Gut barrier dysfunction and microbial translocation in cancer cachexia: a new therapeutic target

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Purpose of Review
Cachexia is a complex metabolic syndrome characterized by skeletal muscle and adipose tissue loss and is frequently associated with emaciation, anorexia, systemic inflammation, and metabolic dysfunction. Lack of a clear understanding of the cause of cancer cachexia has impeded progress in identifying effective therapeutic agents. This review summarizes recent publications on the role of gut barrier function, intestinal microbiota, and inflammation in the etiology of cancer cachexia and new therapeutic interventions that may benefit treatment strategies.

Recent Findings
Significant advances have been made in understanding the composition and metabolic capabilities of the intestinal microbiota and its impact on gut barrier function with implications for certain inflammatory-based diseases. Recent studies reported associations between intestinal permeability and endotoxemia with development of cancer cachexia and other metabolic disorders. Improvements in intestinal function and weight gain along with decreased inflammation have been reported for potential therapeutic agents such as eicosapentaenoic acid, immunoglobulin isolates, and probiotics.

Summary
Continued progress in the scientific understanding of the complex interplay between the intestinal microbiota, gut barrier function, and host inflammatory responses will uncover new therapeutic targets to help avoid the serious metabolic alterations associated with cachexia.

Keywords
cancer cachexia, cytokines, gut barrier, inflammation, microbiota, translocation

INTRODUCTION

Cachexia is a multifactorial condition characterized by systemic inflammation and severe wasting of skeletal muscle, with or without wasting of adipose tissue that causes considerable morbidity and mortality in cancer patients [1,2]. It occurs in 50–80% of cancer patients, has been identified as an independent predictor of treatment failure and decreased survival [3], and continues to be a major public health issue [4■,5■]. Clinical manifestations of cancer cachexia include progressive weight loss, altered immune function, and widespread metabolic changes, which collectively contribute to an increase in fatigue, poor physical function, and diminished quality of life. Weight loss associated with cachexia can be compounded by anorexia with a resultant decrease in energy intake, but it is unclear whether the loss of appetite occurs as a result of systemic inflammation or some other consequence such as nausea, altered taste sensation, swallowing difficulties, or depression. Although a loss of more than 5–10% of body weight is usually taken as a

defining point for cachexia, the degree of weight loss that significantly impacts on prognosis or performance has not been defined [6].

A growing body of evidence indicates that changes in gut permeability and translocation of components of the intestinal microbiota play a key role in eliciting immune-mediated mechanisms that lead to chronic inflammatory, autoimmune, and neoplastic diseases [7]. Research studies using an animal model of colorectal cancer and cachexia have shown that a gradual increase in tumor burden

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KEY POINTS

- Systemic inflammation commonly occurs in patients with cancer cachexia and may contribute to clinical manifestations such as weight loss, anorexia, altered immune function, and metabolic dysfunction.

- Microbial pathogens and intestinal inflammation can compromise intestinal barrier function and result in increased gut permeability, translocation of various microbial substances, and immune activation.

- Recent studies suggest that beneficial commensal bacterial reside among the intestinal microbiota that may support gut homeostasis by maintaining gut barrier function and decreasing immune activation.

- Multimodal treatment strategies that include interventions aimed at maintaining gut barrier function may help counteract the symptom clusters of cancer cachexia.

- Additional research is needed to clarify the role of gut barrier dysfunction, the intestinal microbiota, and systemic inflammation in the cause of cancer cachexia.

leading to cachexia is accompanied by increased gut barrier permeability, elevated plasma endotoxin levels, and evidence of chronic inflammation [8]. Other studies have shown that proinflammatory cytokines as well as procachectic factors from tumor cells are capable of stimulating host inflammatory responses [6]. Several other pathways have also been postulated to participate in the cachectic process including a role for neuroendocrine hormones [9], downregulation of insulin-like growth factor 1 (IGF-1) [3,10], and various mediators involved with the acute-phase protein response (APPR) [11,12].

Several clinical studies have shown that traditional nutrition-based interventions are ineffective at reversing the metabolic abnormalities seen in patients with cancer cachexia [13,14]. In this short review, we summarize recent advances in understanding the complex interplay between the intestinal microbiota, barrier function, and host inflammatory responses as it relates to cachexia, which may lead to new therapeutic targets and treatment strategies.

