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Cancer Cachexia in Pancreatic Cancer Patients: Recent Advances and New Therapeutic Approach

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About 80% of all pancreatic cancer patients suffer from a wasting syndrome defined as the cancer cachexia characterized by abnormally low weight, weakness, and loss of skeletal muscle mass, which directly impacts physical activity, quality of life and overall survival. Over the past decades, we have gained new insights into the underlying mechanism of cachexia associated with pancreatic cancer. The aim of this review was to explore recent findings about cancer cachexia pathophysiology and describe the current pharmacologic approach. Pancreatic cancer cachexia is a multifactorial syndrome mediated by mechanical factors, inflammatory cytokines, neuropeptides, hormones and tumor-derived factors. The treatment of cancer cachexia remains controversial but is currently an active area of research. Several new targeted drugs are under investigation, and we hope to open a new prospect in the management of cancer cachexia in the future.

Key Words: Anorexia-cachexia syndrome, Pancreatic cancer cachexia, Pancreatic adenocarcinoma

INTRODUCTION

Cachexia is a multifactorial syndrome with ongoing loss of skeletal muscle mass, with or without loss of fat mass that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.[1] It can occur in the course of chronic benign disease such as congestive heart failure or human immunodeficiency virus (HIV) infection. However, it is most frequently observed in patients with malignancy, especially in advanced stage of disease. Many patients with advanced cancer suffer from a wasting syndrome characterized by anorexia, loss of weight, sarcopenia, and a poor prognosis, defined as the cancer anorexia-cachexia syndrome.[2]

Cachexia is highly prevalent in pancreatic cancer, and up to 80% of pancreatic cancer patients undergo severe cachexia at the time of death.[3,4] This wasting syndrome is related with poor tolerability of cancer treatment, and furthermore, it can reduce quality of life and expected survival of the patients.[5-7] In addition, preoperative existence of cachexia in pancreatic cancer patients has been associated with poor outcome after pancreatoduodenectomy.[8]

Although new insights into the pathogenesis of cancer cachexia have been gained over the past decades, the underlying mechanisms are still poorly understood. It is currently to be an active area of research for potential treatment targets of cancer cachexia. We believed that improvement in overall survival or quality of life in pancreatic cancer patients could be achieved from a better management of cachexia. This article reviews the current concepts and therapeutic approach of this disabling phenomenon.

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1. Definition and classification of cancer cachexia

The consensus diagnostic criteria of cancer cachexia defined as a case of (1) involuntary weight loss more than 5% in the last 6 months if no starvation present; (2) weight loss more than 2% in individuals with body mass index (BMI less than 20 kg/m^2; or 3) weight loss more than 2% along with skeletal muscle index (SMI) consistent with sarcopenia (males <7.26 kg/m^2, females <5.45 kg/m^2) (Table 1). Any direct measure of skeletal muscle mass (dual-energy X-ray absorptiometry (DEXA), computed tomography (CT), magnetic resonance imaging (MRI)) is recommended in case of fluid retention, massive tumor load or obesity.[9]

This international consensus also described three stages of cachexia; precachexia, cachexia, and refractory cachexia.[9] Severity is based on the degree of depletion of energy store and body protein mass (using BMI) and the rate of ongoing weight loss. In precachexia, patients with early clinical and metabolic signs including anorexia and impaired glucose tolerance can precede considerable involuntary weight loss. Some patients then have progressive weight loss and meet the criteria for cachexia as previously defined. Large retrospective cohort study for pancreatic cancer revealed that a reduction in BMI developed as early as 3 years prior to cancer diagnosis and cachexia-associated symptoms presented at average 2 months before the cancer diagnosis.[10,11] Unfortunately, most patients with pancreatic cancer usually demonstrate in the advanced stage with cachexia symptoms,[12] and their cachexia becomes clinically refractory as a result of progressive unresponsive to cancer treatment. In refractory cachexia stage, patients have worsening performance status with expected survival less than 3 months.

Table 1. Diagnosis of cancer cachexia

Weight loss greater than 5% over the past 6 months; or
Weight loss greater than 2% in individuals with BMI less than 20 kg/m^2; or
Evidence of sarcopenia*withweightlossgreaterthan 2%

*Sarcopenia defined as appendicular skeletal muscle index in males <7.26 kg/m^{2}and infemales <5.45 kg/m^2 determined by DEXA.

