prospective randomized single-blind trial. Age Ageing. 1994; 23(1):40–8.
206. McMurtry CT, Rosenthal A. Predictors of 2-year mortality among older male veterans on a geriatric rehabilitation unit. J Am Geriatr Soc. 1995;43(10):1123–6.
207. Yeh S-S, Schuster MW. Treatment of cachexia in the elderly. In: Mantovani G, Anker SD, Inui A, Morley JE, Fanelli FR, Scevola D, et al., editors. Cachexia and wasting: a modern approach. link.springer.com. Milan: Springer; 2006. p. 701–17.
208. Brinksma A, Huizinga G, Sulkers E, Kamps W, Roodbol P, Tissing W. Malnutrition in childhood cancer patients: a review on its prevalence and possible causes. Crit Rev Oncol Hematol. 2012;83:249–75.
209. Cole TJ. Assessment of growth. Best Pract Res Clin Endocrinol Metab. 2002;16(3):383–98.
210. Wilcox WD, Nieburg P, Miller DS. Failure to thrive. A continuing problem of definition. Clin Pediatr (Phila). 1989; 28(9):391–4.
211. Jolley CD. Failure to thrive. Curr Probl Pediatr Adolesc Health Care. 2003;33(6):183–206.
212. Lai J-S, Cella D, Goldman S. 5. Anorexia/cachexia-related quality of life for children with cancer. Cancer. 2005;104(7): 1531–9.

The International Journal of Biochemistry & Cell Biology 45 (2013) 2179–2185

Contents lists available at ScienceDirect

The International Journal of Biochemistry & Cell Biology

journal homepage: www.elsevier.com/locate/biocel

Review

Control of food intake and muscle wasting in cachexia☆

Marie Amitani, Akihiro Asakawa, Haruka Amitani, Akio Inui*

Department of Psychosomatic Internal Medicine, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan

ARTICLE INFO

Article history:
Available online 30 July 2013

Keywords:
Cachexia
Anorexia
Muscle wasting
Ghrelin
Melanocortin

ABSTRACT

Cachexia is characterized by anorexia, weakness, weight loss, and muscle wasting. Anorexia and muscle wasting are the key features of cachexia and they affect mortality, morbidity, and quality of life. Consistent studies have found that feeding-regulating peptides such as melanocortin, ghrelin, and leptin are related to muscle metabolism, and the balance of catabolism and anabolism in muscle is regulated in the hypothalamus, which also regulates appetite and energy expenditure. In cachexia, proinflammatory cytokines, such as TNF-α, IL-1, IL-6 and Angiotensin II induce muscle atrophy. The mechanism is suggested via upregulation of MuRF1 and MAFbx. In contrast, the orexigenic peptide, AgRP and ghrelin have the effect to decrease proinflammatory cytokines and increase body weight, food intake, and muscle mass.

The understandings of the pathological mechanism of anorexia and muscle metabolism in view of the crosstalk between brain and muscle will open the new way for the management of cachexia. In this review, we describe recent experimental and clinical studies that have examined the regulation of food intake and muscle wasting in cachexia.

This article is part of a Directed Issue entitled: Molecular basis of muscle wasting.

Contents

1. Introduction

Food intake is controlled by a complex network that depends on the central regulation of energy homeostasis. Signals that regulate food intake are ultimately integrated or coordinated by central mechanisms, particularly those in the hypothalamus. Many factors must be considered in the hypothalamic regulation of food intake, and the interactions between adiposity and the central neuropeptidergic cascade downstream of leptin are increasingly being studied.

Cancer cachexia is the main cause of death in approximately 20% of cancer patients (Inui and Meguid, 2003). Cachexia is defined as a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass (Evans et al., 2008). Cachexia is highly associated with anorexia, weakness, weight loss, muscle wasting, and inflammation. Those phenotypes of cachexia affect mortality, morbidity, and quality of life (Lainscak et al., 2008).

☆ This article is part of a Directed Issue entitled: Molecular basis of muscle wasting.

* Corresponding author at: Department of Psychosomatic Internal Medicine, Kagoshima University Graduate School of Medical and Dental Sciences, 8-35-1 Sakuragaoka, Kagoshima 890-8520, Japan. Tel.: +81 99 275 5751; fax: +81 99 275 5749.
E-mail address: inui@m.kufm.kagoshima-u.ac.jp (A. Inui).

1357-2725/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.biocel.2013.07.016

Muscle wasting is the key feature of cachexia (Muscaritoli et al., 2010; Zhou et al., 2010). Prevention of muscle catabolism has been suggested to prolong survival independent of the disease course (Zhou et al., 2010). Although the pathological mechanisms of cachexia and muscle wasting have been under investigation, insights have primarily been gained on the association of muscle wasting and feeding-regulatory peptides such as leptin, ghrelin, and melanocortin (Molfino et al., 2010). Herein, we demonstrate the control of food intake and muscle wasting, focused on the interaction between brain and muscle.

2. Hypothalamic and peripheral regulation of muscle metabolism and food intake

The regulation of food intake is coordinated in the hypothalamus. In particular, the arcuate nucleus of the hypothalamus (ARC) is critical for appetite regulation. Many factors are implicated in the hypothalamic regulation of food intake, melanin-concentrating hormone (MCH), neuropeptide Y (NPY), agouti-related protein (AgRP), proopiomelanocortin (POMC), cocaine-and-amphetamine regulated transcript (CART). Of the peripheral peptides, ghrelin and leptin have the orexigenic and anorexigenic effects respectively, and make the regulatory feedback loop between the periphery and brain. There is another crosstalk between the brain and muscle, where melanocortin and ghrelin have the important role in the mechanism of cachexia (Fig. 1). Among the numerous circulating appetite regulating peptides, these two hormones, ghrelin and leptin are particularly important in cachexia, and we will principally discuss these two hormones here.

2.1. Melanocortins

The melanocortin system is a central component of the regulation of feeding. It is composed of two types of neurons, the neurons; NYP/AgRP and POMC/CART. These neurons are located in the ARC. NPY/AgRP neurons release the orexigenic peptides NPY and AgRP, an antagonist melanocortin, which increase food intake (Williams et al., 2011; Xu et al., 2011). By contrast, POMC neurons synthesize and secrete an anorexigenic peptide, α-melanocyte-stimulating hormone (α-MSH), which activates type4 melanocortin receptor (MC4R) and decreases food intake.

The increase of cytokines stimulates the central melanocortin system (Reyes and Sawchenko, 2002). Cytokines induce the hypothalamic expression of the serotonin, which stimulate POMC anorexigenic pathway. In the result MC4R is activated by serotonin leading to induce anorexia (Tecott, 2007).

A recent study has noted that AgRP, the endogenous inverse agonist at the melanocortin-4 receptor (MC4R), ameliorates cachexia associated with cancer (Joppa et al., 2007), uremia (Cheung et al., 2008), and chronic kidney disease (Cheung and Mak, 2012) by increasing food intake and reducing energy expenditure. Whereas the release of AgRP is diminished by inflammation, AgRP treatment decreases proinflammatory cytokines, and improves energy expenditure, food intake, muscle mass, body weight, fat mass (Joppa et al., 2007; Cheung and Mak, 2012). In contrast to AgRP administration, treatment of tumor-bearing rats with i.c.v. NPY worsens anorexia, suggesting that cachexia does not result from a selective reduction in NPY release (Grossberg et al., 2010a). In addition to AgRP, the administration of MC4-R antagonists increases food intake. The MC4-R blocker decreases cyclic adenosine monophosphate accumulation, indicating inverse agonist activity. Tumor-bearing mice treated with MC4-R blocker maintain lean body mass. Furthermore, orally available selective MC4-R antagonists also stimulate food intake and reduce cancer-induced cachexia in mice (Weyermann et al., 2009).

Together, AgRP and α-MSH will be the clues for the understanding of the underlying mechanism and possible therapeutic target for muscle wasting and anorexia.

2.2. Leptin

Leptin is a 16-kDa protein hormone secreted by adipocytes. Plasma leptin concentration increases in proportion to body fat mass and regulates food intake and energy expenditure to maintain body fat stores. Leptin acts in the hypothalamus, where it inhibits NPY and causes anorexia (Elmquist et al., 1999).

Leptin also plays a key role in cancer anorexia-cachexia syndrome (Engineer and Garcia, 2012). Circulating leptin levels are decreased in cancer cachexia animal models and in cancer cachexia patients (Werynska et al., 2009; Smiechowska et al., 2010). Furthermore, Leptin levels decreases gradually with tumor stage and aggressiveness (Salageanu et al., 2010). In esophageal cancer patients, leptin levels correlate directly with body mass index, tumor necrosis factor-alpha (TNF-α), albumin, and hemoglobin and indirectly with IL-6, IL-8, and high-sensitivity C-reactive protein (Diakowska et al., 2010).

Adipose-derived factors such as leptin, TNF-α, resistin, and adiponectin have been shown to affect muscle metabolism, protein dynamics, or both directly. Leptin mediates the production of inflammatory cytokines independent of its effects on food intake (Burgos-Ramos et al., 2012). Despite low leptin levels, leptin intense the inflammatory response and the levels of inflammatory cytokines. Proinflammatory cytokines, such as TNF-α, interleukin (IL)-1, and IL-6, have been proposed to cause cachexia by increasing the expression of the hypothalamic leptin receptor (Salageanu et al., 2010).

Although it is well known that leptin is an adipokine derived from adiposity, a recent study has suggested that cultured myocytes also release leptin (Wolsk et al., 2012). In skeletal muscle, insulin sensitivity is improved by enhancing intracellular glucose transporter type 4 transport (Sainz et al., 2012).

These studies imply that leptin acts to regulate muscle metabolism and the production of cytokines in addition to the control of appetite and energy expenditure in cachexia.

2.3. Ghrelin

Ghrelin is a peptide hormone that stimulates growth hormone release and positive energy balance via binding to growth hormone secretagogue receptor (GHSR)-1a. Patients with cancer cachexia exhibited increased circulating concentrations of ghrelin (Wolf et al., 2006). In recent study, it is suggested that ghrelin has the effect to decrease inflammatory cytokines. In fact, the inflammatory cytokines are decreased in ghrelin-treated animals. Ghrelin inhibits the expression of IL-1 receptor in the brainstem and decreases the expression of pro-hormone convertase-2, an enzyme involved in the processing of POMC to α-MSH. Ghrelin also increase the expression of AgRP and NPY in the hypothalamus (Deboer et al., 2008). Furthermore, ghrelin reduces the elevated mRNA expression of TNF-α and IL-6 in muscle and normalized plasma glucocorticoid levels (Balasubramaniam et al., 2009). Injection of ghrelin causes ghrelin resistance despite upregulation of hypothalamic GHS-R expression in MCG 101-bearing mice, which show characteristic anorexia, fat loss, and muscle wasting owing to increased concentration of prostaglandinE2 and proinflammatory cytokines (IL-1β, IL-6, TNF-α) (Wang et al., 2006).

Ghrelin has also have attention for its anticatabolic effects (Balasubramaniam et al., 2009; Sugiyama et al., 2012). Treatment with ghrelin and ghrelin receptor agonists increases food intake and improves lean body mass (Deboer et al., 2007, 2008).

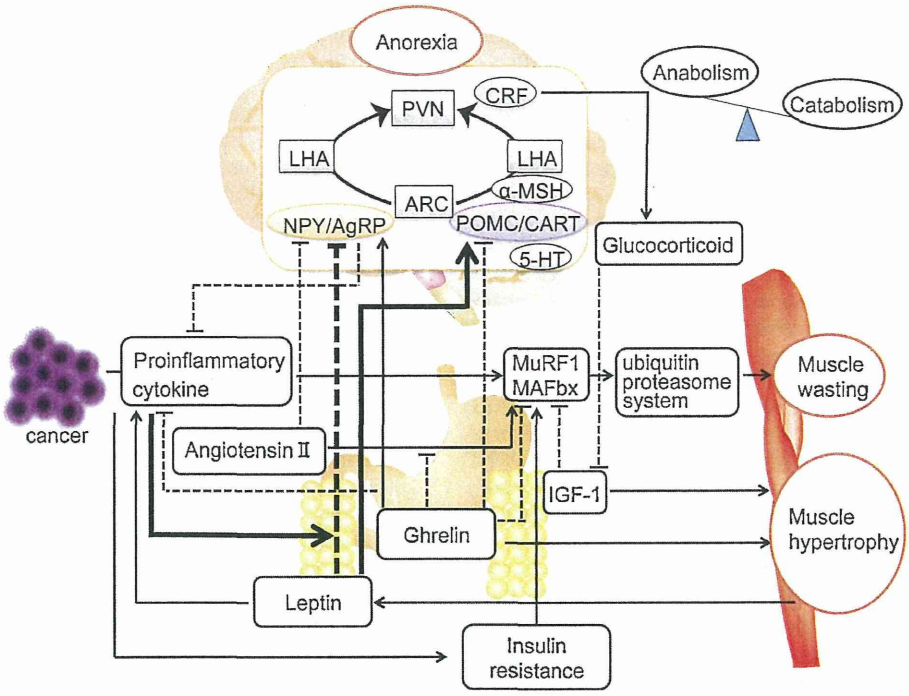


Fig. 1. The crosstalk between brain and muscle. Proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6, induce muscle atrophy via upregulation of MuRF1 and MAFbx. Insulin resistance is present in cancer cachexia. In insulin resistant state, PI3K activity is decreased, leading to increase MuRF1 and MAFbx, resulting in muscle atrophy. IGF-1 induces skeletal muscle hypertrophy, in contrast, inhibit muscle wasting by decreasing MuRF1 and MAFbx. Glucocorticoids induce muscle atrophy by inhibiting the action of insulin and IGF-1. Ghrelin has the effect to decrease inflammatory cytokines. Ghrelin inhibit the expression of MuRF-1 and MAFbx, lead to improve muscle catabolism. Ang II induces skeletal muscle atrophy by increasing MuRF-1. Ang II reduce food intake by inhibiting NPY expression in hypothalamus. Leptin mediates the production of inflammatory cytokines. Although leptin is decreased in cachexia, proinflammatory cytokines increase expression of the hypothalamic leptin receptor, leading to cause anorexia by inhibiting NPY/AgRP and increasing POMC/CART. AgRP has the effect to decrease proinflammatory cytokines and to increase body weight, food intake, and muscle mass. Muscle Ring Finger1 (MuRF1), Muscle Atrophy F-box (MAFbx), insulin-like growth factor 1 (IGF-1), Angiotensin II (Ang II), neuropeptide Y (NPY), agouti-related protein (AgRP), proopiomelanocortin (POMC), cocaine-and-amphetamine responsive transcript (CART), corticotrophin releasing factor (CRF), 5-hydroxytryptamine (5-HT), periventricular nucleus (PVN) arcuate nucleus (ARC), lateral hypothalamic area (LHA).

