shi-quan-da-bu-tang, a famous tonic Chinese medicine prescription in China, has the effect of strengthening the body and strengthening immunity. It has been used for thousand years to treat various diseases, such as rheumatoid arthritis, atopic dermatitis, chronic fatigue syndrome, ulcerative colitis.[78] In the latest retrospective analysis involving 754 participants, compared with the control group, Shi-quan-da-bu-tang could significantly reduce cancer-related fatigue (CRF) in patients and improve their quality of life. In addition, Shi-quan-da-bu-tang can be used either as an adjunctive therapy or as a monotherapy.[79] Recently, Shi-quan-da-bu-tang has been found to exert anti-tumor effects by reducing disease-related fatigue in patients and regulating the immune response in cancer patients. For example, Kawai et al showed that Shi-quan-da-bu-tang combined with chemotherapy may reduce the incidence of adverse reactions, prevent nutritional disorders, increase physical fitness, and thus improve the quality of life of CC patients during survival.[80] In addition, the classic Chinese medicine prescription Xiang-sha-liu-jun-zi-tang created by Y.Ke, Chinese physician in the Qing Dynasty, has been shown in modern studies to be used for the treatment of nausea, vomiting, abdominal distension, diarrhea and other symptoms, and to relieve the pain caused by CC.[81] Atractylenolide I (AI) is a natural sesquiterpene lactone isolated from Atractylodes macrocephala Koidz, known as Baizhu in traditional Chinese medicine. A study using C26 tumor-

carrying BALB/c mice as animal models demonstrated that AI could effectively alleviate the symptoms of CC, enhance the grip strength of mice, and reduce the levels of serum EVs and IL-6 in C26 tumor-carrying mice. Moreover, AI directly inhibited EVs biogenesis and IL-6 secretion in the cultured C26 cells. The inhibitory effect of AI on EVs biosynthesis is achieved by inhibiting the STAT3 / PKM2 / SNAP23 pathway.[82] This result confirmed the effectiveness of AI in the treatment and improvement of CC. In the latest research progress of traditional Chinese medicine on CC, some studies have found that the traditional Chinese medicine Dioscorea radix (DR) and Mu Dan Pi (MDP) have protective effects on muscle atrophy.[75] The results suggest the translational potential of MDP to promote new strategies for the prevention and/or treatment of cachexia. The protective effect of MDP against other types of muscular dystrophy, such as sarcopenia, may be worth investigating. Although the above achievements are not the embodiment of all achievements of traditional Chinese medicine in CC, they are enough to reflect the initial achievements of traditional Chinese medicine in treating and alleviating the progress of CC and improving the living quality.

The Core Role of Nutritional Support Therapy in the Management of CC: From Macro Strategies to Micronutrient Interventions

Nutrition experts at American Cancer Center assert that about 40% cancer patients succumb to malnutrition instead of cancer and treatment.[83] Malnutrition is the common issue of CC patients, which is commonly caused by diet reduced, poor quality of diet, and hypermetabolism common cause.[84] To reduce food intake is thought to be caused by cancer symptoms, such as mechanical disturbance of nutrient intake or absorption, treatment-related side effects, including mucositis, nausea and vomiting, and taste changes. Malnutrition affects not only the macronutrients that provide energy, but also the micronutrients that are essential cofactors for metabolism and maintenance of body mass.[85] The European clinical guidelines for CC and the European Society for enteral and parenteral nutrition (ESPEN) also emphasized the important role of nutrition therapy in the comprehensive treatment of cancer patients. From the clinical outcome of CC, nutritional support therapy can enhance the quality of life of patients with cachexia and even prolong the survival. In the late refractory stage of CC, nutritional support treatment obviously cannot completely reverse the weight loss and metabolic abnormalities of patients, but if considering that the risks and burdens brought by nutritional intervention may surpass its potential benefits, appropriately nutritional intake can improve the quality of life of patients and bring psychological comfort to patients, even the families.The selection of nutrients typically encompasses ω-3 fatty acids, branched chain amino acids, vitamins, minerals or other dietary supplements.[86,87] In a single-nutrient intervention, an adequate dietary protein of dietary protein is a prerequisite for maintaining or increasing skeletal muscle mass.[88] Branched chain amino acids (BCAAs) are components of skeletal muscle proteins that play an important role in stimulating protein synthesis[89] and are therefore thought to play a therapeutic role in diseases associated with muscle wasting. Amino acids include β-hydroxy-β-methyl butyrate, glutamine, glycine, arginine. Dietary fat is an important source of energy and contributes significant caloric value to our diet. Dietary fat is not merely a source of energy, it also as a constitutes the cell membrane, carry fat-soluble vitamins, play an important role in signal transduction and is the precursor of inflammatory mediators. The current high fat ketogenic diet has been investigated nutrition therapy for patients with CC. Ketogenic diet to reduce tumor sources of energy, at the same time provide free fatty acids and ketone bodies as the energy source of muscle. A high-fat diet is expected to block host catabolism during cachexia, mainly by reducing tumor growth.[90] In addition, polyunsaturated fatty acids and conjugated linoleic acid can also be applied to nutrition therapy in CC. Other nutrients include carnitine, myogenin, flavonoids, resveratrol, prebiotics non-digestible oligosaccharides, which can effectively provide nutrition and energy needed by the body for patients.[88] In summary, nutritional support therapy is an essential link based on drug therapy. It is very important to develop individualized nutritional therapy and carry out precise treatment for patients to improve the quality of life of patients with CC to their quality of life, which is of great significance to both patients and their families.