2. Pathophysiology of cancer cachexia

Cancer cachexia arises from a complex interaction between cancer growth and host response resulting ongoing weight loss, a consequence of a negative protein and energy balance mediated by a combination of reduced food intake and increased metabolism.[1,9] The pathophysiology includes a series of complex metabolic mechanisms directly related to the tumor-host interaction (Fig. 1). There are mechanical factors that contribute to reduced food intake, tumor-derived factors released from the tumor itself and humoral factors generated as the host's biological response to the tumor. Several pro-inflammatory cytokines, circulating hormones, neuropeptides,

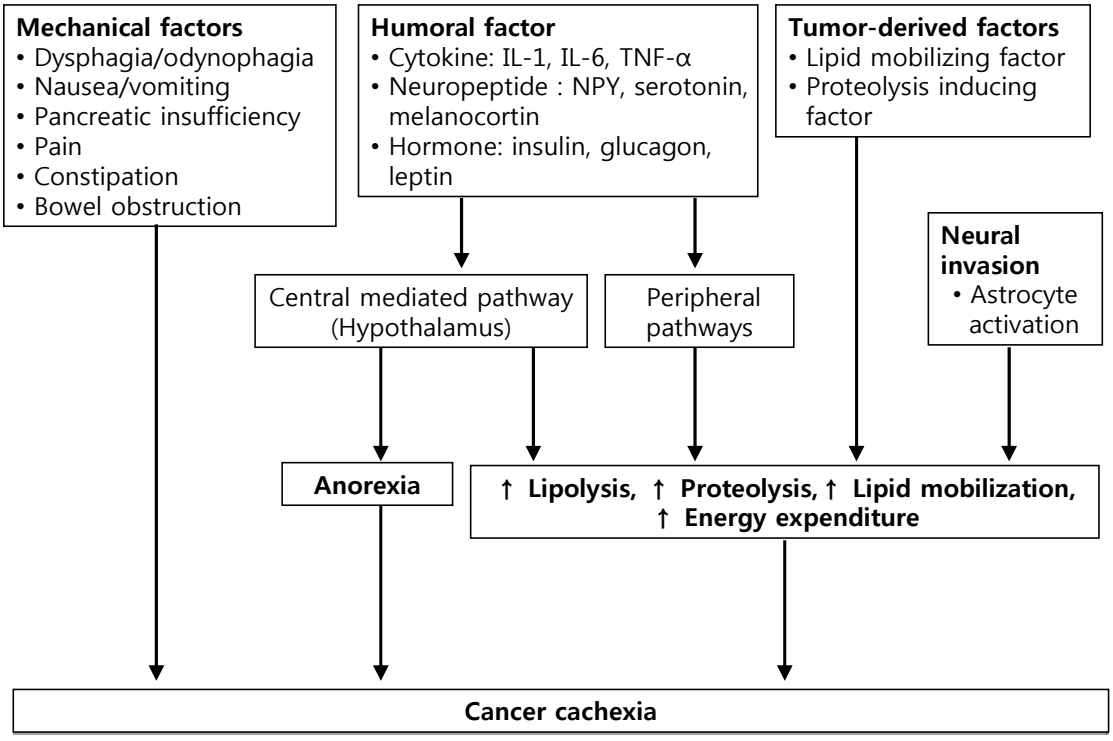

Fig. 1. Pathopysiology of cachexia in pancreatic cancer. There are several factors which contribute to develop cachexia in pancreatic cancer, including mechanical factors, tumor-derived factors, humoral factors and neuronal invasion. Several pro-inflammatory cytokines, circulating hormones, neuropeptides, and neurotransmitters result in anorexia and metabolic alteration, such as increased lipolysis, proteolysism lipid mobilization and energy.
*Adapted from Tan et al. Front Physiol 2014;5:88.1

and neurotransmitters can affect the development of cancer cachexia.[13] In addition recent studies have described the other potentially momentous processes involved in the development of pancreatic cancer cachexia, including astrocytic activation from neural invasion of pancreatic cancer.[14,15]

3. Mechanical factors

Mechanical digestive abnormalities that can reduce food intake and result in a lack of appetite include abdominal pain, nausea, dysphagia, odynophagia, pancreatic insufficiency, constipation, and intestinal obstruction.[16] They can induce and maintain cancer-associated weight loss. These symptoms result from direct cancer invasion to pancreatic duct and/or gastrointestinal tract, particularly the duodenal second portion. Also, some patients who received the resection of pancreas suffer from pancreatic insufficiency and poor oral intake.

