Understanding Tumor Anabolism and Patient Catabolism in Cancer-Associated Cachexia

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Received: 29-May-2022, Manuscript No. jdm-22-18167; **Editor assigned:** 01-Jun-2022, PreQC No: jdm-22-18167 (PQ); **Reviewed:** 15-Jun-2022, QC No. jdm-22-18167; **Revised:** 18-Jun-2022, Manuscript No. jdm-22-18167 (R); **Published:** 22-Jun-2022, DOI: 10.35248/2155-6156.1000942.

Abstract

Cachexia is a multifactorial paraneoplastic syndrome commonly associated with advanced stages of cancer. Cachexia is responsible for poor responses to antitumoral treatment and death in close to one-third of affected patients. There is still an incomplete understanding of the metabolic dysregulation induced by a tumor that leads to the appearance and persistence of cachexia. Furthermore, cachexia is irreversible, and there are currently no guidelines for its diagnosis or treatments for it. In this review, we aim to discuss the current knowledge about cancer-associated cachexia, starting with generalities about cancer as the generator of this syndrome, then analyzing the characteristics of cachexia at the biochemical and metabolic levels in both the tumor and the patient, and finally discussing current therapeutic approaches to treating cancer-associated cachexia.

Keywords: Cachexia • Cancer • Biochemistry • Metabolism

Introduction

Although there have been important advances in cancer therapy aimed at different types of neoplasia, achievements have commonly been directed at treating the tumor instead of the concomitant syndromes that are present due to metabolic aberrations caused by the presence of the malignancy. One of the most relevant syndromes that increase as cancer progresses is cachexia, which compromises the life of the patient and irremediably causes weakness and death. Since there is increasing evidence demonstrating the implications of systemic biochemical pathways in the initiation and development of cancer-associated cachexia, in this review, we will focus our discussion on biochemical tumor aberrations and their impact on the maintenance of cachexia as well as on the host damage at different levels due to the chronic systemic inflammation induced by the presence of cancer. We will also discuss current therapies that attempt to obstruct the progression of cachexia in cancer.

Cancer as a Metabolic Entity

Cancer is commonly seen as a plethora of diseases that modify the cellular metabolism for the continuous preservation of proliferative signaling with an immortal replicative state of cells while they evade anti-growth signals, immune suppression and cell death. For a healthy cell to transform into a malignant cell, it must develop genomic instability that permits mutability for the overexpression of oncogenes such as the transcription factor c-Myc, growth factor receptors such as epidermal growth factor receptor (EGFR), signal transduction proteins such as Ras and phosphatidylinositol-3' kinase (PI3K), and inhibitors of apoptosis such as Bcl2. Additionally, tumor suppressor genes, which include proteins that inhibit cell division and cell proliferation (such as p53 and p16INK4a) and those related to the stimulation of cell death (p53), become inhibited in cancer. However, the upregulation of oncogenes is not sufficient for the tumorigenesis process, and rapidly dividing cells need to increase their ATP production for high energy demands, increase the biosynthesis of biomolecules, and regulate the reduction-oxidation state. This is where tumor metabolism must intervene to secure the success of malignant cells [1].

Metabolism, which is composed of interrelated biochemical reactions that promote the proliferation, survival and controlled growth of cells in the organism, can be separated into catabolic pathways, which generate energy in the form of adenosine triphosphate (ATP) by the rupture of molecules when nutrients are scare, and anabolic pathways, which consume energy to synthesize molecules under supplementation of abundant growth factors. Although under normal states, metabolism is highly regulated according to the cellular requirements, tumor cells are reprogrammed to enhance key metabolic pathways, such as aerobic glycolysis, glutaminolysis, and fatty acid synthesis. Only cells that transform to adopt this malignant metabolic phenotype will be selected within the tumor microenvironment to survive and progress. In fact, several anabolic alterations focused on cell growth and proliferation, and not on increasing ATP as with healthy cells, are commonly found in neoplasia. Regarding glucose and glutamine, most cancer cells develop high avidity for their consumption to generate energy and to build macromolecules for tumor progression, which, together with the constitutive activation of signaling pathways downstream of diverse growth factor receptors (even without circulating growth factors), doubles their total biomass to generate daughter cells. In particular, chemotherapy-resistant malignant cells commonly undergo aerobic glycolysis with high production of lactate, unlike non-proliferating and differentiated cells, which depend on oxidative phosphorylation to produce the ATP required for their maintenance [2].

Together, a series of anabolic and catabolic dysregulation is involved in systemic inflammation, biochemical imbalance, tissue wasting, anorexia and weight loss due to tumor-associated metabolic stress, which induce a state known as cachexia in the patient.