SYSTEMIC INFLAMMATION AND CANCER CACHEXIA

Systemic inflammation is commonly observed in patients with cachexia and has been postulated to play a key role in the etiology of the condition [15■■,16■■,17■]. The metabolic changes that occur with cachexia have been reported to resemble those of infection rather than starvation [18], and

cancer patients who continue to lose weight concurrent with systemic inflammation have poorer performance status [19]. Production of acute-phase proteins, such as C-reactive protein (CRP) and fibrinogen, is considered accurate measure of systemic inflammation and proinflammatory cytokine activity [20]. Increased production of CRP and fibrinogen in cachexia patients have also been associated with reduced quality of life and shortened survival [21,22]. Levels of CRP have been reported to increase in parallel with progressive weight loss in cachectic patients [20], suggesting that proinflammatory cytokine activity increases during the advancement of the disease [23,24].

Some pro-inflammatory cytokines are elevated in patients with cachexia, including tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), [6,15■■], and have been postulated to play a role in the etiology of the condition. Studies have shown that activation of proinflammatory cytokines is associated with decreases in appetite and food intake, increased muscle wasting, and contributes to a hypermetabolic state in the setting of cancer [6,15■■,25]. Other studies in animal models have demonstrated that administration of proinflammatory cytokines can induce cachexia-like effects in the absence of tumors, and such outcomes can be reversed by administering neutralizing antibodies directed at TNF-α, IL-6, IL-1, and interferon (IFN)-γ [15■■,26]. Other circulating mediators that have been postulated to play a role in the metabolic effects associated with cancer cachexia include: upregulation of inflammatory gene expression by nuclear factor-κB, proteolysis-inducing factor [6,27], upregulation of the cytokine myostatin leading to decreased muscle growth and differentiation [28], and downregulation of IGF-1.

The exact cause of the APPR associated with many malignancies and cachexia is not known. It has been hypothesized that the elevated levels of proinflammatory cytokines in cachexia is the result of direct tumor cell production or caused by host inflammatory responses to tumor cells [2]. However, it is also possible that a breakdown in gut barrier function in association with perturbations in the intestinal microbiota may be responsible for persistent immune activation [29■■]. There is increasing evidence to suggest that disturbances in epithelial tight junction barrier, caused by intestinal pathogens or other noxious substances, can lead to localized inflammation and paracellular penetration of proinflammatory antigens and other substances present in the intestinal lumen; passage may involve intact bacteria, lipopolysaccharides or other bacterial components, and digestive enzymes [30]. Intestinal inflammation can lead to release of

proinflammatory cytokines, which can further exacerbate mucosal damage and gut permeability [31]. Although the causative role of gut barrier dysfunction in the context of systemic inflammation associated with cachexia is hypothetical, data from animal model studies indicate that it could play a primary or supplemental role. At the very least, gut barrier dysfunction may exacerbate systemic inflammation in the presence of other sources of inflammation and further contribute to the anorexia, muscle wasting, and other hyper-metabolic changes seen in cachexia.

INTESTINAL CHANGES THAT CAN LEAD TO PERSISTENT IMMUNE ACTIVATION

The gastrointestinal tract is contiguous with the external environment by nature of its exposure to an enormous array of different bacterial species, the intestinal microbiota. The highly differentiated structure of the small intestinal epithelium provides a barrier mechanism that plays a vital role in nutrient absorption and regulating the trafficking of macromolecules between the lumen of the intestine and the systemic circulation [30]. On the luminal side, the gut microbiota exists in symbiosis with the intestinal lining by protecting against pathogenic infection (e.g., competition, emitting bacteriocins, among others.) and producing short-chain fatty acids and other metabolites that support barrier function and energy metabolism [29▪▪,32]. Two primary systems govern the effectiveness of the gut barrier: intestinal permeability, regulated by intercellular tight junctions, and intestinal mucosal defense, provided by gut-associated lymphoid tissue.

Gut barrier dysfunction

Some environmental factors can cause a breakdown of intestinal barrier function that can lead to translocation of intact microorganisms or microbial substances from the lumen of the gastrointestinal tract into the systemic circulation (reviewed in [33▪▪]). For example, certain pathogenic bacteria produce enterotoxins that target epithelial tight junction proteins and cause increased paracellular permeability [34]. Infection with viruses that cause diarrheal disease, such as rotavirus and norovirus, and certain other disease states can also result in a breakdown of the tight junction barrier leading to increased antigen uptake [35]. More importantly, there is speculation that chemotherapy itself can cause molecular changes in tight junctions, which may also contribute to gut barrier dysfunction, inflammation, and diarrhea commonly associated with chemotherapy-induced gut toxicity [36]. The increased 'leakiness'

of the tight junction barrier allows greater absorption or translocation of luminal antigens and other substances into underlying intestinal tissues and the systemic circulation. Processing of these antigenic substances by antigen-presenting cells and helper T lymphocytes leads to an immune activation characterized by increased production and release of proinflammatory cytokines and recruitment of inflammatory cells [30].