4. Humoral factors

The humoral mediators of cancer cachexia include pro-inflammatory cytokines (interleukin-1 (IL-1), interleuin-6 (IL-6), interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), neuropeptides (neuropeptide Y, serotonin, melanocortin) and hormones (insulin, glucagon, leptin). These pathways can be divided into central pathways, which are controlled at brain hypothalamus, and peripheral pathways, which associate with direct lipolysis and proteolysis.

1) Centrally-mediated pathways

Recent evidence suggests that systemic inflammation plays a pivotal role in inducing cancer anorexia by triggering a complex neurochemical pathways in hypothalamus.[17,18] Increased cytokine expression prevents the activation of hypothalamus from responding appropriately to peripheral signals by persistent stimulation of anorexigenic pathways and inhibition of orexigenic pathways.[19,20] Some studies reveal that cancer cachexia is associated with hyperactivation of the pro-opiomelnocortin (POMC)/cocaine and amphetamine-regulated transcript (CART) pathways (one of anorexigneic pathways) which may be triggered by IL-1 and other pro-inflammatory cytokines.[21-24]

Leptin is a protein with homeostatic effect released by fatty tissue, which reduces appetite and increase energy expenditure through the central nervous system (CNS). In situation of weight loss, leptin release is decreased and this stimulation the appetite in the CNS by activation of neuropeptide Y (NRY)/Agouti-related peptide (AgRP) pathway (one of orexigenic pathways) and reduced activity of anorexigenic neuropeptide, such as corticotropin-releasing factor (CRF) and melanocortin. Current studies for cancer cachexia suggest that inflammatory cytokine like IL-1 and TNF-α activate the leptin signaling and disturb the orexigenic response to decreased peripheral leptin level.[19,25]

Serotonin also may play an important role in the development of cancer anorexia through the melanocortin system. Studies suggested that IL-1 stimulates the release of hypothalamic serotonin, which contribute to the persistent activation of POMC/CARD pathway, resulting in decreased appetite and anorexia.[26,27]

2) Peripheral pathways

Inflammatory cytokines not only contribute to the neurochemical changes in the CNS responsible for anorexia, but also have been revealed to induce proteolysis, lipolysis, and the hepatic acute phase protein response (APPR) through the numerous pathways. These processes develop the uncompensated loss of muscle and adipose tissue.

TNF-α is one of the first identified as an endogenous cachexia-inducing factors. TNF-α stimulates protein degradation in the proteasome-ubiquitin system, mediated by transcription factors, such as nuclear factor kappa B (NF-κB) and MyoD.[28-30] Some studies also showed that TNF-α promote lipolysis in vitro with increase in glycerol release in mouse and human adipocyte, through downregulation of perilipin expression, which subsequently induce hormone-sensitive lipase (HSL), a key regulator of lipolysis, to access the surface of lipid droplets for breakdown.[31,32] Additionally, TNF-α has a inhibitory action on adipocyte differentiation, resulting in impaired lipogenesis.[33,34]

IL-6 is another important cytokine in the development of cachexia in pancreatic cancer, particularly associated with activation of the hepatic APPR. Moses et al found that overproduction of IL-6 and elevated APPR (for example; elevated c-reactive protein (CRP) level) have been significantly associated with decreased survival in patients with pancreatic cancer cachexia.35There is strong relationship between increased IL-6 production of peripheral blood mononuclear cells and the presence of elevated APPR.[35-37] The activation of hepatic APPR promote the mobilization of peripheral amino acid stores, mostly from skeletal muscle, contributing to the loss of lean body mass.