Generalities of cachexia

Etymologically, the word "cachexia" refers to a poor disease prognosis; this term originates from the Greek kakos and hexia, meaning "bad condition". Cachexia is a multiorgan syndrome characterized by a progressive and involuntary loss of body weight, particularly from skeletal muscle and adipose tissue due to alterations related to carbohydrate, lipid and protein metabolism. Indeed, according to the literature, the primary tissues affected during the progression of cachexia are both skeletal muscle and white adipose tissue. While the prominent clinical element of cachexia in adults is weight loss, in children it is associated with growth failure. Cachexia also involves systemic inflammation and anorexia (Figure 1), which together lead to physical disability, reduced quality of life, and diminished survival. The cachexia syndrome is multifactorial, cannot be fully reverted by nutritional support and leads to global functional impairment in patients, an external file that holds a picture, illustration, etc.Neoplasia generates cachexia through the chronic presence of systemic inflammation, which is associated with muscle and adipose wasting as well as anorexia. Anorexia can also be promoted by the gastrointestinal obstruction caused by the physical presence of the tumor mass. Together, these aberrations lead to weight loss and, irremediably, to cachexia.

The origin of cachexia is associated with reduced food intake along with abnormal metabolism induced by factors derived from both the tumor

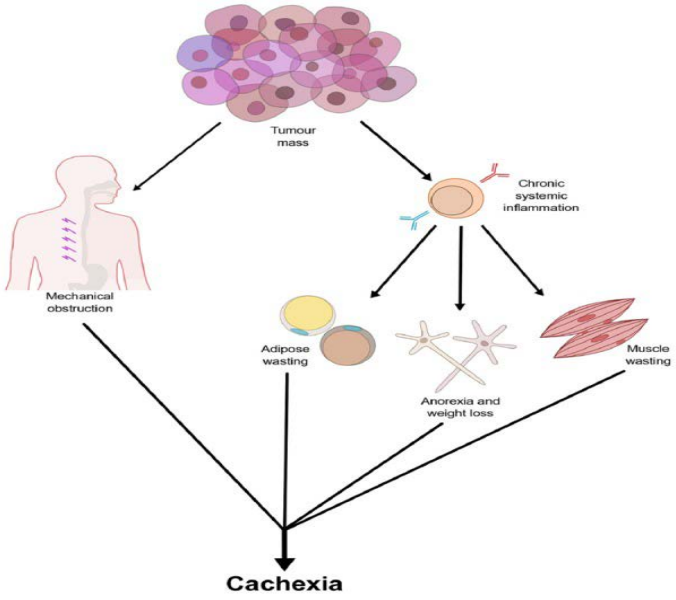

Figure 1: Elements of cancer-associated cachexia.

and the host, which irremediably lead to weight loss. Cachexia involves an energy imbalance resulting from anorexia and an increase in energy expenditure derived from the hypermetabolic condition of the underlying disease. Therefore, cachexia is considered a state of "autocannibalism" in which the tumor grows at the expense of the health of the subject through the consumption of biomolecules necessary for the function of other organs. Typically, advanced cancer individuals develop cachexia, but it can also be present with localized neoplasia. However, cachexia is not a pathognomonic syndrome in cancer. It can also occur in advanced stages of several diseases, including chronic obstructive pulmonary disease, malabsorption, chronic heart failure, acquired immunodeficiency syndrome, severe sepsis and trauma. When present in cancer, cachexia is the cause of death of close to one-third of patients, mostly when weight loss exceeds 30%. Furthermore, the development of cachexia is related to an increase in chemotherapy toxicity and mortality [2].

Up to 50-80% of advanced cancer patients will experience cachexia during the course of their disease, but this percentage is variable depending on the specific type of neoplasia. Cachexia is more common in tumors of upper gastrointestinal tract origin because these tumors may lead to obstruction and, consequently, to a reduction in food intake, as will be discussed in the next section.

Due to the complex clinical findings and lack of medical classifications for cachexia, a 2006 international consensus graded cachexia into cachexia and pre-cachexia. This group defined pre-cachexia as the medical condition of <5% body weight loss over a period of 6 months that is related to a primary chronic disease and characterized by metabolic alterations, inflammation and anorexia. Cachexia, on the other hand, can be defined as a weight loss of >5% over the same period of time, also secondary to a chronic disease and with the same systemic alterations. This new term, pre-cachexia, can be employed in epidemiological and intervention studies aimed at preventing or delaying changes in body composition associated with chronic diseases [3].

The diagnosis of cachexia should exclude other clinical conditions, such as primary depression, starvation, hyperthyroidism, malabsorption, and age-related muscle loss. However, the growing prevalence of obesity and sarcopenic obesity may hinder the diagnosis of cachexia. In fact, in cancer patients with an elevated body mass index and unplanned weight loss of ≥5% could pass unnoticed, and clinical intervention would thus be delayed. Therefore, it is recommended that the body composition of patients should be continuously assessed by computed tomography (CT) image analysis or dual-energy X-ray absorptiometry (DEXA) to analyze fat and skeletal muscle depots [4].

