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Cancer Associated Cachexia; Etiopathogenesis, Molecular Mechanisms and Therapeutic Strategies

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Abstract

Cachexia is a multifunctional syndrome that is characterized by anorexia and extensive loss of adipose tissue and skeletal muscle, is common in many chronic and advanced diseases. Most of cancer patients show variable patterns of body loss that is known as cancer associated cachexia (CAC). Although CAC share common characteristics, the severity of this disease is variable, and seems to be tumor type, site and stage-dependent. The etiology of cachexia is attributed to abnormal metabolism that is thought to be mediated by tumor- and host-derived cytokines and factors. Although the role of cytokines in the etiology of CAC has been reported, the molecular mechanisms regulating its occurrence in cancer patients are not described in details. This review focuses on the etiopathogenesis of CAC and the underlying mechanisms.

Introduction

Cachexia is a multifunctional syndrome that is common in many chronic and advanced diseases including cancer [1]. Accordingly, most cancer patients show variable patterns of cachexia that is known as cancer associated cachexia (CAC) [2]. The severity of CAC is variable and seems to be tumor type, site and stage-dependent [3]. Of note, CAC is significantly marked in patients suffering from gastrointestinal and pancreatic adenocarcinoma [4,5], with lesser extent in patients suffering from other carcinomas such as acute leukemia, malignant lymphoma and sarcoma [6]. The release of cachexia depends strongly on host susceptibility to respond to tumor development and progression via mechanism mediated by the activation of immune system and its associated pathways [7]. As widely reported CAC is associated with physical impairment that is attributed to the loss of body weight, white adipose tissues and skeletal muscle mass [8]. Accordingly, these disastrous conditions are estimated to cause death in cancer patients [9]. Although progressive studies have been made to understand the etiopathogenesis of chachexia syndrome, an effective therapy to cure or to prevent cancer cachexia is not inspection. The development of an efficient therapy for cachexia treatment is hampered by the fact that the cachexia syndrome is not exactly defined, diagnostic criteria are absent, and the mechanisms underlying CAC are not determined in detail. In this review, we provide insight into the etiopathogenesis of CAC, the molecular mechanisms, which are essential for the occurrence of CAC and its therapy.

Etiopathogenesis of Cancer Associated Cachexia

Cachexia as known is a complex syndrome that is associated with body weight loss, tissue wasting, systemic inflammation, metabolic abnormalities [10]. The etiology of CAC is attributed to abnormal metabolism, particularly, catabolism, as a response to cancer-induced anorexia, aggressive therapeutic regimens-induced malabsorption, and excessive release of tumor and host-derived cytokines and factors [11-14]. Also, inflammatory cytokines are thought to play a fundamental role in the pathogenesis of cachexia via mechanism mediated by the activation of ubiquitin-proteasome pathway [15]. Of note, the most noticeable features of cachexia is the loss of muscle mass that may result from the increased protein degradation rates via excessive activation ubiquitin-proteasome pathway [16,17].

Although host and tumor cytokines and factors, which are thought to be implicated in the regulation of CAC have been identified, the mechanism whereby tumors cause cachexia is not completely characterized in detail [11-14]. The induction of cachexia is a stochastic process that may result from random mutations occurring in the tumor. Other plausible explanation for the occurrence of cachexia in cancer patients may result from host response to the molecular action of antitumor drugs that are mostly associated with the inflammatory reactions leading to the release of various cytokines. Apart from anticancer agents-induced cachexia, the induction of cachexia in tumor patients seems to be a tumor strategy to maintain its high energy requirements that are needed for tumor growth and progression. However, the appearance of CAC is associated with the release of energy sources such as glucose, lactate, and fatty acid from white adipose tissue, and amino acids from protein degradation of skeletal muscle mass [18]. Accordingly, in vivo experiments demonstrated that the dietary supplements significantly affect tumor growth [19], an evidence for the important role of metabolic alteration in the regulation of cachexia in tumor patients. Also, the importance of circulating fatty acids for tumor growth has been reported in tumor models of acute fasting or streptozotocin-induced diabetes [20,21]. Although some rapidly proliferating tumors are mostly associated with suver cachexia, severe cachexia has been reported in patients with small tumor burden and low proliferation rate [22]. Thus, it seems that

the variation of the genetic changes in tumors results in significant alterations of tumor metabolism that, in turn, mediate pathways leading to the induction of CAC in response to excessive release of tumor- and host-derived cytokines, cancer-induced anorexia and aggressive therapeutic regimens (Figure 1).