A developing body of evidence also indicates that intermittent or even minor inflammation in the intestinal mucosa can elicit changes in intestinal structure and function leading to increased mucosal permeability (reviewed in [33▪▪,37]). Several studies involving both conventional animals and gene knockout animal models have demonstrated the role of proinflammatory and anti-inflammatory cytokines in modulating intestinal epithelial tight junction barrier. For example, increased production of pro-inflammatory cytokines such as TNF-α, IFN-γ, and various interleukins [30,38–40] have been shown to increase paracellular permeability by impacting the expression or degradation of claudin and occludin tight junction proteins [41,42]. Conversely, certain anti-inflammatory cytokines such as IL-10 and transforming growth factor-β appear to maintain tight junction barrier and protect against intestinal inflammation [30].

Intestinal barrier dysfunction combined with increased translocation of proinflammatory substances into the systemic circulation has been suggested to play a role in the cause of several intestinal diseases and conditions, including celiac disease, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and colorectal cancer [43▪,44▪,45]. Passage of intact microbes or microbial substances like bacterial lipopolysaccharides (endotoxin) into the general circulation can lead to elevated systemic inflammatory responses. One extreme example of uncontrolled systemic inflammation is septic shock, in which the increased production of proinflammatory cytokines can lead to capillary damage, serious metabolic changes, and multiple organ failure [46]. Although the gut has been implicated in the development of systemic inflammation and multiple organ failure in both experimental models and in clinical studies, its exact role in the cause of these conditions is not well understood [47,48]. Similarly, it is plausible that increased bacterial endotoxin translocation can lead to the elevated systemic inflammation observed in patients with cachexia.

Puppa *et al.* [8] provided experimental evidence for the association of gut barrier dysfunction and endotoxemia in cachexia using the ApcMin/+ mouse model of colon cancer. Cachexia progressed

along with barrier dysfunction and was correlated with systemic lipopolysaccharide and IL-6 levels. Zhang et al. [49] studied the relationship between intestinal permeability and cachexia in cancer patients and found that cachectic patients had a significantly higher rate of microbial translocation (MT) than noncachectic patients and healthy controls. In addition, cachectic patients with evidence of MT had higher plasma levels of IL-1α, IL-6, IL-8, and TNF-α than MT(+) noncachectic, MT(−) cachectic patients, and healthy controls. Taken together, these studies provide experimental evidence that gut barrier dysfunction may contribute to the systemic inflammation and the metabolic effects associated with cachexia.

Microbiota dysbiosis

The intestinal microbiota maintains a symbiotic relationship with the human host in several ways including aiding food digestion and nutrient absorption, development and maturation of host mucosa, 'education' and regulation of immune system, and maintenance of the epithelial barrier [50]. Recent advances in our understanding of the composition and metabolic capabilities of the microbiome have led to a greater recognition that alterations in the gut microbiota (dysbiosis) can lead to chronic immune diseases such as IBD, and metabolic disorders including obesity [51–53]. A recurrent theme in many of these studies is the observation that such chronic disorders are associated with a reduction of certain beneficial commensal species present in the intestinal microbiota and accompanying low-grade inflammation in the host. Whether the observed dysbiosis is a secondary phenomenon or truly causal in these diseases and conditions remains to be determined.

A growing body of evidence now indicates that components of the resident microbiota can regulate gut barrier function and inflammation. For example, *Akkermansia muciniphila* is a mucin-degrading bacterium found in the mucus layer of healthy humans that has been associated with restored gut barrier function, decreased endotoxemia, and improved metabolic profile with implications for prevention or treatment of obesity and its associated metabolic disorders [54■]. *Faecalibacterium prausnitzii* is another potentially beneficial intestinal commensal bacteria, which stimulated the production of IL-10 while significantly decreasing IL-12 and IFN-γ in peripheral blood mononuclear cells [55]. Levels of *F. prausnitzii* are found in low abundance in patients with Crohn's disease [56], colorectal cancer, obesity [57], and IBS [58], adding further support to its role as a beneficial commensal. This developing area of science may lead to alternative treatment strategies for certain disease states based on ways to modulate the intestinal microbiota for the purpose of strengthening gut barrier function.

EMERGING THERAPIES WITH MULTIMODAL ACTION

The goals of therapy for cancer cachexia patients are often aimed at improving symptoms and quality of life. Use of conventional nutritional supplementation alone to improve lean body mass has shown limited efficacy in trials (reviewed in [59]). Advances in understanding the pathophysiology of cachexia have led to an increase in trials using a multitarget approach, in which therapies are combined in an effort to address multiple mechanisms that contribute to symptoms [15■■,16■■]. For example, conventional treatment strategies could be expanded to include agents directed at improving gut barrier function or reducing intestinal inflammation to help avoid or curtail forces that contribute to the catabolic drive associated with cachexia. Summarized below are three examples of emerging therapies with purported gut function benefits that, with appropriate scientific support, could eventually be considered among such multimodal treatment strategies for cancer cachexia.