Ghrelin and its analogs improve body weight by regulating the expression of muscle ring finger 1 (MuRF-1) and muscle atrophy f-box (MAFbx) (Palus et al., 2011) further inhibiting the expression of myostatin in skeletal muscle (Lenk et al., 2013). Expression of the muscle-specific E3 ubiquitin ligases MuRF1 and MAFbx are normalized by ghrelin (Balasubramaniam et al., 2009). In angiotensin II induced muscle catabolism, ghrelin also improves body weight loss and skeletal muscle catabolism (Sugiyama et al., 2012).

Although only acyl ghrelin can bind GHSR, both ghrelin and des-acyl ghrelin stimulate proliferating C2C12 skeletal myoblasts to differentiate via activation of p38 (Filigheddu et al., 2007). The expression of des-acyl ghrelin impairs skeletal muscle atrophy induced by either fasting or denervation without stimulating muscle hypertrophy and GHSR-1a-mediated activation of the growth hormone/insulin-like growth factor-1 (IGF-1) axis (Porporato et al., 2013). In GHSR-deficient mice, both acyl ghrelin and des-acyl ghrelin induce phosphorylation of Akt in skeletal muscle and impair fasting-induced atrophy, implicating acyl ghrelin and des-acyl ghrelin in the blocking of skeletal muscle atrophy independent of growth hormones (Porporato et al., 2013).

Thus it is suggested that ghrelin and ghrelin receptor agonist has the therapeutic potential, which lead to improve skeletal muscle wasting as well as anorexia owing to its suppressive effect on muscle proteolysis and its anti-inflammatory action.

3. Cytokine actions within the regulatory feedback loop

In anorexia-cachexia syndrome, the balance between proinflammatory and anti-inflammatory cytokines is important for the development of the cachexia (Argiles et al., 2003). Inflammatory cytokines such as IL-1β, IL-6, TNF-α, and interferon-γ (IFN-γ) are potential causes of reduced food intake and increased energy expenditure (Plata-Salaman, 2001). By contrast, anti-inflammatory cytokines, including IL-4, IL-10, IL-12, and IL-15, have anti-cachectic properties. IL-15 increases glucose uptake in skeletal muscle (Busquets et al., 2006), and is reported as an anabolic factor for skeletal muscle. Muscle-derived IL-15 can decrease fat deposition and adipocyte metabolism via a muscle-to-fat endocrine pathway, and overexpression of IL-15 induces skeletal muscle hypertrophy in vitro (Quinn et al., 2002; Quinn, 2008). The administration of IL-12 to mice with colon-26 carcinoma alleviates body weight loss and other abnormalities associated with cachexia.

Proinflammatory cytokines initiate a cascade of events that ultimately leads to a state of wasting, malnourishment, and eventually death (Ramos et al., 2004). Those cytokines are involved in cancer related anorexia by increasing the levels of corticotrophin-releasing hormone, a central nervous anorexigenic neurotransmitter, lead to suppress food intake. They also mediate muscle atrophy. In particular, IL-1β, IL-6, TNF-α and leukemia inhibitory factor (LIF) have been associated with the initiating event in muscle catabolism in clinical and experimental cachexia. Acute and chronic central administration of IL-1β results in muscle atrophy (Braun et al., 2011). This effect is dependent on hypothalamic-pituitary-adrenal axis activation, as central nervous system IL-1β-induced atrophy is abrogated by adrenalectomy. These data suggest that central nervous system inflammation induces muscle atrophy via activation of the hypothalamic-pituitary-adrenal axis (Braun et al., 2011). IL-6 plays

an important role in regulating fat metabolism in muscle, increasing rates of fatty acid oxidation and attenuating the lipogenic effects of insulin. TNF-α levels are elevated in the circulations of patients with cancer cachexia (Argiles et al., 2003). TNF-α binds to its receptor and induces the activation of the NF-κB family of transcription factors (Von Haehling et al., 2002; Glass, 2005). NF-κB activation was shown to be required for cytokine-induced loss of skeletal muscle proteins (Glass, 2005). IL-6 plays a crucial role in the para-neoplastic syndromes, including anorexia and cachexia (Barton, 2005). LIF expression in the pituitary is necessary to drive increased POMC mRNA expression and adrenocorticotropic hormone release by pituitary corticotrophs in response to inflammation (Ray et al., 1998; Chesnokova and Melmed, 2000). Gp130 is the signal-transducing subunit of the LIF-receptor complex. This process is depend on gp130-mediated activation of Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling, which underlies the induction of POMC mRNA expression by leptin, suggesting that LIF may activate hypothalamic POMC neurons in a similar manner (Stefana et al., 1996; Bates et al., 2003). Indeed, LIF induces anorexia by directly activating POMC neurons (Grossberg et al., 2010a, 2010b).

In an animal model of anorexia-cachexia syndrome with deregulated expression of a number of cytokines including IL-10, pharmacologic intervention to impair protein synthesis restores cytokine production to near normal levels, delays anorexia-cachexia progression, and extends host survival (Robert et al., 2012). These findings suggest a new therapeutic possibility for the treatment of anorexia-cachexia syndrome that targets protein synthesis by blocking the production of procachexic factors. Those cytokines act via the hypothalamic central melanocortin system to regulate skeletal muscle metabolism (Braun and Marks, 2011).

4. Pathological mechanism of muscle wasting

Progressive impairment of skeletal muscle is associated with debility, morbidity, and mortality. In catabolic balance, proteolysis and lipolysis are induced leading to the depletion of protein mass and adipose tissue. Muscle wasting appears primarily to be mediated by the activation of the ubiquitin proteasome system (Attaix et al., 1999; Baracos, 2002). Three enzymatic components are required for the muscle metabolism regulating process, an E1 ubiquitin-activating enzyme, an E2 ubiquitin-conjugating enzyme, and an E3 ubiquitin ligating enzyme. Skeletal muscle atrophy occurs via the induction of the E3 ubiquitin ligases. In the model of skeletal muscle atrophy, two ubiquitin ligases have been identified: MuRF1 (Bodine et al., 2001) and MAFbx, also called atrogin-1 (Gomes et al., 2001). These ubiquitin ligases are significantly upregulated under atrophy conditions. The expression of MuRF1 and MAFbx is negatively regulated by insulin/IGF-I signaling (Sacheck et al., 2004).

Another cause of muscle wasting is the TNF-induced weak inducer of apoptosis (TWEAK) and tumor necrosis factor receptor-associated factor 6 (TRAF6), which has been identified as a novel inducer of skeletal muscle wasting. Adult skeletal muscles express minimal levels of Fn14, the bona fide TWEAK receptor. Specific conditions of atrophy such as denervation, immobilization, and unloading rapidly induce the expression of Fn14, leading to TWEAK-induced activation of various proteolytic pathways in skeletal muscle (Kumar et al., 2012).

Angiotensin II (Ang II) induces body weight loss and skeletal muscle catabolism through the ubiquitin-proteasome pathway. Ang II is elevated in cachexia and induces skeletal muscle atrophy by increasing the expression of E3 ligases atrogin-1/MuRF-1. Ang II reduces phosphorylation of AMP-activated protein kinase, an enzyme that regulates NPY expression (Yoshida et al., 2012). Intra-cerebro-ventricular Ang II infusion reduced food intake, and Ang II dose-dependently reduces NPY and orexin expression in hypothalamus (Yoshida et al., 2012). In recent important study, pharmacological blockade of ActRIIB pathway prevents muscle wasting and furthermore dramatically prolongs survival, in the animals in which tumor growth is not inhibited and fat loss and production of proinflammatory cytokines are not reduced (Zhou et al., 2010). ActRIIB pathway blockade abolished the activation of the ubiquitin-proteasome system and the induction of atrophy-specific ubiquitin ligases in muscles and also markedly stimulated muscle stem cell growth (Zhou et al., 2010). This study suggested an important link between activation of the ActRIIB pathway and the development of cancer cachexia.

Branched-chain amino acids such as leucine and valine significantly suppress the loss of body weight through an increase in protein synthesis and a decrease in degradation. Branched-chain amino acids exert anticatabolic effects by promoting protein synthesis and inhibiting intracellular proteolytic pathways (Berk et al., 2008). A recent study has shown that dietary leucine supplementation inhibits muscle protein breakdown in rats. In cultured muscle cells, insulin and leucine have been found to act additively in down regulating E2 ubiquitin-conjugating enzyme expression (Sadiq et al., 2007), whereas branched-chain amino acids reduces atrogin-1 and MuRF1 expression (Herningtyas et al., 2008; Op Den Kamp et al., 2009).

The eicosanoids affect the inflammatory process and are implicated in the process of cancer cachexia. They are unsaturated C20 fatty acids which can be separated into two main groups: lipoxygenase products including leukotrienes and lipoxins, and prostanoids including prostaglandins, prostacyclin and thromboxane. Eicosanoids play a role in generating inflammatory response, which induces peripheral tissue loss. Additionally, eicosanoids play a role in signaling the inflammatory mediators or catabolic factors, for example proteolysis-inducing factor (Ross and Fearon, 2002).

5. Glucocorticoid and insulin signaling

Endogenous glucocorticoids and impaired insulin signaling are also important for muscle catabolism (Dardevet et al., 1998; Schakman et al., 2005; Hu et al., 2009). The stimulation of muscle proteolysis requires 2 events; increased glucocorticoid levels and impaired insulin signaling. Glucocorticoids inhibit protein synthesis and increase the rate of protein breakdown. Glucocorticoids induce muscle atrophy by inhibiting the action of insulin and IGF-1. Growth hormones and IGF-1 stimulate skeletal muscle protein synthesis, whereas the expression of cytokines in skeletal muscle may negatively regulate the autocrine synthesis of IGF-I (Broussard et al., 2003; Frost and Lang, 2004). IGF-I increases muscle mass, whereas myostatin inhibits its development. Although IGF-I is a potent determinant of protein degradation in vitro and is antagonized by glucocorticoids, the glucocorticoid antagonist is insufficient to block muscle wasting (Pickering et al., 2003). In the presence of insulin/IGF-I, Akt-mediated phosphorylation inhibits FoxO nuclear translocation, suppressing FoxO-dependent transcription of atrogin-1 and MuRF1, which in turn inhibits skeletal muscle atrophy (Op Den Kamp et al., 2009).

FoxO activation is associated with the progression of muscle atrophy in cachexia (Reed et al., 2012). The FoxO pathway is activated in skeletal muscle during cachexia. Inhibition of FoxO transcriptional activity prevents muscle fiber atrophy during cachexia and induces hypertrophy (Reed et al., 2012).

Muscle hyperexpressing IGF-1 in both young and aged animals display definitively increased fiber cross-sectional area. By contrast, loss of muscle mass or reduction of fiber size in tumor-bearing mice is not modified by IGF-1 expression (Penna et al., 2010). These

Table 1
Clinical studies on the treatment of cachexia and sarcopenia.

Drug	Company	Type	Pathological condition	Phase of trials	References
Megace ES	Par Pharmaceutical	Carnitine + celecoxib +/− megestrol acetate	Cancer	Phase III	Madeddu et al. (2012)
Anamorelin	Helsinn Therapeutics	Ghrelin receptor agonist	Cancer	Phase III	Garcia et al. (2013)
EPA	Nestle, Danone, Abbott, Fresenius	SOD agonist and UPP activator	Cancer	Phase II/III	Barber (2001), Hardman (2004) and Fearon et al. (2006)
H-4864-GMP	Bachem	Human ghrelin	Cancer	Phase II	Neary et al. (2004)
GT_X-024 (enobosarm)	GT_X	Selective androgen receptor modular (SARM)	Cancer	Phase II	Dalton et al. (2011) and Dobs et al. (2013)
U-1250	Bachem	Synthetic human ghrelin	Cancer	Phase II	Strasser et al. (2008)
P-0861	Polypeptide Laboratories	Synthetic human ghrelin	Cancer	Phase II	Lundholm et al. (2010)
SUN11031	Asubio Pharmaceuticals	Synthetic human ghrelin	COPD	Phase II	Levinson and Gertner (2012)
INCB018424	Incyte	Jak1/2 inhibitor	Leukemia	Phase II	Eghtedar et al. (2012)
OHR118	OHR Pharmaceutical	Peptide nucleic acid immunomodulator	AIDS	Phase II	Chasen et al. (2011)
Celecoxib (Celebrex)	Pfizer	COX-2 inhibitor	Cancer	Phase II	Mantovani et al. (2010)
MT-102	PsiOxus Therapeutics	β-blocker	Cancer	Phase II	Stewart Coats et al. (2011)
ALD518 (BMS-945429)	Alder Biopharmaceuticals	Humanized IL-6 monoclonal antibody	Cancer	Phase II	Bayliss et al. (2011)
CK-2017357	Cytokinetics	Skeletal muscle troponin activator	ALS	Phase II	Shefner et al. (2012)

5-HT2b/2c = 5-hydroxytryptamine 2b/2c; EPA = eicosapentaenoic acid; SOD = superoxide dismutase; UPP = ubiquitin proteasome pathway; COPD = chronic obstructive pulmonary disease; AIDS = acquired immune deficiency syndrome; COX-2 = cyclooxygenase-2; ALS = amyotrophic lateral sclerosis; MC4 = melanocortin-4; CRF2R = corticotropin-releasing factor 2 receptor.

results demonstrate that muscle wasting is not associated with the downregulation of molecules involved in anabolic response and appears inconsistent with reduced activity of the IGF-1 signaling pathway (Penna et al., 2010).