Tumoral origins of cachexia

The specific etiology of cancer-related cachexia is complex, and it may be incompletely understood in some patients. Additionally, the heterogeneity of the clinical presentation of cancer-related cachexia can lead to its underdiagnoses. In this section, we will describe in detail the pathophysiology of the alterations induced by the tumor that irremediably lead to cachexia, starting with the mass effect of the neoplasm, which retards food transit toward the gastrointestinal tract, continuing with the chronic systemic inflammation that is generated as a response to the presence of the tumor, and ending with the biochemical disruption inside the cancer cells that promotes cachexia.

Mechanical influence of the tumor in cachexia

One specific effect of the tumor on the patient is its mechanical impact on the digestive tract, which reduces food ingestion and in turn may promote anorexia, therefore leading to diminished body weight. Indeed, close to 50% of cancer patients at diagnosis affirmed irregularities in their eating behavior, and this percentage grew to 65% in terminally ill cancer patients.

The proportion of patients who experience cancer-associated cachexia depends on the specific type of cancer and its state of progression. The reported frequency of weight loss was 30-40% in patients suffering from acute non-lymphocytic leukemia, non-Hodgkin's lymphoma or breast cancer, while the frequency of weight loss was close to 60% in both colon and pulmonary cancers. On the other hand, the highest incidence of weight loss can be found in tumors of upper gastrointestinal origins, such as esophageal and head and neck cancers (with an incidence over 70%) and particularly in pancreatic and in gastric cancers (with a frequency over 80%). This effect can be associated with stenosis of the gastrointestinal tract, particularly in head and neck, esophageal and gastric malignancies, due to primary dysphagia, which mechanically limits food ingestion [5-7]. In the case of pancreatic cancer patients, tumor invasion can obstruct the pancreatic duct and the second part of the duodenum, which induces pain, gastroparesis, duodenal stenosis, and constipation, among other symptoms.

Another consequence of the presence of the tumor is early satiety, which at any stage of cancer is linked to a 30% increase in the risk of death. Early satiety is related to malabsorption secondary to alterations at the mucosa level as well as to the obstruction of food passage through the gut. Indeed, obstruction is common in bowel neoplasia and tumors of the abdominal area, with a frequency ranging from 4 to 24% in colorectal cancer and 5 to 42% in ovarian tumors. Additionally, abdominal tumors can disturb motility and promote ileus, which may contribute to emetic symptoms, which minimize food ingestion.

Initiation of cachexia by tumor-induced chronic systemic inflammation

Inflammation is acknowledged as a driving force in several chronic diseases and functions as a strong outcome predictor in the patient. In this subsection, we will cover the general implications of systemic inflammation in cachexia. Subsequently, in each section of this review, we will discuss the specific role of inflammation in every aspect of cancer-associated cachexia.

According to one proposed mechanism for the development of cancer cachexia, it is the result of a global physiological response driven by the increase in the chronic production and secretion of pro-inflammatory cytokines as the disease progresses (Figure 2). Cytokines are proteins that act

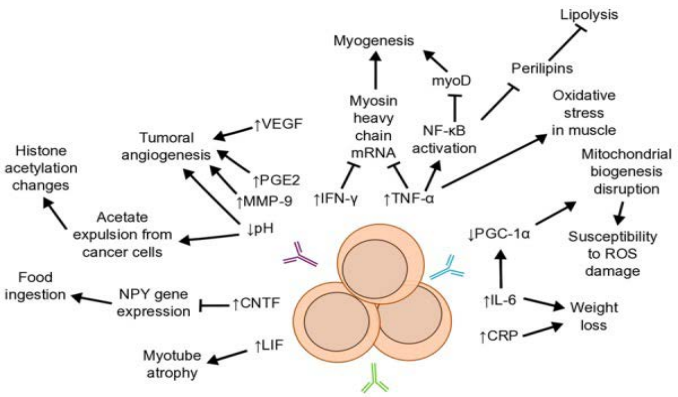

Figure 2: The effects of chronic systemic inflammation are strong promoters of cancer-induced cachexia.

as paracrine intercellular mediators, and they can induce or inhibit the immune response. Chronic inflammation is the consequence of permanently elevated pro-inflammatory cytokine levels, in opposition to the acute inflammation represented by cytokine waves. In fact, the notion of a continuous systemic inflammatory background helps to distinguish this syndrome from other conditions, such as anorexia [8,9].