5. Tumor factors

In addition to several humoral factors such as cytokines,

hormones and neurotransmitters, tumor-derived factors contribute to metabolic dysregulation in pancreatic cancer cachexia. There are two most well studied factors, lipid mobilizing factor (LMF) and proteolysis-inducing factor (PIF).

LMF was first discovered from a cachexia-inducing murine tumor model and the urine of patients with unresectable pancreatic cancer with weight loss.[38] This material was 43 kDa and was suggest to be homologous with the plasma protein zinc-α_2-glycoprotein (ZAG).[38] LMF/ZAG not only induces lipid mobilization through various signal pathways but also augment substrate utilization and activates mitochondrial oxidative pathways in brown adipose tissue. Consequently, LMF/ZAG causes lipolysis with increased energy expenditure, and catatbolism.[39-41] Recently, LMF/ZAG is proposed as a serum biomarker in pancreatic cancer cachexia.[42]

PIF was isolated in 1996 from a mouse tumor model of cachexia, as a 24 kDa glycoprotein inducing skeletal muscle catabolism.[43] PIF was detected in the urine of 80% of pancreatic cancer patients with cachexia, and rate of weight loss was greater in patients who have PIF in their urine.[44] Also, when PIF from urine of cancer cachexia patients administered intravenously to normal mice, PIF induced significant weight loss without reduction in food and water intake.[45] Some studies suggest that PIF-mediated protein degradation may be mediated by the ubiquitin-proteasome proteolytic pathway in skeletal muscle; that process results from activation of NFκB.[46-48] Also, PIF inhibits the protein synthesis on skeletal muscle through activation of double-stranded RNA dependent protein kinase (PKR).[49]

6. Other mechanisms

Recent studies have suggested that neural invasion of pancreatic cancer is related to astrocyte activation and development of cachexia in pancreatic cancer patients.[14,15] Neuronal invasion of pancreatic cancer induce the activation of astrocytes and microglia in the spinal cord. These activated astrocytes can subsequently develop lipolysis and muscle atrophy in pancreatic cancer patients, although more researches is needed to determine the underlying mechanisms involving cachexia.[14]

7. Treatment of cancer cachexia

The primary end-points of optimal treatment of cancer cachexia are improvements in cachexia-associated symptoms such as anorexia and fatigue, lean body mass, resting energy expenditure, quality of life, and performance status through inhibition of effect of pro-inflammatory cytokines.[50] Although there has been recently remarkable advances in preclinical and clinical research in era of cancer cachexia , the currently available treatment options are still limited.

8. Nutritional support

Nutritional risk is highest among pancreatic cancer patients.[51] However, despite several trials of conventional and/or aggressive nutritional support using different feeding techniques, the cachectic state is difficult to be overcomed by nutritional support alone.[52] A small multicenter randomized trial for patients with advanced pancreatic cancer showed a meaningful improvement in weight and body mass composition as well as quality of life with L-Carnitine supplementation.[53]

9. Pharmacologic treatment

The two major options for pharmacological therapy have been, till now, either progestational agents or corticosteroids. Recently, there are various drugs studied for treatment of cancer cachexia.

Megestrol acetate is semi-synthetic progesterone widely used as an appetite stimulant. The pharmacologic activity of megestrol acetate was considered as reduced release of pro-inflammatory cytokines (IL-1, IL-6, TNF-α) and stimulation of NPY in the hypothalamus.[54,55] Several randomized control trials have demonstrated that megestrol acetate (480-800 mg/ day) significantly improves appetite, nausea, food intake, and weight gain among patients with cancer cachexia, including those with pancreatic cancer.[56-59] Megestrol acetate is generally well-tolerated with low incidence of adverse events, such as skin rash, hyperglycemia, adrenal insufficiency, and thromboembolic events.57 Since its approval in 1993, several meta-analyses have revealed that megestrol acetate has better effect of improved appetite, weight, and quality of life compared than placebo or other drugs (cisapride, dronabinol, corticosteroids, nandrolone).[60,61]

Corticosteroids, such as dexamethasone, have been studied to treat cancer-associated anorexia and cachexia.[62,63] The mecha nism of action is likely associated with the inhibition of IL-1, TNF-α, and leptin as well as the stimulation of NPY.[64] However, the effects of corticosteroid could not be maintained longer than 4 weeks and related to long-term side effects, such as insulin resistance, fluid retention, steroid-induced myopathy, skin fragility, adrenal insufficiency, and sleep and cognitive disorders.65Owing to their short term symptomatic benefits with long term adverse effects, corticosteroids are just considered as treatment option in patients with short expected survival.