On the other hand, IL-6 and TNF-α cause insulin resistance, IGF-1 resistance, and reduce the levels of testosterone and luteinizing hormone. IL-6 family ligands activate the JAK/STAT3 pathway. Skeletal muscle STAT3 phosphorylation, nuclear localization, and target gene expression are activated in cancer cachexia. STAT3 activation is a common feature of muscle wasting, activated in muscle by IL-6 in vivo and in vitro and by different types of cancer (Bonetto et al., 2012). STAT3 is a primary mediator of muscle wasting in cancer cachexia and other conditions of IL-6 family signaling (Bonetto et al., 2012).

6. Possible treatments for cancer-cachexia and muscle wasting

Weight loss, fatigue, and markers of systemic inflammation are most strongly and consistently associated with adverse quality of life, reduced functional capabilities, increased symptoms and shorter survival (Wallengren et al., 2013). Recently, several different therapeutic entities has emerged and under investigation in pre-clinical and in clinical models. The therapeutic target for cachexia is including ghrelin and ghrelin analogs, selective androgen receptor modulators (SARMs), testosterone, insulin-like growth factor, myostatin antibodies, and also melanocortin-4 receptor antagonist. Recently, several interventional trials have been performed in humans, and some promising treatments are in phase III (Table 1).

Ghrelin is a leading candidate for muscle wasting treatment because ghrelin levels are elevated in cancer cachexia and ghrelin controls mediators involved in the cachectic process (Argiles and Stemmler, 2013). In the clinical study, ghrelin treatment markedly increased energy intake and increased appetite (Neary et al., 2004). In other study, daily and long-term provision of ghrelin to weight-losing cancer patients with solid tumors improved appetite, and attenuated catabolism in a randomized, double-blind, phase 2 study (Lundholm et al., 2010).

Anamorelin, an orally activated ghrelin receptor agonist, has been shown to increase body weight and anabolic hormone levels in healthy volunteers and is being investigated for the treatment of cancer cachexia. Anamorelin increases appetite and body weight in cancer patients (Garcia et al., 2013). A phase III, randomized, placebo-controlled clinical trial assessing anamorelin hydrochloride in patients with cachexia is recruiting patients (Fearon et al., 2013).

The traditional Japanese medicine rikkunshito helps stimulate endogenous ghrelin secretion by blocking the serotonin 2b/2c receptor pathway and enhancing GHSR activity. Rikkunshito has been shown to increase food intake in rats that have cancer or have been administered chemotherapeutics (Fujitsuka et al., 2011). Although ghrelin attenuates anorexia-cachexia in the short term, it does not prolong survival (Fujitsuka et al., 2011), whereas rikkunshito improves anorexia, gastrointestinal dysmotility, muscle wasting, and anxiety-related behavior and prolongeds survival in animals and patients with cancer (Fujitsuka et al., 2011). The appetite-stimulating effect of rikkunshito is blocked by (D-Lys3)-GHRP-6. The active components of rikkunshito, hesperidin and atractylodin, potentiate ghrelin secretion and receptor signaling, respectively, and atractylodin prolonged survival in tumor-bearing rats (Fujitsuka et al., 2011). A potentiator of ghrelin signaling such as rikkunshito may represent a novel approach for the treatment of cancer cachexia (Hattori, 2010; Fujitsuka et al., 2012). Larger clinical trials are required to develop ghrelin into an available and reimbursable pharmaceutical intervention (Strasser, 2012).

Enobosarm, nonsteroidal SARMs has tissue-selective anabolic effects in muscle and bone. Selective androgen receptor modulators have been developed for the treatment of muscle wasting. In a double-blind, placebo-controlled phase II trial, enobosarm improved lean body mass and physical function in healthy elderly men (Dalton et al., 2011).

A weight-loss study conducted on cancer patients using a randomized controlled trial of weekly nandrolone decanoate for 4 weeks in combination with standard chemotherapy (Bossola et al., 2007) demonstrated significantly longer survival time in the group receiving androgen therapy with a trend for less severe weight loss with nandrolone decanoate. Testosterone is capable of reducing systemic inflammatory cytokines such as TNF-α, IL1-β, and IL-6 and stimulating the anti-inflammatory cytokine IL-10 (Malkin et al., 2004).

Recent studies also propose the combination therapies like megestrol acetate plus L-carnitine, celecoxib (Madeddu et al., 2012). We hope the progress of clinical trials and the establishment of new therapeutic guidelines in the future.

7. Conclusion

Anorexia-cachexia and muscle wasting affect morbidity, mortality, and quality of life. A considerable amount of recent progress has been made in the understanding of the brain-muscle crosstalk, which mediate the food intake and muscle atrophy. Although the pathological mechanism of anorexia-cachexia and muscle wasting has been revealed, available and satisfactory treatment has not yet emerged. These findings help to give hope for the future novel drug target. Further clinical randomized studies are needed to enhance beneficial nutritional and improve clinical outcomes of patients with cachexia.

Acknowledgements

I appreciate to the staffs of Kagoshima University for their enthusiastic support.

References

Argiles JM, Busquets S, Lopez-Soriano FJ. Cytokines in the pathogenesis of cancer cachexia. Current Opinion in Clinical Nutrition and Metabolic Care 2003;6:401–6.
Argiles JM, Stemmler B. The potential of ghrelin in the treatment of cancer cachexia. Expert Opinion on Biological Therapy 2013;13:67–76.
Attaix D, Combaret L, Tilignac T, Taillandier D. Adaptation of the ubiquitin-proteasome proteolytic pathway in cancer cachexia. Molecular Biology Reports 1999;26:77–82.
Balasubramaniam A, Joshi R, Su C, Friend LA, Sheriff S, Kagan RJ, et al. Ghrelin inhibits skeletal muscle protein breakdown in rats with thermal injury through normalizing elevated expression of E3 ubiquitin ligases MuRF1 and MAFbx. American Journal of Physiology – Regulatory, Integrative and Comparative Physiology 2009;296:R893–901.
Baracos VE. Hypercatabolism and hypermetabolism in wasting states. Current Opinion in Clinical Nutrition and Metabolic Care 2002;5:237–9.
Barber MD. Cancer cachexia and its treatment with fish-oil-enriched nutritional supplementation. Nutrition 2001;17:751–5.
Barton BE. Interleukin-6 and new strategies for the treatment of cancer, hyperproliferative diseases and paraneoplastic syndromes. Expert Opinion on Therapeutic Targets 2005;9:737–52.
Bates SH, Stearns WH, Dundon TA, Schubert M, Tso AW, Wang Y, et al. STAT3 signalling is required for leptin regulation of energy balance but not reproduction. Nature 2003;421:856–9.
Bayliss TJ, Smith JT, Schuster M, Dragnev KH, Rigas JR. A humanized anti-IL-6 antibody (ALD518) in non-small cell lung cancer. Expert Opinion on Biological Therapy 2011;11:1663–8.
Berk L, James J, Schwartz A, Hug E, Mahadevan A, Samuels M, et al. A randomized, double-blind, placebo-controlled trial of a beta-hydroxyl beta-methyl butyrate, glutamine, and arginine mixture for the treatment of cancer cachexia (RTOG 0122). Supportive Care in Cancer 2008;16:1179–88.
Bodine SC, Latres E, Baumhueter S, Lai VK, Nunez L, Clarke BA, et al. Identification of ubiquitin ligases required for skeletal muscle atrophy. Science 2001;294:1704–8.
Bonetto A, Aydogdu T, Jin X, Zhang Z, Zhan R, Puzis L, et al. JAK/STAT3 pathway inhibition blocks skeletal muscle wasting downstream of IL-6 and in experimental cancer cachexia. American Journal of Physiology – Endocrinology and Metabolism 2012;303:E410–21.
Bossola M, Pacelli F, Tortorelli A, Doglietto GB. Cancer cachexia: it's time for more clinical trials. Annals of Surgical Oncology 2007;14:276–85.
Braun TP, Marks DL. Hypothalamic regulation of muscle metabolism. Current Opinion in Clinical Nutrition and Metabolic Care 2011;14:237–42.
Braun TP, Zhu X, Szumowski M, Scott GD, Grossberg AJ, Levasseur PR, et al. Central nervous system inflammation induces muscle atrophy via activation of the hypothalamic-pituitary-adrenal axis. Journal of Experimental Medicine 2011;208:2449–63.
Broussard SR, Mccusker RH, Novakofski JE, Strle K, Shen WH, Johnson RW, et al. Cytokine-hormone interactions: tumor necrosis factor alpha impairs biologic activity and downstream activation signals of the insulin-like growth factor I receptor in myoblasts. Endocrinology 2003;144:2988–96.
Burgos-Ramos E, Canelles S, Perianes-Cachero A, Arilla-Ferreiro E, Argente J, Barrios V. Adipose tissue promotes a serum cytokine profile related to lower insulin sensitivity after chronic central leptin infusion. PLoS ONE 2012;7:e46893.
Busquets S, Figueras M, Almendro V, Lopez-Soriano FJ, Argiles JM. Interleukin-15 increases glucose uptake in skeletal muscle. An antidiabetogenic effect of the cytokine. Biochimica et Biophysica Acta 2006;1760:1613–7.
Chasen M, Hirschman SZ, Bhargava R. Phase II study of the novel peptide-nucleic acid OHR118 in the management of cancer-related anorexia/cachexia. Journal of the American Medical Directors Association 2011;12:62–7.
Chesnokova V, Melmed S. Leukemia inhibitory factor mediates the hypothalamic pituitary adrenal axis response to inflammation. Endocrinology 2000;141:4032–40.
Cheung WW, Mak RH. Melanocortin antagonism ameliorates muscle wasting and inflammation in chronic kidney disease. American Journal of Physiology Renal Physiology 2012;303:F1315–24.
Cheung WW, Rosengren S, Boyle DL, Mak RH. Modulation of melanocortin signaling ameliorates uremic cachexia. Kidney International 2008;74:180–6.
Dalton JT, Barnette KG, Bohl CE, Hancock ML, Rodriguez D, Dodson ST, et al. The selective androgen receptor modulator GTx-024 (enobosarm) improves lean body mass and physical function in healthy elderly men and postmenopausal women: results of a double-blind, placebo-controlled phase II trial. Journal of Cachexia, Sarcopenia and Muscle 2011;2:153–61.
Dardevet D, Sornet C, Savary I, Debras E, Patureau-Mirand P, Grizard J. Glucocorticoid effects on insulin- and IGF-I-regulated muscle protein metabolism during aging. Journal of Endocrinology 1998;156:83–9.
Deboer MD, Zhu X, Levasseur PR, Inui A, Hu Z, Han G, et al. Ghrelin treatment of chronic kidney disease: improvements in lean body mass and cytokine profile. Endocrinology 2008;149:827–35.
Deboer MD, Zhu XX, Levasseur P, Meguid MM, Suzuki S, Inui A, et al. Ghrelin treatment causes increased food intake and retention of lean body mass in a rat model of cancer cachexia. Endocrinology 2007;148:3004–12.
Diakowska D, Krzystek-Korpacka M, Markocka-Maczka K, Diakowski W, Matusiewicz M, Grabowski K. Circulating leptin and inflammatory response in esophageal cancer, esophageal cancer-related cachexia-anorexia syndrome (CAS) and non-malignant CAS of the alimentary tract. Cytokine 2010;51:132–7.
Dobs AS, Boccia RV, Croot CC, Gabrail NY, Dalton JT, Hancock ML, et al. Effects of enobosarm on muscle wasting and physical function in patients with cancer: a double-blind, randomised controlled phase 2 trial. Lancet Oncology 2013;14:335–45.
Eghtedar A, Verstovsek S, Estrov Z, Burger J, Cortes J, Bivins C, et al. Phase 2 study of the JAK kinase inhibitor ruxolitinib in patients with refractory leukemias, including postmyeloproliferative neoplasm acute myeloid leukemia. Blood 2012;119:4614–8.
Elmquist JK, Elias CF, Saper CB. From lesions to leptin: hypothalamic control of food intake and body weight. Neuron 1999;22:221–32.
Engineer DR, Garcia JM. Leptin in anorexia and cachexia syndrome. International Journal of Peptides 2012;2012:287457.
Evans WJ, Morley JE, Argiles J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. Clinical Nutrition 2008;27:793–9.
Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. Nature Reviews Clinical Oncology 2013;10:90–9.
Fearon KC, Barber MD, Moses AG, Ahmedzai SH, Taylor GS, Tisdale MJ, et al. Double-blind, placebo-controlled, randomized study of eicosapentaenoic acid diester in patients with cancer cachexia. Journal of Clinical Oncology 2006;24:3401–7.
Filigheddu N, Gnocchi VF, Coscia M, Cappelli M, Porporato PE, Taulli R, et al. Ghrelin and des-acyl ghrelin promote differentiation and fusion of C2C12 skeletal muscle cells. Molecular Biology of the Cell 2007;18:986–94.
Frost RA, Lang CH. Alteration of somatotropic function by proinflammatory cytokines. Journal of Animal Science 2004;82(E-Suppl.):E100–9.
Fujitsuka N, Asakawa A, Amitani H, Hattori T, Inui A. Efficacy of ghrelin in cancer cachexia: clinical trials and a novel treatment by rikkunshito. Critical Reviews in Oncogenesis 2012;17:277–84.
Fujitsuka N, Asakawa A, Uezono Y, Minami K, Yamaguchi T, Niijima A, et al. Potentiation of ghrelin signaling attenuates cancer anorexia-cachexia and prolongs survival. Translational Psychiatry 2011;1:e23.
Garcia JM, Friend J, Allen S. Therapeutic potential of anamorelin, a novel, oral ghrelin mimetic, in patients with cancer-related cachexia: a multicenter, randomized, double-blind, crossover, pilot study. Supportive Care in Cancer 2013;21:129–37.
Glass DJ. Skeletal muscle hypertrophy and atrophy signaling pathways. International Journal of Biochemistry and Cell Biology 2005;37:1974–84.
Gomes MD, Lecker SH, Jagoe RT, Navon A, Goldberg AL. Atrogin-1, a muscle-specific F-box protein highly expressed during muscle atrophy. Proceedings of the National Academy of Sciences of the United States of America 2001;98:14440–5.
Grossberg AJ, Scarlett JM, Marks DL. Hypothalamic mechanisms in cachexia. Physiology and Behavior 2010a;100:478–89.
Grossberg AJ, Scarlett JM, Zhu X, Bowe DD, Batra AK, Braun TP, et al. Arcuate nucleus proopiomelanocortin neurons mediate the acute anorectic actions of leukemia inhibitory factor via gp130. Endocrinology 2010b;151:606–16.