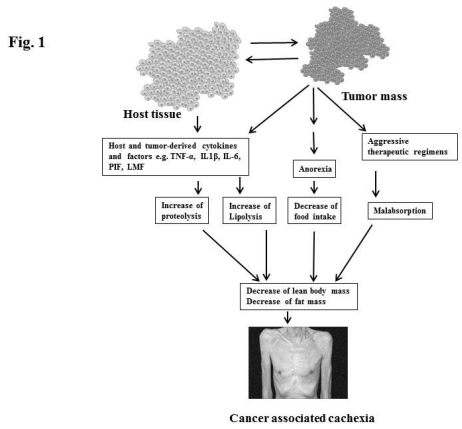

Figure 1: Etiopthogenesis of cancer associated cachexia.

Molecular Mechanisms of Cancer-mediated Cachexia

The induction of cachexia during the course of tumor malignancy is caused by complex metabolic disorders. Although the basal metabolism in cancer patients with malignant diseases significantly elevated [23], and results from the reduction of the voluntary energy expenditure that is manifested clinically as fatigue, apathy, and depression [24], not from the restricted intake and alterations in the mechanisms that are associated with the usual fasting–feeding conditions. Also, the increase of lipolysis, along with the decrease of lipogenesis, enhances the loss of white adipose tissue and subsequently leads to a rapid decrease of the lipoprotein lipase activity in the white adipose [25,26]. As a consequence, the levels of the circulating triglycerides and lipase maturation factor 1 (LMF-1) increase leading to the loss of body fat and, in turn, increases lipid metabolism in cancer patients [27]. In solid tumors the production of lactate is in excess and its conversion to glucose occurs in the liver by the Cori cycle, a mechanism that leads to the increase of the production of hepatic glucose. Thus, the appearance of glucose intolerance in most of tumor patients may be the consequence of the increased hepatic production of glucose and restricted insulin production [28,29]. The mechanism whereby the loss of skeletal muscle mass is thought to result from the circulation of the proteolysis inducing factor (PIF) in the blood. This PIF has the ability to induce proteolysis and subsequently inhibiting protein synthesis [30,31]. Also, PIF can mediate the activation of the ubiquitin–proteasome pathway that is considered to be the principal mediator of the catabolism of cellular protein [30]. Of note, the main mechanism whereby PIF induces catabolism in skeletal muscle is mediated the up-regulation of the ATP-ubiquitin-dependent proteolytic pathway [31,32].

Although the reduction of food intake influences the energy expenditure, the imbalance between pro-inflammatory and anti-inflammatory is essential for the development of CAC [4,33]. The role of cytokines such as, tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), interleukins-1(IL-1) and interleukins-6 (IL-6) in the modulation of CAC has been reported [33]. Also, cytokines such as vascular endothelial growth factors A and C (VEGF-A and VEGF-C) and interleukin-8 (IL-8) have been shown to be involved indirect role the modulation of CAC via a mechanism mediated by the recruitment and degranulation of inflammatory cells. However, the recruitment and degranulation of inflammatory cells result in the stimulation of other pro-inflammatory agents that finally lead to the remodeling and degradation of extracellular matrix [34]. More importantly, the induction of these pro-inflammatory cytokines is regulated by pro-cachectic factors such as PIF via mechanism mediated by the transcription factors NF-κB and/or AP-1 [35-38]. The molecular mechanism whereby cancer triggers cachexia is outlined in Figure 2.

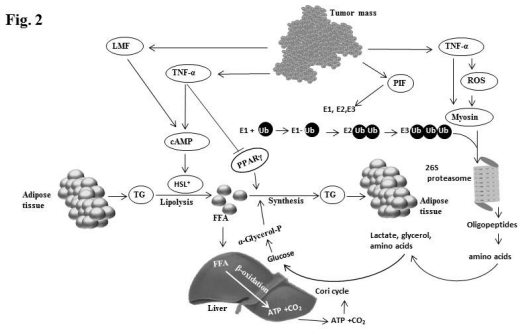

Figure 2: Molecular mechanism responsible for the loss of adipose tissue and skeletal muscle during cancer associated cachexia. The production of cancer associated factors and cytokines e.g. lipid-mobilizing factor (LMF), tumor necrosis factor (TNF)-α and proteolysis-inducing factor (PIF). The increased levels of TNF-α and LMF in tumor patients results in the hydrolysis of triglycerides in adipose tissues through the breakdown of cyclic AMP (cAMP) that, in turn, reduces the activation of hormone-sensitive lipase (HSL). Also, high level of TNF-α can suppress the peroxisome proliferator-activated receptor γ (PPARγ) and subsequently inhibits the biosynthesis of TG. Once TNF-α-induced free fatty acids (FFAs) enter the liver, the β-oxidation of FAA produces energy in the form of adenine triphosphate (ATP) in addition to the production CO_2. ATP drives the cori cycle to convert lactate, glycerol, amino acids to glucose. The induction of proteolysis inducing factor (PIF) increases the production of proteasome subunits and thereby enhances protein degradation in skeletal muscle.