Dronabinol is effective in reducing nausea and increasing appetite with a tendency to weight stabilization. The appetite-stimulant effect of dronabinol associated with interaction with endorphin receptors, interference with IL-1 synthesis, activation of cannabinoid receptors involved in the neuronal circuit of leptin and inhibition of prostaglandin synthesis.[20] A phase II study showed that dronabinol decreased anorexia in 68% of patients, but 16% of patients had to stop administration due to CNS adverse events, such as euphoria, hallucinations, psychosis, and vertigo.[66] However, in result of first clinical trial that compared megestrol acetate with dronabinol, megestrol acetate was appears to be superior to dronabinol in aspect of increasing appetite and weight gain.[67] Dronabinol serves as an alternative treatment option as an appetite stimulant and anti-emetic.

Non-steroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 (COX-2) inhibitors, ibuprofen, and indomethacin, reduce release of acute phase proteins and pro-inflammatory cytokines.[68,69] NSAIDs are suggested to inhibit prostaglandin synthesis and thereby prevent downstream effects of systemic inflammation. Preliminary results of some studies for NSAIDs, such as indomethacin and ibuprofen, have been shown to effect to increase weight and muscle mass, improve quality of life, and prolong survival in advanced cancer patients, especially when combined with progestogens.[69-72] However, further large studies are needed to validate the clinical role of NSAIDs in the management of cancer cachexia.

Thalidomide have anti-inflammatory and immunomodulatory properties that downregulate the production of TNF-α and other cytokines, inhibit NF-κB, downregulate COX-2, and inhibit aniogenesis.[73] In 2005, Gorden et al. published the results of a single center, double blinded, placebo-controlled, randomized study aimed at assessing the efficacy and safety of thalidomide in attenuating weight loss in pancreatic cancer patients with cachexia.[74] The study population consisted of 50 patients (who had lost at least 10% of their body weight) randomized to administer thalidomide 200 mg/day or a placebo for 24 weeks. The conclusion of the study strongly suggested that thalidomide was effective for attenuating loss of weight and lean body mass in patients with cancer cachexia. Thalidomide was typically well-tolerated. Adverse events included peripheral neuropathy, dizziness, somnolence, constipation, rash, and possible increased risk of venous thromboembolism. These results are significant but further large-scale clinical trials are needed to validate the efficacy of thalidomide in treating pancreatic cancer cachexia.

Cyproheptadine is an antiserotoninergic agent with antihistamine properties. Despite some promising results of pilot studies, controlled clinical trials have not yet proved its efficacy in cancer cachexia patients.[75,76] Pizotifen is an antiserotoninergic drug studied in the treatment of anorexia associated with other benign causes, which has not been investigated in cancer patients.

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), a long-chain polyunsaturated fatty acid of the omega-3 family, are have been revealed to suppress production of pro-inflammatory cytokines, including IL-1, TNF-α, and IL-6.[77,78] EPA can also inhibit the downstream effect of LMF and PIF.[79-81] Their efficacy in cancer cachexia has not been fully validated in well-organized clinical trials.[82-84] Two systematic literature reviews conclude the EPA and DHA in monotherapy show no significant improvement in appetite, fat free mass, survival and quality of life compared with placebo.[85,86] The efficacy of EPA in cancer cachexia treatment remains uncertain although recent study suggest that EPA supplementation may not be effective as a single agent or even in combination with megestrol acetate in patients with cancer cachexia.

Current studies are investigating an approach of drug combinations to attenuate cancer cachexia. A recent data from a large multicenter trial with 332 patients comparing medroxyprogesterone, megestrol acetate, and oral supplementation with EPA, L-carnitine, and thalidomide found that the combination therapy was significantly effective in improving lean body mass and appetite than any other treatment arms with single drug treatment.[87]

10. New therapeutic targets

Due to lack of the available drugs that have shown sustained effects on weight stabilization and improvement in survival, various researches have continued to explore new therapeutic targets and to develop new drugs.