Hardman WE. (n-3) fatty acids and cancer therapy. Journal of Nutrition 2004;134:3427S–30S.
Hattori T. Rikkunshito and ghrelin. International Journal of Peptides 2010:2010.
Herningtyas EH, Okimura Y, Handayaningsih AE, Yamamoto D, Maki T, Iida K, et al. Branched-chain amino acids and arginine suppress MaFbx/atrogin-1 mRNA expression via mTOR pathway in C2C12 cell line. Biochimica et Biophysica Acta 2008;1780:1115–20.
Hu Z, Wang H, Lee IH, Du J, Mitch WE. Endogenous glucocorticoids and impaired insulin signaling are both required to stimulate muscle wasting under pathophysiological conditions in mice. Journal of Clinical Investigation 2009;119:3059–69.
Inui A, Meguid MM. Cachexia and obesity: two sides of one coin? Current Opinion in Clinical Nutrition and Metabolic Care 2003;6:395–9.
Joppa MA, Gogas KR, Foster AC, Markison S. Central infusion of the melanocortin receptor antagonist agouti-related peptide (AgRP(83-132)) prevents cachexia-related symptoms induced by radiation and colon-26 tumors in mice. Peptides 2007;28:636–42.
Kumar A, Bhatnagar S, Paul PK. TWEAK and TRAF6 regulate skeletal muscle atrophy. Current Opinion in Clinical Nutrition and Metabolic Care 2012;15:233–9.
Lainscak M, Filippatos GS, Gheorghiade M, Fonarow GC, Anker SD. Cachexia: common, deadly, with an urgent need for precise definition and new therapies. American Journal of Cardiology 2008;101:8E–10E.
Lenk K, Palus S, Schur R, Datta R, Dong J, Culler MD, et al. Effect of ghrelin and its analogues, BIM-28131 and BIM-28125, on the expression of myostatin in a rat heart failure model. Journal of Cachexia, Sarcopenia and Muscle 2013;4:63–9.
Levinson B, Gertner J. Randomized study of the efficacy and safety of SUN11031 (synthetic human ghrelin) in cachexia associated with chronic obstructive pulmonary disease. e-SPEN Journal 2012;7:e171–5.
Lundholm K, Gunnebo L, Korner U, Iresjo BM, Engstrom C, Hyltander A, et al. Effects by daily long term provision of ghrelin to unselected weight-losing cancer patients: a randomized double-blind study. Cancer 2010;116:2044–52.
Madeddu C, Dessi M, Panzone F, Serpe R, Antoni G, Cau MC, et al. Randomized phase III clinical trial of a combined treatment with carnitine + celecoxib +/– megestrol acetate for patients with cancer-related anorexia/cachexia syndrome. Clinical Nutrition 2012;31:176–82.
Malkin CJ, Pugh PJ, Jones RD, Kapoor D, Channer KS, Jones TH. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. Journal of Clinical Endocrinology and Metabolism 2004;89:3313–8.
Mantovani G, Maccio A, Madeddu C, Serpe R, Antoni G, Massa E, et al. Phase II nonrandomized study of the efficacy and safety of COX-2 inhibitor celecoxib on patients with cancer cachexia. Journal of Molecular Medicine (Berlin) 2010;88:85–92.
Molfino A, Laviano A, Rossi Fanelli F. Contribution of anorexia to tissue wasting in cachexia. Current Opinion in Supportive and Palliative Care 2010;4:249–53.
Muscaritoli M, Anker SD, Argiles J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clinical Nutrition 2010;29:154–9.
Neary NM, Small CJ, Wren AM, Lee JL, Druce MR, Palmieri C, et al. Ghrelin increases energy intake in cancer patients with impaired appetite: acute, randomized, placebo-controlled trial. Journal of Clinical Endocrinology and Metabolism 2004;89:2832–6.
Op Den Kamp CM, Langen RC, Haegens A, Schols AM. Muscle atrophy in cachexia: can dietary protein tip the balance? Current Opinion in Clinical Nutrition and Metabolic Care 2009;12:611–6.
Palus S, Schur R, Akashi YJ, Bockmeyer B, Datta R, Halem H, et al. Ghrelin and its analogues, BIM-28131 and BIM-28125, improve body weight and regulate the expression of MuRF-1 and MAFbx in a rat heart failure model. PLoS ONE 2011;6:e26865.
Penna F, Bonetto A, Muscaritoli M, Costamagna D, Minero VG, Bonelli G, et al. Muscle atrophy in experimental cancer cachexia: is the IGF-1 signaling pathway involved? International Journal of Cancer 2010;127:1706–17.
Pickering WP, Baker FE, Brown J, Butler HL, Govindji S, Parsons JM, et al. Glucocorticoid antagonist RU38486 fails to block acid-induced muscle wasting in vivo or in vitro. Nephrology, Dialysis, Transplantation 2003;18:1475–84.
Plata-Salaman CR. Cytokines and feeding. International Journal of Obesity and Related Metabolic Disorders 2001;25(Suppl. 5):S48–52.
Porporato PE, Filigheddu N, Reano S, Ferrara M, Angelino E, Gnocchi VF, et al. Acylated and unacylated ghrelin impair skeletal muscle atrophy in mice. Journal of Clinical Investigation 2013.
Quinn LS. Interleukin-15: a muscle-derived cytokine regulating fat-to-lean body composition. Journal of Animal Science 2008;86:E75–83.
Quinn LS, Anderson BG, Drivdahl RH, Alvarez B, Argiles JM. Overexpression of interleukin-15 induces skeletal muscle hypertrophy in vitro: implications for treatment of muscle wasting disorders. Experimental Cell Research 2002;280:55–63.
Ramos EJB, Suzuki S, Marks D, Inui A, Asakawa A, Meguid MM. Cancer anorexia-cachexia syndrome: cytokines and neuropeptides. Current Opinion in Clinical Nutrition and Metabolic Care 2004;7:427–34.
Ray DW, Ren SG, Melmed S. Leukemia inhibitory factor regulates proopiomelanocortin transcription. Annals of the New York Academy of Sciences 1998;840:162–73.
Reed SA, Sandesara PB, Senf SM, Judge AR. Inhibition of FoxO transcriptional activity prevents muscle fiber atrophy during cachexia and induces hypertrophy. FASEB Journal 2012;26:987–1000.
Reyes TM, Sawchenko PE. Involvement of the arcuate nucleus of the hypothalamus in interleukin-1-induced anorexia. Journal of Neuroscience 2002;22:5091–9.
Robert F, Mills JR, Agenor A, Wang D, Dimarco S, Cencic R, et al. Targeting protein synthesis in a Myc/mTOR-driven model of anorexia-cachexia syndrome delays its onset and prolongs survival. Cancer Research 2012;72:747–56.
Ross JA, Fearon KC. Eicosanoid-dependent cancer cachexia and wasting. Current Opinion in Clinical Nutrition and Metabolic Care 2002;5:241–8.
Sacheck JM, Ohtsuka A, Mclary SC, Goldberg AL. IGF-I stimulates muscle growth by suppressing protein breakdown and expression of atrophy-related ubiquitin ligases, atrogin-1 and MuRF1. American Journal of Physiology – Endocrinology and Metabolism 2004;287:E591–601.
Sadiq F, Hazlerigg DG, Lomax MA. Amino acids and insulin act additively to regulate components of the ubiquitin-proteasome pathway in C2C12 myotubes. BMC Molecular Biology 2007;8:23.
Sainz N, Rodriguez A, Catalan V, Becerril S, Ramirez B, Lancha A, et al. Leptin reduces the expression and increases the phosphorylation of the negative regulators of GLUT4 traffic TBC1D1 and TBC1D4 in muscle of ob/ob mice. PLoS ONE 2012;7:e29389.
Salageanu A, Tucureanu C, Lerescu L, Caras I, Pitica R, Gangura G, et al. Serum levels of adipokines resistin and leptin in patients with colon cancer. Journal of Medicine and Life 2010;3:416–20.
Schakman O, Gilson H, De Coninck V, Lause P, Verniers J, Havaux X, et al. Insulin-like growth factor-I gene transfer by electroporation prevents skeletal muscle atrophy in glucocorticoid-treated rats. Endocrinology 2005;146:1789–97.
Shefner J, Cedarbaum JM, Cudkowicz ME, Maragakis N, Lee J, Jones D, et al. Safety, tolerability and pharmacodynamics of a skeletal muscle activator in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis 2012;13:430–8.
Smiechowska J, Utech A, Taffet G, Hayes T, Marcelli M, Garcia JM. Adipokines in patients with cancer anorexia and cachexia. Journal of Investigative Medicine 2010;58:554–9.
Stefana B, Ray DW, Melmed S. Leukemia inhibitory factor induces differentiation of pituitary corticotroph function: an immuno-neuroendocrine phenotypic switch. Proceedings of the National Academy of Sciences of the United States of America 1996;93:12502–6.
Stewart Coats AJ, Srinivasan V, Surendran J, Chiramana H, Vangipuram SR, Bhatt NN, et al. The ACT-ONE trial, a multicentre, randomised, double-blind, placebo-controlled, dose-finding study of the anabolic/catabolic transforming agent, MT-102 in subjects with cachexia related to stage III and IV non-small cell lung cancer and colorectal cancer: study design. Journal of Cachexia, Sarcopenia and Muscle 2011;2:201–7.
Strasser F. Clinical application of ghrelin. Current Pharmaceutical Design 2012;18:4800–12.
Strasser F, Lutz TA, Maeder MT, Thuerlimann B, Bueche D, Tschop M, et al. Safety, tolerability and pharmacokinetics of intravenous ghrelin for cancer-related anorexia/cachexia: a randomised, placebo-controlled, double-blind, double-crossover study. British Journal of Cancer 2008;98:300–8.
Sugiyama M, Yamaki A, Furuya M, Inomata N, Minamitake Y, Ohsuye K, et al. Ghrelin improves body weight loss and skeletal muscle catabolism associated with angiotensin II-induced cachexia in mice. Regulatory Peptides 2012;178:21–8.
Tecott LH. Serotonin and the orchestration of energy balance. Cell Metabolism 2007;6:352–61.
Von Haehling S, Genth-Zotz S, Anker SD, Volk HD. Cachexia: a therapeutic approach beyond cytokine antagonism. International Journal of Cardiology 2002;85:173–83.
Wallengren O, Lundholm K, Bosaeus I. Diagnostic criteria of cancer cachexia: relation to quality of life, exercise capacity and survival in unselected palliative care patients. Supportive Care in Cancer 2013.
Wang W, Andersson M, Iresjo BM, Lonnroth C, Lundholm K. Effects of ghrelin on anorexia in tumor-bearing mice with eicosanoid-related cachexia. International Journal of Oncology 2006;28:1393–400.
Werynska B, Kosacka M, Golecki M, Jankowska R. Leptin serum levels in cachectic and non-cachectic lung cancer patients. Pneumonologia i Alergologia Polska 2009;77:500–6.
Weyermann P, Dallmann R, Magyar J, Anklin C, Hufschmid M, Dubach-Powell J, et al. Orally available selective melanocortin-4 receptor antagonists stimulate food intake and reduce cancer-induced cachexia in mice. PLoS ONE 2009;4:e4774.
Williams KW, Scott MM, Elmquist JK. Modulation of the central melanocortin system by leptin, insulin, and serotonin: co-ordinated actions in a dispersed neuronal network. European Journal of Pharmacology 2011;660:2–12.
Wolf I, Sadetzki S, Kanety H, Kundel Y, Pariente C, Epstein N, et al. Adiponectin, ghrelin, and leptin in cancer cachexia in breast and colon cancer patients. Cancer 2006;106:966–73.
Wolsk E, Mygind H, Grondahl TS, Pedersen BK, Van Hall G. Human skeletal muscle releases leptin in vivo. Cytokine 2012;60:667–73.
Xu Y, Elmquist JK, Fukuda M. Central nervous control of energy and glucose balance: focus on the central melanocortin system. Annals of the New York Academy of Sciences 2011;1243:1–14.
Yoshida T, Semprun-Prieto L, Wainford RD, Sukhanov S, Kapusta DR, Delafontaine P. Angiotensin II reduces food intake by altering orexigenic neuropeptide expression in the mouse hypothalamus. Endocrinology 2012;153:1411–20.
Zhou X, Wang JL, Lu J, Song Y, Kwak KS, Jiao Q, et al. Reversal of cancer cachexia and muscle wasting by ActRIIB antagonism leads to prolonged survival. Cell 2010;142:531–43.