Therapeutic Strategies for Cancer Associated Cachexia

The continuous preclinical studies with the aim to identify the potential molecular targets for the treatment of muscle wasting, addressed a crucial role for the involvement of ubiquitin ligases in pathological muscle degradation. Although increased muscle protein degradation is the main mechanism underlying muscle wasting in

cancer, it is uncertain whether the destruction of ubiquitin-proteasome pathway reverse CAC. However, the most effective therapeutic strategy for the treatment or prevention of CAC is the eradication of cancer with surgical and/or nonsurgical therapy.

The available therapeutic strategies for CAC treatment are either pharmacological or nutritional approaches. However, the ideal therapeutic approach for the treatment of CAC is with drug compound that acquires the ability to increase food intake, prevent muscle loss and improve muscle weight. Unfortunately, accumulated evidence revealed that nutritional strategies are insufficient to reverse CAC [38]. Thus, the development of therapeutic strategies based on the combination of both nutritional and pharmacological approaches may only be able to prevent cachectic syndrome. Thus, the nutritional therapeutic might help to increase food intake, whereas the pharmacological approaches might counteract the metabolic alterations. Because of the mediators of CAC are not completely investigated the design of an efficient therapeutic protocol for the prevention or treatment of cachectic syndrome is complicated.

Both tumor- and host-derived factors, mainly cytokines are involved in the modulation of cachexia and thereby are considered a great obstacle for the development of an efficient drug or even the design of a management therapeutic protocol for the treatment of cachectic syndrome.

Currently, megestrol acetate (MA) and medroxyprogesterone are the most used drugs for the treatment of CAC. These compounds can improve appetite, caloric intake and nutritional status as shown in several clinical trials [38,39]. Compounds, such as MA are well tolerated in patients with advanced cancer and have been found to improve body weight and sense of appetite, particularly, in patients with tumors underlying resistance to hormonal treatments [40,41]. Also, data obtained from several clinical studies revealed that MA is thought to be one of the most investigated appetite stimulants of the available therapeutic approaches of cachexia [42,43]. Moreover, accumulated evidences indicate that both MA and medroxyprogesterone acetate treatment are able to improve the quality of the life of cancer patients underlying chemo-and/or radiotherapy [44-47]. Interestingly, the therapeutic action of the MA is not only limited to the improvement of the appetite and subsequently the body weight, but also ameliorate muscle mass and performance via mechanism mediated by the inhibition of protein degradation machinery [48].

Although the therapeutic efficiency of MA promising, the molecular mechanisms regulating its therapeutic action in cachexia syndrome are not discussed in detail.

In addition to its effect on appetite, MA has been reported to increase the levels of neuropeptide Y and to enhance the inhibition of Ca2+ channel current, leading to the reduction of the activity of the ventromedial hypothalamic nucleus neurons mediating the satiety mechanism [49]. Also, MA can influence the molecular mechanisms regulation of both metabolic and inflammatory processes [50]. Accordingly, in vitro analysis demonstrated the ability of suppress the production of both serotonin and cytokines including interleukin-1b (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-α (TNFα), host-derived factors that function as mediators for the development of cachexia during the course of malignancy [51]. Furthermore, the treatment with MA has been found to increase the level of the circulating IL-15, a cytokine that functions as an anabolic factor for skeletal muscle [52]. Of note the alterations of cytokines concentration, in response to the treatment, do not influence muscle mass, but rather increases fat mass [52]. This may result from the increase in food intake and the effect of the progestagen on the differentiation of adipocytes [53].

The mechanism whereby MA inhibit protein degradation and subsequently the loss of muscle mass, an evidence for MA to function as an anti-proteolytic agent is mediated by the suppression of the ubiquitin, E2 and atrogin-1 levels in muscles [54]. This noted anti-proteolytic function of MA thought to be based on an inhibition of the ATP-ubiquitin dependent proteolytic mechanism. Accordingly, the ubiquitin proteasome pathway is considered as a promising therapeutic target for CAC.

Conclusion

Cachexia is a complex syndrome that is associated with body weight loss, tissue wasting, systemic inflammation, metabolic abnormalities, in addition to alterations in nutritional status. Accumulated experimental and clinical reports demonstrate that cancer associated cachexia results from fundamental metabolic alterations as a consequence of the accumulation of host- and tumor derived cytokines and factors. Thus, underlying metabolic disturbances are thought to occur in the early stage of tumor development without any sign for weight loss, as a marker for cachexia. The occurrence of cachexia is not attributed solely to the decrease of food intake or to tumor/host; it results from extremely metabolic alterations in tissues in response tumor catabolic factors. The enhancement of these tumor catabolic factors is mediated by pro-inflammatory cytokines and cellular factors derived from host and tumor tissues. These cytokines and cellular factors are thought to be the host mediators leading to the destruction and/or excessive activation of variable signaling pathways that ultimately mediates cachectic syndrome in cancer patients. Thus, understanding the fundamental mechanisms of the cachectic syndrome in cancer patients will help to design a therapeutic strategy for the treatment CAC and to improve the quality life of cancer patients.

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