Eicosapentaenoic acid

Eicosapentaenoic acid (EPA) is an omega-3 fatty acid that has been evaluated in a number of trials because of its potential to impact both the metabolic aberrations that underlie cachexia weight loss and modulation of inflammatory responses. Many of these initial trials were able to demonstrate benefits with EPA supplementation in areas of reducing the production of various cytokines and improving overall weight gain, appetite, and quality of life in patients with cachexia because of a variety of cancer types [16■■,60]. However, analysis of controlled trials using the Cochrane approach was unable to demonstrate a clear benefit to EPA supplementation compared with placebo [61]. This conclusion might be explained by the fact that most study participants were in an advanced stage of cachexia and possibly compromised in terms of medication compliance or ability to respond to EPA intake. Notably, a recent clinical study showed that EPA was particularly effective when combined with a targeted exercise regime [62], providing additional support for multimodal approaches for patient management.

Immunoglobulin/protein isolate

Serum-derived bovine immunoglobulin (SBI)/protein isolates are highly digestible plasma protein

concentrates that improve appetite, weight gain, and intestinal growth and barrier function when added to the diets of livestock animals (reviewed by Torrallardona [63]). Commercial SBI products EnteraGam™ is a serum-derived bovine immunoglobulin/protein isolate (SBI) specially formulated by Entera Health, Inc. for use as a prescription medical food for patients with limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foods or certain nutrients because of therapeutic or chronic medical needs). typically contain over 90% protein (by weight), with over 50% of the protein consisting of immunoglobulins (Ig), mainly IgG. Nonclinical studies have consistently demonstrated positive effects of SBI in terms of maintaining mucosal integrity, reducing the expression of proinflammatory cytokines and altering the lymphocyte response to immune activation in weaned piglets and experimental models of intestinal inflammation in mice, rats, and pigs [63].

Several small-scale human trials have evaluated the safety of SBI and effectiveness at improving intestinal absorption, gastrointestinal symptom scores, and quality of life measures in patients with HIV-associated enteropathy or diarrhea pre-dominant IBS. An open-label study conducted by Asmuth *et al.* [64], evaluated SBI supplementation in HIV patients and found improvements in daily bowel movements, stool consistency scores, an increase in intestinal CD4 cell counts, and reductions in inflammatory biomarkers, including intestinal fatty acid-binding protein, a protein associated with enterocyte damage, and matrix metalloproteinases-9/tissue inhibitor of metalloproteinases-1 ratios [64]. In a study of infants recovering from malnutrition, SBI improved fractional absorption of dietary lipid and of total energy increased significantly in relation to the amount of SBI in the diet [65]. Numerical improvements in nitrogen retention were also noted with SBI suggesting improved absorptive function.

Probiotics

Recent progress in understanding how the intestinal microbiota affects health and disease has led to increased interest in ways that probiotics and prebiotics could be used to promote human health (reviewed in [66]). Probiotics have been shown to favorably influence the development and stability of the microbiota, strengthen the mucosal barrier by trophic effects on the intestinal epithelium, and stimulate both specific and nonspecific components of the immune system [67■,68–70]. Although the need continues for well controlled clinical studies, the strength of evidence for probiotics has been demonstrated in a number of areas including

necrotizing enterocolitis in premature infants [71], preventing antibiotic-associated diarrhea [72], and countering infection and allergy related to respiratory health [73,74].

A novel approach using eight strains of probiotic bacteria was shown to induce remission in 53% of treated individuals with ulcerative colitis [75] and reduced symptoms of colitis with improved structural integrity of the gut barrier [76]. The administration of a strain of *Lactobacillus rhamnosus* (LGG) has shown clinical benefit in individuals with IBD [77]. Data demonstrating that alterations to the composition of the microbiota often accompany diseases that are characterized by systemic MT. It is a realistic goal to develop probiotics to strengthen gut barrier function or decrease intestinal inflammation.

CONCLUSION

Compromised gut barrier function because of alterations in the gut microbiota or intestinal inflammation can lead to translocation of microbial substances and the development of systemic inflammation with potential consequences for patients prone to cachexia. Efforts to preserve the integrity of the gut epithelial barrier and/or limit intestinal inflammation in cancer patients may help avoid the serious metabolic alterations associated with cachexia.

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Conflicts of interest

There are no conflicts of interest.

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