Cachexiaの診断，病態と治療（総論）

Diagnosis, pathology and treatment of cachexia

鈴木　甫／浅川明弘／網谷東方／乾　明夫

SUMMARY

Cachexiaは食欲不振，持続的な体重減少，骨格筋の減少を主徴とした病態であり，癌をはじめ多くの基礎疾患に合併して認められる。その病態の背景にはサイトカインによる全身性の炎症があり，たんぱく質とエネルギーのバランスが負に傾くことが特徴である。Cachexiaの治療は薬物療法のみならず，心理・栄養など，多方面からの包括的なアプローチが重要である。

KEY WORDS

- cachexia
- 包括的治療
- QOL
- 診断基準
- 食欲・体重調節

I
はじめに

悪液質（cachexia）は食欲不振，体脂肪量ならびに骨格筋減少（サルコペニア）を主徴とした病態で，癌をはじめ，後天性免疫不全症候群，リウマチ，慢性肺疾患，心不全，炎症性腸疾患など，多くの基礎疾患に合併して認められる。古くは紀元前4世紀，古代ギリシアのヒポクラテスのころより認識されていたとされるが，近年の医学の進歩により，患者自身のQOLや生命予後との関連が明らかになってきたことで，治療の必要な病態として強く認識されるようになった[1]。

癌に伴う癌悪液質（cancer cachexia）は消化器系癌を中心に，進行性癌患者全体の60～80％に認められ，癌死因の20～25％を占めるといわれる[2)-4)]。一般にcancer cachexiaは，癌の進行に伴い不可逆性の栄養障害に進展していくとされるが（図1），癌腫によって発生率や進行速度はさまざまである[5]。

Cancer cachexiaは高齢者や小児にも多くみられ，高齢者では全身状態の悪化，小児では成長障害を引き起こすため，その治療介入は重要である[2]。また，発熱，痛み，腸閉塞，抑うつなどや癌の浸潤・転移に伴う合併症，外科手術・化学療法・放射線療法など，2次的要因に基づくcachexiaも存在し，その後の治療耐性に大きく影響する[6) 7)]。

本稿では主にcancer cachexiaを中心に，診断，病態ならびに治療について概説する。

II
Cachexiaの診断

2008年，国際悪液質学会により発表されたcachexiaの診断基準（図2）によると，cachexiaは「悪液質の原因疾患の存在下で，12ヵ月以内に5％以上体重が減少し，かつ筋力低下，疲労，食欲不振，除脂肪量低下，血液検査異常の5項目のうち3項目を満たす場合」とされる。この基準にてcachexiaと診断された場合は「治療が必要なcachexia」であり，薬物療法のみならず栄養療法や心理カウンセリングなどを含めた包括的な治療が早急に必要となる。

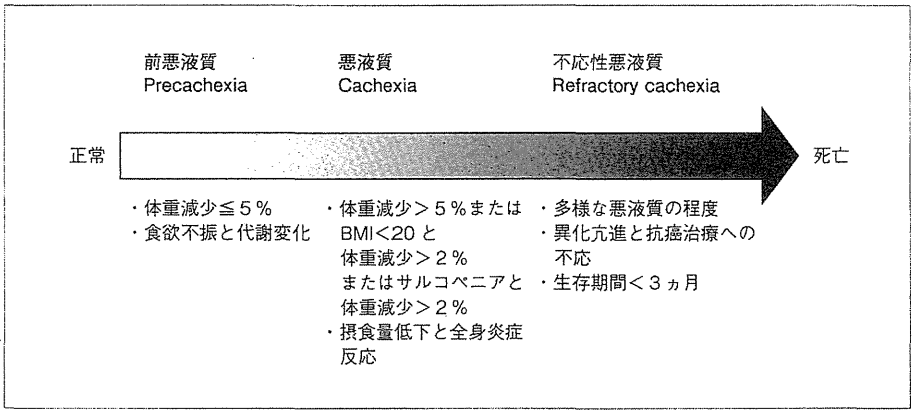


図1．Cachexiaのステージ

（文献18）より改変・引用）

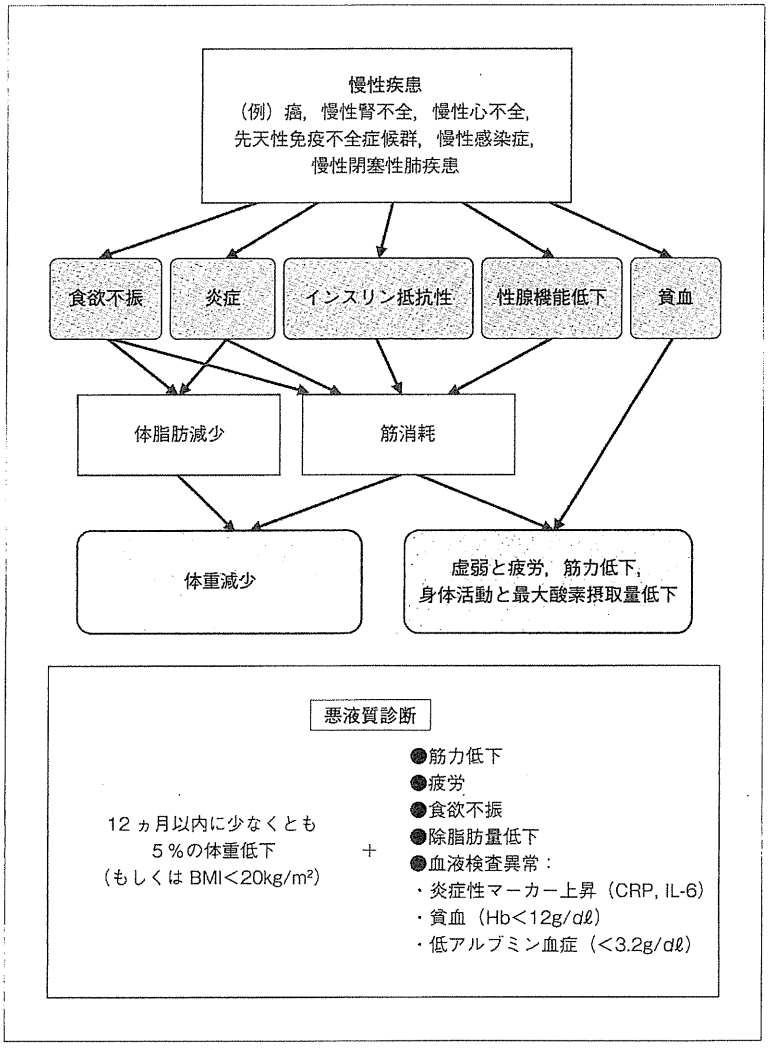


図2．Cachexiaの診断

（文献19）より改変・引用）

Ⅲ Cachexiaの病態

食欲不振やサルコペニアをはじめとするcachexiaの複雑な病態を理解する際，サイトカインが重要なファクターとなる。腫瘍壊死因子(tumor necrosis factor-α；TNF-α)，インターロイキン-1(interleukin-1；IL-1)，IL-6，インターフェロン-γ（interferon-gamma；IFN-γ）などのサイトカインは癌細胞や宿主の免疫担当細胞から過剰に産生・放出され，全身性の炎症を引き起こす。その結果，たんぱく質とエネルギーのバランスが負に傾くのではないかという考え方が，cachexiaの病態・成因におけるコンセンサスを得ている[2) 3) 8) -12)]。

Cachexiaの代表的な病態の1つとして，食欲不振・体重減少がある。一般に，末梢のエネルギー状態を中枢に伝え制御する食欲・体重調節機構は，主に視床下部において統合的に調節されており，これはヒトの進化の長い歴史のなかで，飢餓への応答として備わったメカニズムである。末梢のエネルギー状態を伝える代表的な因子としてレプチンならびにグレリンがあり，レプチンは体脂肪量に応じて血中に分泌される満腹ホルモンで[13)]，体脂肪量が増加すると血中レプチンが増加して視床下部の食欲促進系が抑制され，体脂肪量が減少すると血中レプチンも低下し食欲促進系が活性化される。一方，1999年に成長ホルモン分泌促進因子受容体の内因性リガンドとして胃から分離・同定されたグレリンは，食欲促進や体重増加作用を発現する末梢で唯一の空腹ホルモンで，中枢に液性・神経性に作用して，強力な食欲促進系の神経ペプチドY(neuropeptide Y；NPY)/アグーチ関連ペプチド(agouti-related peptide；AgRP）を活性化させる[14)]。こうしたレプチンやグレリンなどによる食欲・体重調節機構が，サイトカインによって破綻する病態がcachexiaではないかと考えられる。すなわち，サイトカインがレプチン様のシグナル（体脂肪量が十分に存在するという「誤った」シグナル）を視床下部に伝え，結果的に飢餓に対する応答であるNPY/AgRP系を中心とした食欲促進系が抑制されるために，食欲不振，基礎代謝量の増加，持続的な体重減少といったcachexiaの病態が形成されることが強く示唆されている[8)]。

サルコペニアもcachexiaの代表的な病態の1つであるが，これにもサイトカインの関与が多数報告されている。たとえばTNF-αなどのサイトカインはたんぱく質分解系であるユビキチン-プロテアソーム系を活性化するが，一方で，インスリン様成長因子（insulin like growth

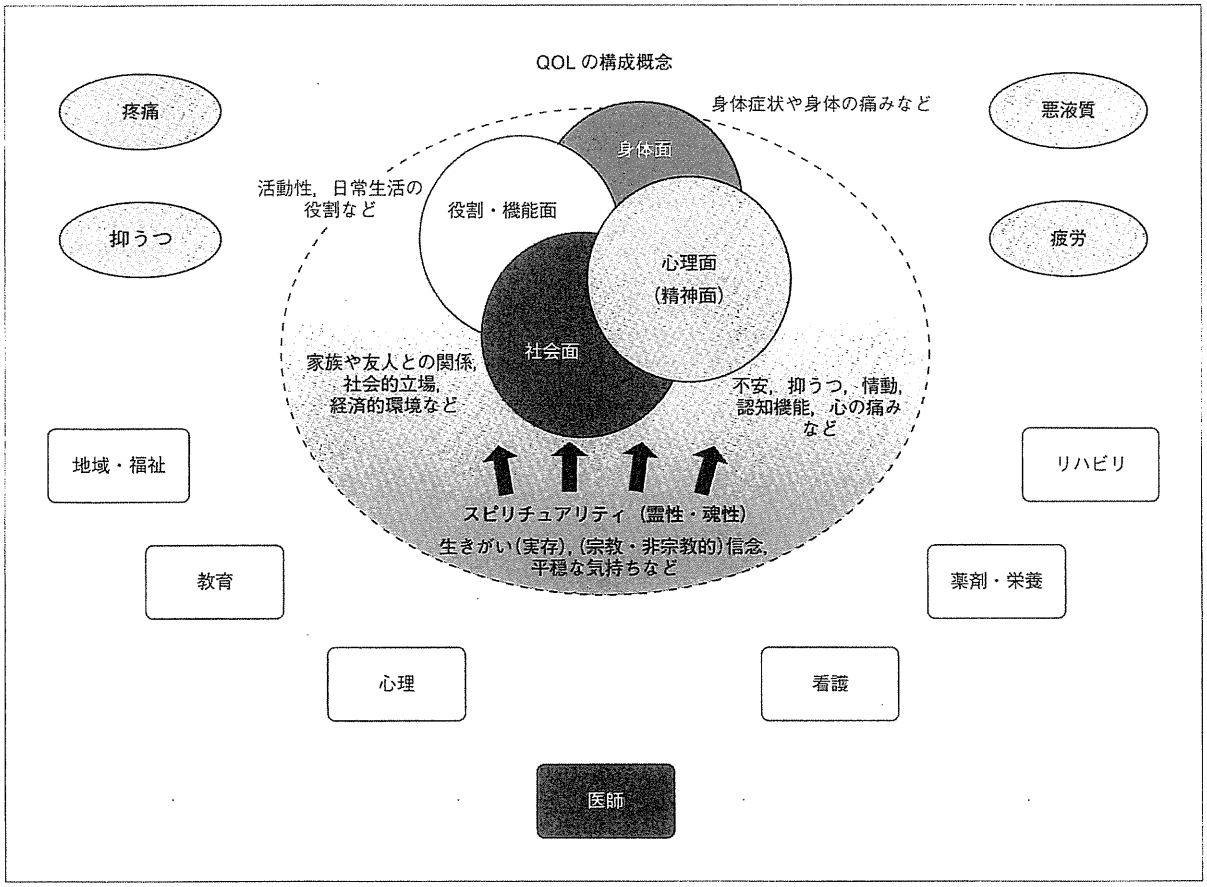


図3．Cachexiaに対する包括的医療

（文献20）より一部改変・引用）

factor：IGF）などのたんぱく質合成・筋線維再生における因子の発現を抑制する[15]。その結果，飢餓とは異なるcachexiaの特徴である骨格筋の崩壊・萎縮が引き起こされる[10) 15)]。ほかにも，lipid mobilizing factor（LMF），proteolysis inducing factor（PIF）などの癌組織から産生される局所因子が，脂肪や筋肉組織に直接作用し組織の崩壊を導くことが報告されている[10)16)]。さらに，炎症性サイトカインは疲労，痛み，不安，抑うつなどのsickness behaviorを引き起こす[17)]。

IV Cachexiaの治療

Cachexia治療の目標は，患者の病態を心身両面から検討し，包括的な医療を行うことにある[2)]。現在のところ，薬物療法単独でのcachexia治療は不可能であり，薬物療法・栄養療法・心理療法・リハビリテーションを基本とした多方面からのアプローチが症状緩和に重要となる。実際には，cachexiaの成因論に基づいた薬物療法を選択し，併発する痛み，疲労，抑うつなどの周辺症状に対し，心身両面から治療していくこととなる。この実現のためには，医師や看護師，薬剤師，栄養士，臨床心理士，ソーシャルワーカーなど，業種を超えた連携が不可欠である（図3）。

V おわりに

Cachexiaの診断，病態ならびに治療について概説した。肥満や糖尿病，メタボリックシンドロームなどの過栄養病態と対極をなすcachexiaは，その複雑な病態，多彩な臨床症状からいまだ多くの研究や議論の余地を残しており，さらなる解明が待たれる。