Exercise and Psychological Support: Key Adjunctive Treatments for Improving Muscle Strength and Psychological Burden in Patients with CC

Other treatments include exercise or psychotherapy. A randomized trial conducted on 90 cancer patients who received active tumor treatment showed that aerobic exercise, resistance exercise and a combination of the two improved muscle strength in the upper and lower extremities compared with usual care.[91] In this regard, it has been noted that CC patients lack of a certain motivation for regular structured exercise and the willing to exercise when they are able to perform certain activities, leading to insufficient exercise and contributes to the occurrence of skeletal muscle atrophy.[92] And regular physical activity can reduce the incidence of cancer, mitigate the negative effects associated with cancer treatment, and improve its effectiveness and patient outcomes.[93] Therefore, regular physical activity is necessary for patients who can perform it. Psychotherapy is also very important for patients with CC. When patients go to the ultimate cachexia, their body's catabolism increases exponentially,[94,95] cachexia no longer has any remission response to anti-tumor therapy, patients often become abnormally emaciated, and death becomes imminent. All these undoubtedly aggravate the psychological burden and mental pain of patients and their families. For this, psychological support is the key link to alleviate this stage.

Discussion

CC remains a significant and unresolved challenge in the management of advanced cancer patients. Characterized by relentless skeletal muscle wasting and irreversible weight loss, this condition severely diminishes patients' quality of life and significantly impacts their response to cancer treatments. Despite extensive research, the pathogenesis of CC is still not fully understood, and effective treatments remain elusive. This review aims to summarize the understanding of CC at the current scientific research level and provide a comprehensive description of its clinical manifestations, clinical treatment and pathogenesis. It pointed out the limitations and uncertainties of known mechanisms and treatment methods, highlighting the effectiveness of traditional Chinese medicine among various treatment approaches and the potential of future treatment strategies.

CC is a multifactorial syndrome involving complex interactions between the tumor and the host. The pathogenesis encompasses a wide range of biological processes, including systemic inflammation, altered metabolism, and immune dysregulation. The involvement of multiple organs such as skeletal muscle, adipose tissue, liver, and the central nervous system underscores the complexity of this condition. Systemic inflammation driven by cytokines such as TNF-α, IL-6, and IL-1β plays a central role in the development of CC. These cytokines activate signaling pathways like JAK/STAT3 and NF-κB, leading to muscle atrophy and fat wasting. Additionally, cancer cells often exhibit a high metabolic rate, leading to increased energy demands. This, combined with anorexia and altered nutrient absorption, results in a catabolic state characterized by muscle and fat depletion. The immune system is also significantly impacted in CC, with increased production of pro-inflammatory cytokines and impaired immune function. This not only contributes to muscle wasting but also affects the overall response to cancer treatments.

Despite the availability of various therapeutic approaches, the management of CC remains challenging. Current treatments include nutritional support, pharmacological interventions, and lifestyle modifications. However, these approaches often fall short due to the underlying metabolic alterations and the complex nature of the condition. Nutritional interventions, while essential, are insufficient to reverse the catabolic state of CC. High-calorie diets and specific nutrients such as ω-3 fatty acids and branched-chain amino acids may provide some benefits, but their efficacy is limited. Pharmacological interventions, including ghrelin, corticosteroids, and progestins, have been explored for their potential to mitigate muscle wasting and improve appetite. However, many of these treatments have significant side effects and provide only temporary relief. For example, corticosteroids can improve appetite but may exacerbate muscle wasting in the long term. Exercise and psychological support are important adjuncts to treatment, but their effectiveness is often limited by the patient's physical condition and motivation. Regular physical activity can help maintain muscle mass and improve overall well-being, but it is not a standalone solution.

The future of CC management lies in a more comprehensive and personalized approach. Emerging research highlights the potential of novel therapeutic strategies, including targeted therapies and immune modulation. New drugs

targeting specific signaling pathways involved in muscle atrophy and fat wasting are under investigation. For example, inhibitors of the JAK/STAT3 and NF-κB pathways show promise in preclinical studies. Inflammation is at the core of tumor cachexia, making the regulation of immune responses impossible to ignore. Anti-inflammatory agents and immunomodulatory drugs play a significant role here. The combined treatment approach of nutritional support, drug intervention and lifestyle changes will make the therapeutic effect more significant. In addition, providing personalized and precise medical care is also necessary. Tailoring treatment plans based on the specific requirements and individual characteristics of each patient can maximize the treatment effect. Traditional Chinese medicine has achieved initial success in the treatment of tumor cachexia. It focuses on restoring body balance and enhancing overall vitality, especially in improving the symptoms of advanced tumor cachexia and enhancing the quality of life of patients, providing a comprehensive supplement based on Western medical treatment methods. The combined treatment approach of traditional Chinese and Western medicine holds a high therapeutic prospect for CC.

In conclusion, CC is a complex and multi-faceted disease. The currently known treatment methods offer some moderate time for the treatment of CC, but the inability to completely cure and suppress the loss of body energy remains a huge challenge to be faced in the future. Future research must focus on clarifying the underlying mechanisms and developing efficient targeted therapies to effectively reverse catabolic states and improve the quality of life of CC patients. The combined application of traditional Chinese medicine and Western medicine may offer new insights and innovative solutions to this long-standing problem.

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