OHR/AVR 118 is a recently developed, broad-spectrum peptide-nucleic acid immunomodulator that target both TNF-α and IL-6. A phase II study including patients with advanced cancer and cachexia presented an improvement in anorexia, dyspepsia, strength anddepression.[88] A phase IIb study is currently underway to evaluate the safety and efficacy of OHDR/AVR118(NCT01206335).

ALD518 (also known as BMS-945429), a humanized monoclonal IL-6 antibody, showed promising beneficial results in phase II randomized, double-blinded, placebo-controlled trials with non-small cell lung cancer (NSCLC) patients with cachexia.[89,90] This agent was safe and well tolerated. ALD518 has effect of increasing hemoglobin level and preventing loss

of lean body mass with significant improvement of fatigue score.[89,90]

Ghrelin is the endogenous ligand of the growth hormone receptor that produces the release of growth hormone and NPY.[91] In addition, Ghrelin induces the release of anti-inflammatory cytokine, IL-10, which suppressed the production of pro-inflammatory cytokines, including IL-1β, Il-6 and TNF-α.[92-94] Several controlled clinical trials using oral ghrelin mimetic named RC-1291 or anamorelin, demonstrated an improvement in increasing appetite and weight in cancer cachexia patients.[95-97] Macimorelin is a novel oral ghrelin compound, with a good oral availability and stability, which binds the growth hormone secretagogue receptor (GHSR) 1a with similar affinity to ghrelin.[98] These findings promoted further inves tigation for ghrelin analogs andmore phase II trials are ongoing (NCT01505764, NCT01614990).

MT-102, a novel anabolic/catabolic transforming agent, has a multi-targeting effect on three potential pharmacological pathways in cancer cachexia, primarily reduced catabolism through nonselective β-blockade, improve fatigue and thermogenesis through blocking central 5-HT 1a receptor, and increased anabolism through partial activation of β-2 receptor.[99] Two phase II studies in stage III/IV colorectal cancer and NSCLC are under investigation (ACT-ONE and ACT-TWO; NCT01238107).[99]

BYM338 (bimagrumab) is a fully humanized monoclonal antibody blocking the activin II receptor type IIB (ActRIIB) and preventing receptor occupation by myostatin. Myostatin, a member of the TGF-β superfamily, is expressed almost exclusively in skeletal muscle and acts as a negative regulator of muscle growth, through binding to the ActRIIB by activating multiple downstream pathways.[100] Inhibition of muscle differentiation by myostatin is mediated, in part, through Smad 2/3 phosphorylation-dependent inhibition of the Akt/mTOR pathway.[100] In preclinical study, ActRIIB blockade prevented muscle loss and prolonged survival in C-26 tumor-bearing mice.[101] A multicenter, randomized, double-blind, placebo-controlled phase II trials to investigate the efficacy of BYM 338 in attenuating loss of body mass in cachectic patients with stage IV NSCLC or stage III/IV pancreatic cancer has been completed and in preparation to report the results (NCT01433263). LY2495655 is another humanized anti-myostatin antibody currently under investigation. A phase II study in patients with locally advanced or metastatic pancreatic cancer is ongoing to evaluate two different doses of LY2495655 in combination with standard of care chemotherapy in improving survival, lean body mass and physical performance (NCT01505530).

CONCLUSION

Although cachexia is a major problem in cancer and many chronic diseases, cachexia treatment is still largely ignored even for inpatient management or limited to dietary counseling to treat weight loss with poor efficacy. Regarding that approximately 80% of pancreatic cancer suffer from cachectic symptoms and up to 30% die from cachexia-related complications, importance of treatment for cancer cachexia, especially in pancreatic cancer patients, should be acquired in the future.[1,102] Although pancreatic cancer cachexia is considered as multifactorial syndrome mediated by mechanical factors, pro-inflammatory cytokines, neuropeptides, hormones and tumor-derived factors, further researches to understand the basic mechanism involved in induction and maintenance of pancreatic cancer cachexia are further needed. Recently, some preliminary studies for targeted agents have been shown promising results. We hoped that new therapeutic strategies will be developed to improve the quality of lifer and prolong the survival of pancreatic cancer patients in the future.

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