REFERENCES

1) Dewys WD, Begg C, Lavin PT, et al : Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med **69** : 491-497, 1980
2) Inui A : Cancer anorexia-cachexia syndrome : current issues in research and management. CA Cancer J Clin **52** : 72-91, 2002
3) Laviano A, Meguid MM, Inui A, et al : Therapy insight : Cancer anorexia-cachexia syndrome--when all you can eat is yourself. Nat Clin Pract Oncol **2** : 158-165, 2005
4) Fazal S, Saif MW : Supportive and palliative care of pancreatic cancer. JOP **8** : 240-253, 2007
5) Monitto CL, Berkowitz D, Lee KM, et al : Differential gene expression in a murine model of cancer cachexia. Am J Physiol Endocrinol Metab **281** : E289-E297, 2001
6) Ross PJ, Ashley S, Norton A, et al : Do patients with weight loss have a worse outcome when undergoing chemotherapy for lung cancers? Br J Cancer **90** : 1905-1911, 2004
7) Jeremić B, Miličić B, Milisavljevic S : Clinical prognostic factors in patients with locally advanced (stage Ⅲ) nonsmall cell lung cancer treated with hyperfractionated radiation therapy with and without concurrent chemotherapy : single-Institution Experience in 600 Patients. Cancer **117** : 2995-3003, 2011
8) Inui A : Cancer anorexia-cachexia syndrome : are neuropeptides the key? Cancer Res **59** : 4493-4501, 1999
9) Donohoe CL, Ryan AM, Reynolds JV : Cancer cachexia: mechanisms and clinical implications. Gastroenterol Res Pract **2011** : 601434, 2011
10) Tisdale MJ : Cachexia in cancer patients. Nat Rev Cancer **2** : 862-871, 2002
11) Fearon K, Arends J, Baracos V : Understanding the mechanisms and treatment options in cancer cachexia. Nat Rev Clin Oncol **10** : 90-99, 2013
12) Fearon KC : Cancer Cachexia and fat-muscle physiology. New Engl J Med **365** : 565-567, 2011
13) Zhang Y, Proenca R, Maffei M, et al : Positional cloning of the mouse obese gene and its human homologue. Nature **372** : 25-432, 1994
14) Kojima M, Hosoda H, Date Y, et al : Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature **402** : 656-660, 1999
15) Saini A, Al-Shanti N, Stewart CE : Waste management - cytokines, growth factors and cachexia. Cytokine Growth Factor Rev **17** : 475-486, 2006
16) Tisdale MJ : Biology of cachexia. J Natl Cancer Inst **89** : 1763-1773, 1997
17) Inui A : Cytokines and sickness behavior : implications from knockout animal models. Trends Immunol **22** : 469-473, 2001
18) Fearon K, Strasser F, Anker SD, et al : Definition and classification of cancer cachexia : an international consensus. Lancet Oncol **12** : 489-495, 2011
19) Evans WJ, Morley JE, Argilés J, et al : Cachexia : a new definition. Clin Nutr **27** : 793-799, 2008
20) 下妻晃二郎：臨床腫瘍学におけるQOL研究の意義．がん医療におけるQOL研究の世界的動向-乳癌治療を中心に．血腫瘍 **41**：490-497, 2000

すずき・はじめ
鹿児島大学大学院医歯学総合研究科心身内科学分野／鹿児島大学大学院医歯学総合研究科口腔顎顔面外科学分野
あさかわ・あきひろ
鹿児島大学大学院医歯学総合研究科心身内科学分野准教授
あみたに・はるか
鹿児島大学大学院医歯学総合研究科心身内科学分野助教
いぬい・あきお
鹿児島大学大学院医歯学総合研究科心身内科学分野教授

Cachexiaの新しい治療

New treatment of cachexia

網谷真理恵／網谷東方／浅川明弘／乾　明夫

SUMMARY

悪液質（cachexia）病態の解明が進むなかで，新規治療薬の開発が進められている。グレリンおよびグレリンアナログ，選択的アンドロゲン受容体調節薬（SARMs），テストステロン，ミオスタチン抗体，メラノコルチン4受容体（MC4R）拮抗薬など，研究新薬やほかの用途に承認された薬などの臨床試験が数多く実施され，一部は進行中である。悪液質治療薬の新規開発が行われることで，悪液質によりQOLが低下した患者の予後改善および生存日数の延長につながることを望む。

KEY WORDS

■ 悪液質
■ 食欲不振
■ 炎症性サイトカイン
■ グレリン

I
はじめに

悪液質（cachexia）がもたらす栄養不良には，食欲不振が大きく影響している。さらに，炎症性サイトカインに誘発される全身の炎症反応による代謝異常のため，骨格筋分解の亢進，インスリン抵抗性，脂質分解の亢進などの同化障害が生じ異化亢進された状態にある。この代謝障害が高度になり，癌悪液質（cancer cachexia）のステージが“前悪液質（precachexia）”，“悪液質（cachexia）”，“不応性悪液質（refractory cachexia）”と進行すると，栄養補給を行っても有効に同化することができなくなり，栄養不良は不可逆的な状態になる。食欲低下により摂食量が減少するため，栄養補助食品や経管栄養，静脈栄養などを適切に用いて栄養管理を行うことは必要不可欠だが，悪液質，特にrefractory cachexiaが出現すると，異化亢進による代謝障害が生じ，栄養補給を行っても胸水や腹水ならびに全身浮腫などの症状が出現するため，QOLを低下させることにもなりうる。そのため，悪液質のステージを評価し，適切な栄養管理を行うことが重要となる。

近年悪液質の機序は解明されつつあり，悪液質による低栄養状態を改善する薬剤開発の試みがなされている。悪液質においては，炎症性サイトカインが代謝異常および食欲不振において中心的な役割を担っているため，食欲不振と炎症性サイトカインによる炎症の制御を標的とした治療薬の開発が進められている。

II
薬物療法

悪液質の要因を心身両面から十分に検討したうえで，チーム医療として悪液質に対処し，そのなかで栄養療法，運動療法に加えて薬物投与を考慮する（図1）[1][2]。

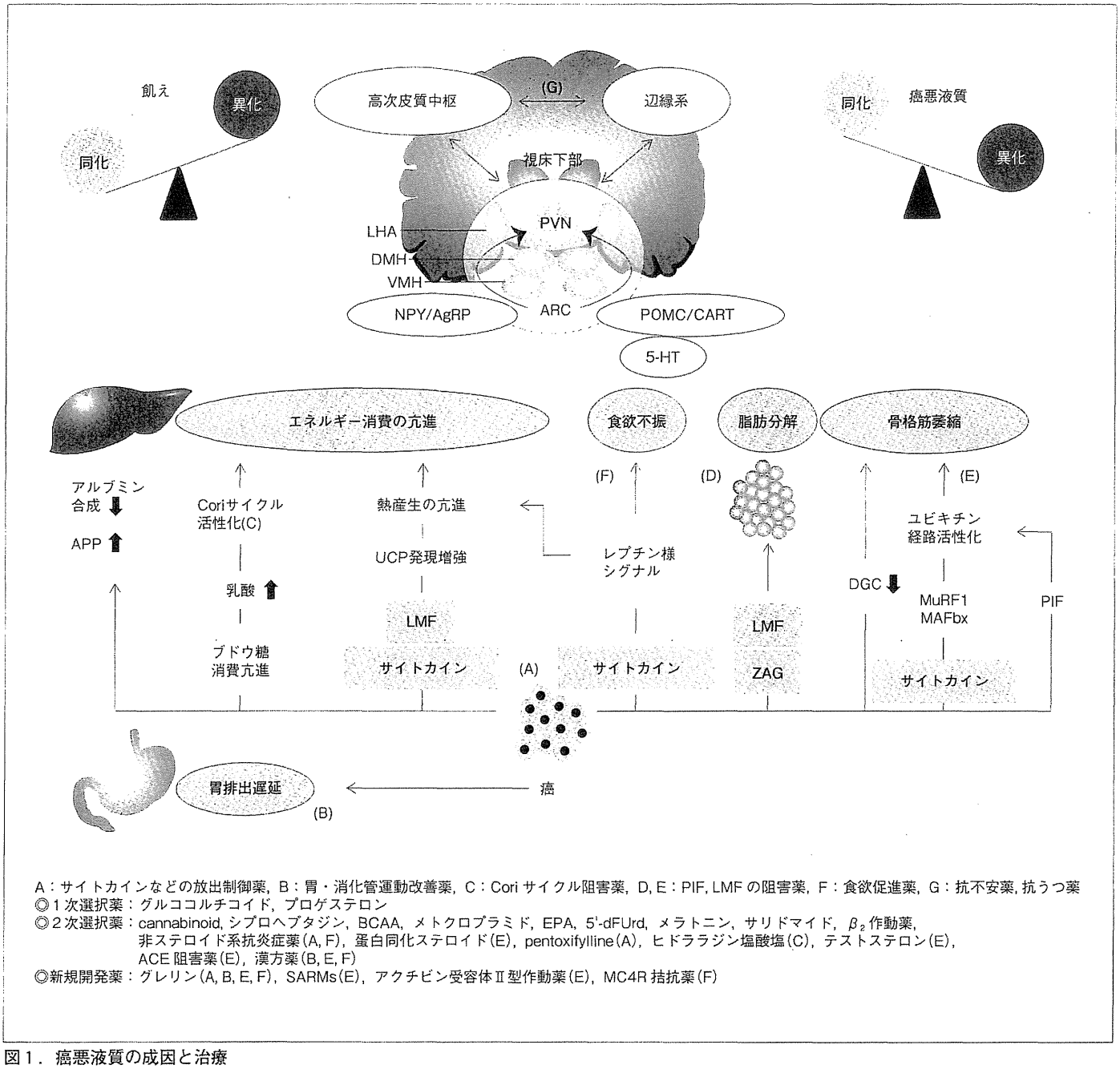
1．サイトカイン抑制薬

癌組織や担癌宿主から放出されるサイトカインなどを抑制する薬剤で，グルココルチコイド，プロゲステロン，エイコサペンタエン酸（eicosapentaenoic acid；EPA），5'-deoxy-5-fluorouridine（5'-dFUrd），メラトニン，サリドマイド，非ステロイド系抗炎症薬〔cyclooxygenase-2（COX-2）阻害薬〕，アンジオテンシン変換酵素（angiotensin converting enzyme；ACE）阻害薬などが試みられている。また，グレリンもサイトカインを抑制する作用をもつ。多価不飽和脂肪酸であるEPAは，炎症抑制をはじめproteolysis-inducing factor（PIF），lipid mobilizing factor（LMF）の産生低下，脂肪および骨格筋の分解抑制をもたらすことで悪液質患者のQOLを維持するなどの効果があり，わが国においても癌患者に対し広く用いられている。

サイトカインは食欲不振のほか，発熱，疲労，抑うつなどの病的行動（sickness behavior）に関与するため[3][4]，その改善効果も期待される。

2．胃・消化管運動改善薬

悪液質においては，胃排出能の低下に基づく早期の満腹感が生じる。メトクロプラミドのような消化管運動改善薬は，担癌患者の食欲不振，消化管蠕動不全への使用が推奨されている。セロトニン（5-hydroxytryptamine；5-HT）4受容体作動薬のモサプリドクエン酸塩やイトプリド塩酸塩は，胃排出能を促進するのみならず，胃近位部の受容性弛緩を促進し早期満腹感の軽減に有効である。



A：サイトカインなどの放出制御薬，B：胃・消化管運動改善薬，C：Cori サイクル阻害薬，D, E：PIF, LMF の阻害薬，F：食欲促進薬，G：抗不安薬，抗うつ薬
◎1次選択薬：グルココルチコイド，プロゲステロン
◎2次選択薬：cannabinoid, シプロヘプタジン，BCAA，メトクロプラミド，EPA，5'-dFUrd，メラトニン，サリドマイド，β_2作動薬，非ステロイド系抗炎症薬(A, F)，蛋白同化ステロイド(E)，pentoxifylline(A)，ヒドララジン塩酸塩(C)，テストステロン(E)，ACE 阻害薬(E)，漢方薬(B, E, F)
◎新規開発薬：グレリン(A, B, E, F)，SARMs(E)，アクチビン受容体Ⅱ型作動薬(E)，MC4R 拮抗薬(F)

図1．癌悪液質の成因と治療

悪液質は食欲低下，エネルギー消費の亢進，脂肪減少，骨格筋の減少を特徴とし，その成因に応じて治療を考慮する必要がある。1次選択薬はグルココルチコイドとプロゲステロンであるが，プロゲステロンは日本では認可されていない。2次選択薬としては，多くの薬剤が臨床応用されつつある。

ARC：弓状核，VMH：腹内側核，DMH：背側核，LHA：外側野，PVN：室傍核，NPY：neuropeptide Y，POMC：proopiomelanocortin，CART：cocaine-and amphetamine-regulated transcript，ZAG：zinc-α2-glycoprotein，MuRF1：muscle ring-finger protein 1，MAFbx：muscle atrophy F-box，APP：acute phase protein，UCP：uncoupling protein，DGC：dystrophin glycoprotein complex

（文献1）2）より改変・引用）

表1．悪液質とサルコペニアに対する臨床研究

薬物／化合物	会社名	メカニズム	対象疾患／対象者	開発状況	文献
Megace® ES	Par Pharmaceutical	酢酸メゲストロール	癌／エイズ	FDA承認	Belller, et al：1997 Bruera, et al：1990 Loprinzi, et al：1990
Anamorelin	Helsinn Therapeutics	グレリン受容体作動薬	癌	第Ⅲ相	Garcia, et al：2013
Vitor™	Ark Therapeutics	ACE阻害薬	癌	第Ⅲ相	Smith, 2006
EPA	Nestle, Danone, Abbott, Fresenius	SOD作動薬およびUPP活性化	癌	第Ⅱ／Ⅲ相	Hardman, et al：2004 Barber, et al：2001 Fearon, et al：2006
H-4864-GMP	Bachem	合成ヒトグレリン	癌	第Ⅱ相	Neary, et al：2004
GTx-024（Ostarine）	GTx	SARM	癌	第Ⅱ相	Dobs, et al：2011
U-1250	Bachem	合成ヒトグレリン	癌	第Ⅱ相	Strasser, et al：2008
P-0861	Polypeptide Laboratories	合成ヒトグレリン	癌	第Ⅱ相	Lundholm, et al：2010
SUN11031	Asubio Pharmaceuticals	合成ヒトグレリン	慢性閉塞性肺疾患	第Ⅱ相	Levinson, et al：2012
INCB018424	Incyte	Jak1/2阻害	白血病	第Ⅱ相	Eghtedar, et al：2012
OHR118	OHR Pharmaceutical	ペプチド核酸免疫調節	エイズ	第Ⅱ相	Chasen, et al：2011
Celecoxib（Celebrex）	Pfizer	COX-2阻害	癌	第Ⅱ相	Mantovani, et al：2010
BYM338	Novartis	ヒトモノクローナル抗体	癌	第Ⅱ相	不明
MT-102	PsiOxus Therapeutics	β受容体遮断	癌	第Ⅱ相	Stewart, et al：2011
ALD518（BMS-945429）	Alder Biopharmaceuticals	ヒト化IL-6モノクローナル抗体	癌	第Ⅱ相	Bayliss, et al：2011
CK-2017357	Cytokinetics	骨格筋トロポニン活性	筋萎縮性側索硬化症	第Ⅱ相	Shefner, et al：2012
AEZS-130（EP-01572）	Aeterna Zentaris	グレリン受容体作動薬	健常者	第Ⅰ相	Piccoli, et al：2007
Lenalidomide	Celgene	サリドマイドアナログ	癌	第Ⅰ相	Sharma, et al：2006
Olanzapine	Eli Lilly	H_1受容体作動薬 5-HT_2受容体拮抗薬	癌	第Ⅰ相	Braiteh, et al：2008
ACE031	Acceleron Pharma	アクチビン受容体Ⅱ型作動薬	健常者	第Ⅰ相	Attie, et al：2013
LGD-4033	Ligand Pharmaceuticals	SARM	健常者	第Ⅰ相	Basaria, et al：2013
GLPG0492	Galapagos	SARM	健常者	第Ⅰ相	Nique, et al：2012
BL-6020/979	Santhera Pharmaceuticals	MC4R拮抗薬	癌	前臨床	Dallmann, et al：2011
IL-15	Immunex, Amgen	サイトカイン	癌	前臨床	Harcourt, et al：2005
PG-873637	Procter & Gamble Pharmaceuticals	CRF2R作動薬	癌	前臨床	Argilés, et al：2008

SOD：superoxide dismutase, UPP：ubiquitin proteasome pathway, IL-6：interleukin-6, H_1：histamine 1, CRF2R：corticotropin-releasing factor 2 receptor

（文献38）より改変・引用）

3．食欲促進薬

わが国では主にグルココルチコイドが悪液質治療に用いられているが，欧米ではプロゲステロン製剤であるmegestrolも癌悪液質治療に使用可能である。プロゲステロンは，サイトカイン合成の抑制により摂食量を増加させる。Cannabinoidはマリファナ成分の1つであり，強力な制吐作用および癌性疼痛を軽減する作用を有すると同時に，食欲を促進する効果もある。

また抗5-HT薬や分岐鎖アミノ酸製剤（branched-chain amino acid：BCAA）を用いて，5-HTを遮断することによる食欲不振，悪液質の改善効果が報告されている。BCAAは，食欲不振をもたらす5-HTの作用を低下させることで食欲を改善し，さらに筋組織の維持にも効果があることが知られている。また，抗精神病薬であるオランザピンの副作用である食欲亢進を利用して悪液質治療に応用する試みも行われている。

4．漢方薬

漢方薬の六君子湯は，臨床的に食欲促進効果を有することが知られてきたが，5-$HT_{2b/2c}$受容体を阻害し，グレリンの分泌を刺激することにより食欲低下，消化管機能不全，骨格筋萎縮，不安行動を改善することが明らかにされた。さらに，動物モデルおよび癌患者において生存日数を延ばすことが報告されている[5]。現在，膵癌患者の悪液質に対する六君子湯の無作為化第Ⅱ相比較試験が進行中である。

Ⅲ
新たな治療薬の開発

悪液質の基礎的病態の解明が進み，いくつかの研究では大きな効果をもたらす可能性を秘めた治療アプローチが見出されている。グレリンおよびグレリンアナログ，選択的アンドロゲン受容体調節薬（selective androgen receptor modulators；SARMs），テストステロン，インスリン様成長因子（insulin-like growth factor：IGF）-1，ミオスタチン抗体，メラノコルチン4受容体（melanocortin 4 receptor；MC4R）拮抗薬などの研究新薬や，ほかの用途に承認された薬などの臨床試験が数多く実施され，一部は進行中である[6)-33)]（表1）[38)]。

1．グレリン

胃から空腹時に分泌されるグレリンには，食欲促進作用のみならず骨格筋萎縮に対する改善効果も期待されている。グレリンやグレリン受容体作動薬の臨床応用も試みられつつある。臨床研究では，悪液質患者に対しグレリンが食欲を亢進させ，摂食量を増加する作用をもつことが報告されている[9)14)17)]。Anamorelinは経口投与可能なグレリン受容体作動薬で，健常者では体重増加と同化作用を促すことが報告され，現在は癌患者の治療薬として開発が進んでいる。Anamorelinはすでに第Ⅱ相臨床試験を終了し，癌患者に対しても食欲を亢進させ体重を増加させることが報告されている[9)]。スイスのHelsinn社は2011年8月23日より，非小細胞肺癌に伴う食欲不振／悪液質患者を対象とした，anamorelinのグローバル多施設共同無作為化二重盲検プラセボ対照の第Ⅲ相臨床試験を開始しており[34)]，国内では小野薬品工業株式会社が第Ⅱ相臨床試験を実施中である。

また，カナダのAeterna Zentaris社は2012年3月8日，癌悪液質をもつ患者を対象に，グレリン受容体作動薬であるAEZS-130（macimorelin）の安全性と薬効を評価する第ⅡA相臨床試験を開始したと発表している。

2．SARMs

SARMsは骨格筋の減少に対する治療薬として注目されている。癌悪液質が認められる患者159例を対象とするランダム化プラセボ比較第Ⅱ相臨床試験では，SARMsによる体重増加が有意に認められた[15)35)]。SARMsであるGTx-024は第Ⅲ相臨床試験に進み，進行非小細胞肺癌患者における悪液質の予防または治療を試みている。

3．ミオスタチン 抗体

ミオスタチンは骨格筋量を負に調整し，骨格筋の肥大を抑制する働きをもつ。ミオスタチンとアクチビン受容体のアクチビンⅡ型受容体B（activin type Ⅱ receptor B；ActRⅡb）は悪液質における骨格筋減少の主要因子であり，癌患者ではアクチビンAの増加や骨格筋でのアクチビンAの活性化が認められる。

また，ActRⅡbの阻害は骨格筋の減少を防ぐのみならず，大腸癌マウスの生存を改善することが報告され，悪液質の治療として注目されている[36)]。

4．MC4R拮抗薬

食欲促進ペプチドであるアグーチ関連蛋白（agouti-related protein；AgRP）は内因性のMC4R拮抗薬であり，食欲を亢進させる。AgRPは摂食量を増加しエネルギー消費を減らすことで，癌，尿毒症，慢性腎不全に伴う悪液質を緩和することが動物実験で示唆されている。さらにAgRP投与だけでなく，MC4R拮抗薬を投与された担癌マウスは摂食量が増加し，体重を維持できた。近年では，経口投与が可能な選択的MC4R拮抗薬が開発され，担癌マウスの悪液質も改善させる効果があることがわかり，今後の臨床応用への可能性として注目を集めている[37)]。

Ⅳ
まとめ

悪液質病態のさらなる解明により，グレリンもしくはグレリン受容体作動薬，SARMsの臨床研究も進んでいる。悪液質治療薬の新規開発が行われることで，悪液質によりQOLが低下した患者の予後改善および生存日数の延長につながることを望む。

REFERENCES

1) Inui A：Cancer anorexia-cachexia syndrome：current issues in research and management. CA Cancer J Clin 52：72-91, 2002
2) 網谷真理恵，小木曽和磨，網谷東方，他：臨床的側面から．太田惠一朗 編．がん緩和ケアにおける胸水・腹水管理．東京，真興交易医書出版部，17-34，2010
3) Inui A：Cancer anorexia-cachexia syndrome：are neuropeptides the key ? Cancer Res 59：4493-4501, 1999
4) Inui A：Cytokine and sickness behavior：implications from knockout animal models. Trends Immunol 22：469-473, 2001
5) Fujitsuka N, Asakawa A, Uezono Y, et al：Potentiation of ghrelin signaling attenuates cancer anorexia-cachexia and prolongs survival. Transl Psychiatry 1：e23, 2011
6) Beller E, Tattersall M, Lumley T, et al：Improved quality of life with megestrol acetate in patients with endocrine-insensitive advanced cancer：a randomised placebo-controlled trial. Australasian Megestrol Acetate Cooperative Study Group. Ann Oncol 8：277-283, 1997
7) Bruera E, Macmillan K, Kuehn N, et al：A controlled trial of megestrol acetate on appetite, caloric intake, nutritional status, and other symptoms in patients with advanced

cancer. Cancer 66 : 1279-1282, 1990
8) Loprinzi CL, Ellison NM, Schaid DJ, et al : Controlled trial ofmegestrol acetate for the treatment of cancer anorexia and cachexia. J Natl Cancer Inst 82 : 1127-1132, 1990
9) Garcia JM, Friend J, Allen S : Therapeutic potential of anamorelin, a novel, oral ghrelin mimetic, in patients with cancer-related cachexia ; a multicenter, randomized, double-blind, crossover, pilot study. Support Care Cancer 21 : 129-137, 2013
10) Smith N : Ark plans second Phase Ⅲ study of Vitor in cancer cachexia after mixed results. APM Health Europe, 2006
11) Hardman WE : (n-3) fatty acids and cancer therapy. J Nutr 134(Suppl.) : 3427S-3430S, 2004
12) Barber MD : Cancer cachexia and its treatment with fish-oil-enriched nutritional supplementation. Nutrition 17 : 751-755, 2001
13) Fearon KC, Barber MD, Moses AG, et al : Double-blind, placebo-controlled, randomized study of eicosapentaenoic acid diester in patients with cancer cachexia. J Clin Oncol 24 : 3401-3407, 2006
14) Neary NM, Small CJ, Wren AM, et al : Ghrelin increases energy intake in cancer patients with impaired appetite ; acute, randomized, placebo-controlled trial. J Clin Endocrinol Metab 89 : 2832-2836, 2004
15) Dobs AS, Boccia, RV, Croot CC, et al : Effects of enobosarm on muscle wasting and physical function in patients with cancer ; a double-blind, randomised controlled phase 2 trial. Lancet Oncol 14 : 335-345, 2013
16) Strasser F, Lutz TA, Maeder MT, et al : Safety, tolerability and pharmacokinetics of intravenous ghrelin for cancer-related anorexia/cachexia ; a randomised, placebo-controlled, double-blind, double-crossover study. Br J Cancer 98 : 300-308, 2008
17) Lundholm K, Gunnebo L, Körner U, et al : Effects by daily long term provision of ghrelin to unselected weight-losing cancer patients ; a randomized double-blind study. Cancer 116 : 2044-2052, 2010
18) Levinson B, Gertner J : Randomized study of the efficacy and safety of SUN11031 (synthetic human ghrelin) in cachexia associated with chronic obstructive pulmonary disease. e-SPEN J 7 : e171-e175, 2012
19) Eghtedar A, Verstovsek S, Estrov Z, et al : Phase 2 study of the JAK kinase inhibitor ruxolitinib in patients with refractory leukemias, including postmyeloproliferative neoplasm acute myeloid leukemia. Blood 119 : 4614-4618, 2012
20) Chasen M, Hirschman SZ, Bhargava R : Phase Ⅱ study of the novel peptide-nucleic acid OHR118 in the management of cancer-related anorexia/cachexia. J Am Med Dir Assoc 12 : 62-67, 2011
21) Mantovani G, Maccio A, Madeddu C, et al : Phase II nonrandomized study of the efficacy and safety of COX-2 inhibitor celecoxib on patients with cancer cachexia. J Mol Med (Berl) 88 : 85-92, 2010
22) Stewart Coats AJ, Srinivasan V, Surendran J, et al : The ACT-ONE trial, a multicentre, randomised, double-blind, placebo-controlled, dose-finding study of the anabolic/catabolic transforming agent, MT-102 in subjects with cachexia related to stage Ⅲ and Ⅳ non-small cell lung cancer and colorectal cancer: study design. J Cachexia Sarcopenia Muscle 2 : 201-207, 2011
23) Bayliss TJ, Smith JT, Schuster M, et al : A humanized anti-IL-6 antibody (ALD518) in non-small cell lung cancer. Expert Opin Biol Ther 11 : 1663-1668, 2011
24) Shefner J, Cedarbaum JM, Cudkowicz ME, et al : Safety, tolerability and pharmacodynamics of a skeletal muscle activator in amyotrophic lateral sclerosis. Amyotroph Lateral Scler 13 : 430-438, 2012
25) Piccoli F, Degen L, MacLean C, et al : Pharmacokinetics and pharmacodynamic effects of an oral ghrelin agonist in healthy subjects. J Clin Endocrinol Metab 92 : 1814-1820, 2007
26) Sharma RA, Steward WP, Daines CA, et al : Toxicity profile of the immunomodulatory thalidomide analogue, lenalidomide ; phase I clinical trial of three dosing schedules in patients with solid malignancies. Eur J Cancer 42 : 2318-2325, 2006
27) Braiteh F, Dalal S, Khuwaja A, et al : Phase I pilot study of the safety and tolerability of olanzapine (OZA) for the treatment of cachexia in patients with advanced cancer. J Clin Oncol 26 (Suppl.) : 20529, 2008
28) Attie KM, Borgstein NG, Yang Y, et al : A single ascending-dose study of muscle regulator ACE-031 in healthy volunteers. Muscle Nerve 47 : 416-423, 2013
29) Basaria S, Collins L, Dillon EL, et al : The safety, pharmacokinetics, and effects of LGD-4033, a novel nonsteroidal oral, selective androgen receptor modulator, in healthy young men. J Gerontol A Biol Sci Med Sci 68 : 87-95, 2013
30) Nique F, Hebbe S, Triballeau N, et al : Identification of a 4-(hydroxymethyl) diarylhydantoin as a selective androgen receptor modulator. J Med Chem 55 : 8236-8247, 2012
31) Dallmann R, Weyermann P, Anklin C, et al : The orally active melanocortin-4 receptor antagonist BL-6020/979 : a promising candidate for the treatment of cancer cachexia. J Cachexia Sarcopenia Muscle 2 : 163-174, 2011
32) Harcourt LJ, Holmes AG, Gregorevic P, et al : Interleukin-15 administration improves diaphragm muscle pathology and function in dystrophic mdx mice. Am J Pathol 166 : 1131-1141, 2005
33) Argilés JM, Figueras M, Ametller E, et al : Effects of CRF2R agonist on tumor growth and cachexia in mice implanted with Lewis lung carcinoma cells. Muscle Nerve 37 : 190-195, 2008
34) Fearon K, Arends J, Baracos V : Understanding the mechanisms and treatment options in cancer cachexia. Nat Rev Clin Oncol 10 : 90-99, 2013
35) Dalton JT, Barnette KG, Bohl CE, et al : The selective androgen receptor modulator GTx-024 (enobosarm) improves lean body mass and physical function in healthy elderly men and postmenopausal women ; results of a double-blind, placebo-controlled phase II trial. J Cachexia Sarcopenia Muscle 2 : 153-161, 2011
36) Zhou X, Wang JL, Lu J, et al : Reversal of cancer cachexia and muscle wasting by ActRIIB antagonism leads to prolonged survival. Cell 142 : 531-543, 2010
37) Weyermann P, Dallmann R, Magyar J, et al : Orally available selective melanocortin-4 receptor antagonists stimulate food intake and reduce cancer-induced cachexia in mice. PLoS One 4 : e4774, 2009
38) Amitani M, Asakawa A, Amitani H, et al : Control of food intake and muscle wasting in cachexia. Int J Biochem Cell Biol 45 : 2179-2185, 2013

あみたに・まりえ
鹿児島大学大学院医歯学総合研究科社会・行動医学講座心身内科学分野
あみたに・はるか
鹿児島大学大学院医歯学総合研究科社会・行動医学講座心身内科学分野助教
あさかわ・あきひろ
鹿児島大学大学院医歯学総合研究科社会・行動医学講座心身内科学分野准教授
いぬい・あきお
鹿児島大学大学院医歯学総合研究科社会・行動医学講座心身内科学分野教授

緩和ケアチームからみたcachexiaへのアプローチ

Approach to cachexia by palliative care team

米田孝一／浅川明弘／乾　明夫

SUMMARY

緩和ケアは癌患者に寄り添い，疼痛や身体的，心理的，スピリチュアルな問題に対処することにより，患者のQOLを向上させるためのチーム医療である。癌患者では食思不振，摂食量低下，体重減少の頻度は高く，それらの症状が心理・行動やほかの身体症状に対して影響を及ぼす。緩和ケアチームは全人的医療を展開し，一人ひとりの患者のcachexiaを含む諸症状と心理的影響に対応する。

KEY WORDS

- cachexia
- 緩和ケア
- 輸液
- 経口摂取
- 心理的影響

I
はじめに

緩和ケアチームの役目は，患者の気がかりを汲み取り，最善の対応策を提供することである。気がかりというオープンクエスチョンのなかには，痛み，倦怠感，食欲不振，食事に対する希望，病状や死に対する不安，家族のことや人生について思うことなど，身体的，心理的，スピリチュアルな面も含めた多種多様なものがある。本稿ではcachexiaと緩和ケアについて述べる。

II
緩和ケア

1．緩和ケアとは

世界保健機関（WHO）による緩和ケアの定義によれば，生命を脅かす疾患に伴う問題に直面している患者と家族に対し，疼痛や身体的，心理的，スピリチュアルな問題を早期から正確に評価し対処することにより，苦痛の予防と軽減を図り，QOLを向上させるアプローチである。

わが国では2007年に「がん対策基本法」が施行された。この基本理念は，①がんの克服を目指し，総合的な研究を推進して，がんの予防，診断，治療などに係る技術の向上や研究の成果を普及させる，②がん患者がどこに住んでいても，等しく適切ながん医療を受けることができる，③患者の置かれている状況に応じて，本人の意向を十分尊重してがんの治療方法等が選択されるように，がん医療を提供する体制の整備をする，というものである。

このような流れのなかで，「がん対策推進基本計画」が掲げられ，疾患の早期から緩和ケアが提供される体制を作ることが促されている。そして，①がん診療連携拠点病院を中心として緩和ケアチーム，緩和ケア病棟，在宅療養支援診療所等による地域連携の推進，②精神心理的な苦痛に対する心のケア等を含めた全人的な緩和ケアの提供，③医師を対象とした普及啓発，④より質の高い緩和ケアを実施していくための緩和ケアに関する専門的な知識や技能を有する医師，精神腫瘍医，緩和ケアチームの育成が，取り組むべき施策として掲げられている。

2．緩和ケアチーム

わが国において，ホスピスや緩和ケア病棟で亡くなる患者は全体の５％に満たず，ほとんどの患者が一般病棟で亡くなっているため，一般病棟で緩和ケアを提供することが求められている。緩和ケアチームの設置はがん診療連携拠点病院の指定要件に盛り込まれており，一般病棟で各科の担当医から依頼を受け，患者の総合的な評価を行い，包括的な支援を行うために多職種で行う。その構成員には，身体症状緩和担当医，精神症状緩和担当医，専従看護師，専任薬剤師，理学療法士，作業療法士，管理栄養士，臨床心理士，ソーシャルワーカー，音楽療法士，宗教家，ボランティアなどがいる。緩和ケアチームは，一般病棟で主治医団・担当医からの依頼を受け，多職種によるコンサルテーションを行い，主治医団とともに治療計画を立て，的確な助言を行う。

III
緩和ケアにおけるcachexia

1．Cachexia

Cachexiaは食欲不振や体重減少を主徴とし，体脂肪量とともに骨格筋筋肉量が減少した病態である。癌をはじめ，心不全，慢性閉塞性肺疾患，炎症性腸疾患，

慢性腎不全，後天性免疫不全症候群などさまざまな疾患でみられる。この病態はQOLや予後を悪化させるため，治療が必要である。Cachexiaの診断，病態，発生メカニズムの詳細は他稿に譲ることにするが[1]，これまで明確な定義がなされていなかった診断基準が，2007年12月に開かれたthe cachexia consensus conferenceをふまえて，2008年に発表された[2]。

2．緩和ケアチームとしての関わり

筆者が緩和ケアチームで経験したコンサルテーションには，疼痛，食欲不振，腹部膨満感，嘔気，排便異常，呼吸困難，浮腫，身の置き所のない感じ，家族に対する心配，あとどれくらい生きられるのか，楽に逝かせてほしい，死に対する恐怖，不安，不眠，せん妄などの主訴があった。特に進行癌，終末期癌患者において食欲不振を訴えることは多く，緩和ケアチームが受けるコンサルテーションでもその頻度は高い。そこで，食欲不振→栄養不良→cachexiaの悪化を食い止めるためにも，患者の訴えに耳を傾け，早期の対応が必要である。また，すでにcachexiaの病態となっている場合には，その状態への慎重な対応が求められる。

IV
栄養療法

終末期癌患者を対象とした在宅経静脈栄養に関する研究において[3)-7)]，高カロリー輸液の効果を認めた病態では消化管閉塞を伴っており，高カロリー輸液の効果があるのはそのような場合に限定されることが示唆される。また，輸液療法はcachexiaや生命予後延長の改善には効果がないことを示唆する報告[8)9)]も存在する。

消化管閉塞の患者では終末期まで経口摂取が可能な場合があり，摂取量が少量であっても経静脈栄養よりも経口による栄養補給が推奨される。そのため緩和ケアにおいては，経口摂取量を改善させるための工夫が重要である[10)]。経口摂取を促すために筆者らは，特殊な酵素で素材を処理して調理された摂取回復支援食（あいーと®）を用いることがある。噛まずに飲み込んでも消化がよく栄養素が吸収されやすいのが特徴であり，さらに料理の見た目は全く普通の料理と一緒であり，視覚的な効果による食欲増加が期待でき食べる喜びも得られるため，患者の満足度は高い。

日本緩和医療学会による『終末期がん患者の輸液療法に関するガイドライン2013年版』[11)]では，「生命予後が1ヵ月程度と考えられる，経口的に水分摂取は可能だが，がん悪液質（cachexia）による食思不振のため栄養摂取が低下している消化管閉塞のない終末期がん患者に対して，生命予後の延長を目的とした輸液を行わないこと」を推奨レベル1B（強い推奨，低いエビデンスレベル）としている。したがって，cachexiaは積極的な非経口的栄養療法の適応ではなく，経静脈栄養は補助的手段として用いてできるだけ経口・経腸栄養を行い，消化管通過障害などで経腸栄養を行えない場合には経静脈栄養を選択することが望ましい。

V
Cachexiaにおける心理的影響

Cachexiaの病態に伴う心理的な影響は，食欲低下，摂食量の減少，体重減少，心理社会的な要因などに関連した否定的な感情と定義されている[12)]。心理社会的な影響には否認，怒り，取り引き，抑うつの経験などが含まれ，これらはエリザベス・キュブラー・ロスの「悲哀の5段階」にも重なる。

その心理的影響を減らすには，cachexiaの病態に関連する症状にいかに

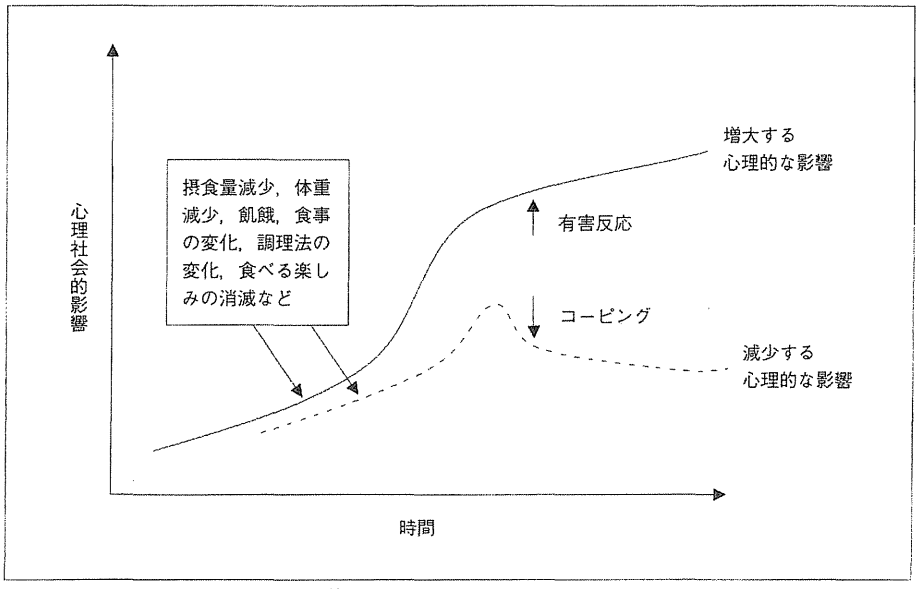


図1．Cachexiaによる心理的な影響

（文献12）より改変・引用）

コーピング（対処）するかによる[13]（図1）[12]。そのため，緩和ケアでは患者に向き合い，気がかりを傾聴し，それに対応することが重要である。たとえば，摂食行動が阻害されたことによる心理的影響がある場合には，摂食行動を取り戻すケアをすることで心理的な影響を減少させることができる。

心身医学の手法に認知行動療法がある。これは認知や思考の歪みの変容，行動の変容を行うものである。強いストレスを受けたり，うつ状態になっているときには認知に歪みが生じ，抑うつ感や不安感，非適応的な行動が強まり，さらなる認知の歪みが引き起こされるようになる。たとえば，未来に関する否定的な見方，全か無かの思考，破局的な見方，独断的な推論，過度の一般化，べき思考，自己関係づけなどである。そこでまず，患者に自らの認知パターンに注目するように勧め，そのようになった根拠や理由を尋ねたりほかの選択肢を探ったりしながら認知パターンを振り返り，客観的に現実を見つめ直すようにする。同時に，問題に対処する方法を身につけたり，対人関係を改善するコミュニケーション術を身につけたりする目的で，実際に行動を起こして望ましい行動形成をする。

Ⅵ おわりに

「最期のときまで口から食事をしたい」，「管につながれたくない」と願う患者もいるため，消化管閉塞がないかぎりは輸液をせずに経口摂取ができるように工夫をすることの重要性は高い。Cachexiaがもたらす症状を緩和することは，心理的な影響を緩和することにもつながり，逆に心理的な影響を緩和することがcachexiaの症状緩和にもつながる。

緩和ケアチームは最期まで患者の願いを叶える役目を担っている－患者に寄り添いながら。

REFERENCES

1) Inui A : Cancer anorexia-cachexia syndrome : current issues in research and management. CA Cancer J Clin 52 : 72-91, 2002
2) Evans WJ, Morley JE, Argiles J, et al : Cachexia : a new definition. Clin Nutr 27 : 793-799, 2008
3) August DA, Thorn D, Fisher RL, et al : Home parenteral nutrition for patients with inoperable malignant bowel obstruction. JPEN J Parenter Enteral Nutr 15 : 323-327, 1991
4) Mercadante S : Parenteral nutrition at home in advanced cancer patients. J Pain Symptom Manage 10 : 476-480, 1995
5) Pasanisi F, Orban A, Scalfi L, et al : Predictors of survival in terminal-cancer patients with irreversible bowel obstruction receiving home parenteral nutrition. Nutrition 17 : 581-584, 2001
6) Bozzetti F, Cozzaglio L, Biganzoli E, et al : Quality of life and length of survival in advanced cancer patients on home parenteral nutrition. Clin Nutr 21 : 281-288, 2002
7) Duerksen DR, Ting E, Thomson P, et al : Is there a role for TPN in terminally ill patients with bowel obstruction? Nutrition 20 : 760-763, 2004
8) Gutman M, Singer P, Gimmon Z : Is there an indication for parenteral nutrition support in the terminally ill cancer patient? Harefuah 147 : 224-228, 2008
9) Dev R, Dalal S, Bruera E : Is there a role for parenteral nutrition or hydration at the end of life? Curr Opin Support Palliat Care 6 : 365-370, 2012
10) Ripamonti C, Twycross R, Baines M, et al : Working Group of the European Association for Palliative Care : Clinical-practice recommendations for the management of bowel obstruction in patients with end-stage cancer. Support Care Cancer 9 : 223-233, 2001
11) 日本緩和医療学会緩和医療ガイドライン委員会編：終末期がん患者の輸液療法に関するガイドライン2013年版．東京，金原出版，2013
12) Hopkinson JB, Fenlon DR, Okamoto I, et al : The deliverability, acceptability, and perceived effect of the Macmillan approach to weight loss and eating difficulties : a phase II, cluster-randomized, exploratory trial of a psychosocial intervention for weight and eating related distress in people with advanced cancer. J Pain Symptom Manage 40 : 684-695, 2010
13) Oberholzer R, Hopkinson JB, Baumann K, et al : Psychological effects of cancer cachexia : a systematic literature search and qualitative analysis. J Pain Symptom Manage 46 : 77-95, 2013

よねだ・こういち
鹿児島大学大学院医歯学総合研究科社会・行動医学講座心身内科学分野特任講師
あさかわ・あきひろ
鹿児島大学大学院医歯学総合研究科社会・行動医学講座心身内科学分野准教授
いぬい・あきお
鹿児島大学大学院医歯学総合研究科社会・行動医学講座心身内科学分野教授