A permanent and uncontrolled inflammatory environment has multiple effects on the host at different levels in the pathogenesis of cachexia. LIF is a recognized inducer of myotube atrophy that damages myocytes. CNTF inhibits the gene expression of neuropeptide Y, a potent appetite stimulant in the arcuate nucleus of the brain. VEGF, PGE2, MMP-9 and an acidic environment are associated with tumoral angiogenesis. Furthermore, a reduction in the pH of the tumor microenvironment stimulates the expulsion of acetate from malignant cells, which promotes histone acetylation aberrations within the tumor mass. Both IFN-γ and TNF-α block myosin heavy chain mRNA production to minimize the myogenesis process. Moreover, TNF-α-induced NF-κB functions as an alternative route to impede myogenesis via the blockade of myoD [10]. Lipolysis is indirectly allowed through the NF-κB-mediated inhibition of perilipins. TNF-α also induces oxidative stress in muscle, which degrades muscle proteins. The upregulation of IL-6 is associated with inhibition of PGC-1α, which makes systemic cells susceptible to reactive oxygen species damage secondary to a reduction in mitochondrial biogenesis. IL-6 and CRP are promoters of weight loss. Abbreviations: LIF: leukemia inhibitory factor; CNTF: ciliary neurotrophic factor; pH: potential of hydrogen; VEGF: vascular endothelial growth factor; MMP-9: metalloproteinase 9; PGE2: prostaglandin E2; IFN-γ: interferon-γ; TNF-α: tumor necrosis factor α; NF-κB: nuclear factor kappa beta; myoD: myogenic differentiation l; PGC-1α: peroxisome proliferator-activated receptor gamma co-activator 1-α; IL-6: interleukin 6; CRP: C-reactive protein; ROS: reactive oxygen species.

It is recognized that the acute-phase response is produced by the presence of the tumor itself. Innate immune effectors, such as macrophages, are some of the principal sources of immune mediators, such as tumor necrosis factor (TNF)-α. Immunohistochemical analyses of subcutaneous fat tissue from gastrointestinal cancer cachexia patients have revealed abundant macrophage markers, including CD68. Currently, there are controversial results regarding the presence of high circulating TNF-α levels in cancer cachexia, which could be due to the short half-life of TNF-α and/or its possible localized paracrine secretion. TNF-α, together with interleukin (IL)-1, promotes the activation and nuclear translocation of nuclear factor-kappa beta (NF-κB) to alter gene expression, which causes catabolic signals that induce protein loss in skeletal muscle cells through specific muscle ubiquitin ligases, as will be discussed later. TNF-α also stimulates lipolysis in human adipocytes through the activation of extracellular signal-regulated kinases (ERKs) and mitogen-activated protein kinase (MAPK), leading to the malfunction of perilipins, which regulate the integrity of lipid droplets (as will be discussed later).

Other Th1 response-related cytokines associated with cachexia are IL-6 and interferon (IFN)-γ [11-15]. IL-6, which is mostly produced as an acute-phase protein by the liver, is related to the development of cachexia, and supraphysiological concentrations of this cytokine led to a reduction in lean mass. However, several tumors also secrete IL-6. One proposed mechanism of the IL-6 involvement in cachexia in this regard is based on the knowledge that IL-6, through JAK signaling and the activation of the transcription factor signal transducer and activator of transcription 3 (STAT3), modulates the gene expression of acute-phase proteins, leading to mitochondrial biogenesis disruption. Additionally, monoclonal antibodies against Th1 cytokines prevent body mass loss in mouse models of melanoma and prostate cancer. IFN-γ is predominantly synthesized by T lymphocytes and NK cells. Together with TNF-α, IFN-γ is a well-known inhibitor of myosin heavy chain IIb mRNA in skeletal muscle cells. In the Lewis lung tumor mouse model, early immunological therapy with monoclonal antibodies directed against IFN-γ inhibited both neoplastic growth and tumor-associated wasting.

C-reactive protein (CRP), an acute-phase protein released by the liver, also contributes to inflammation. An increase in CRP concentrations is ubiquitously employed in different clinical scenarios to measure systemic inflammation. CRP concentrations, together with the consistent hypoalbuminemia observed in cachexia patients, are utilized in the Glasgow Prognostic Score (GPS) to predict outcomes of diverse tumor types. One British longitudinal study of more than 20,000 patients with diverse tumor types showed a correlation between elevated CRP concentrations and hypoalbuminemia among different cancers, which suggested that the GPS might work as a prognostic factor independent of tumor site. Another longitudinal study aiming to analyze the relationship between cachexia and GPS in pancreatic adenocarcinoma cachectic patients under palliative care demonstrated that elevated CRP levels were related to decreased albumin concentrations and poorer survival. Indeed, albumin levels below 3 g/dL have been related to worse outcomes in patients with stage 3 or 4 ovarian cancer. Furthermore, there is an association between CRP and weight loss; weight loss was favored in patients with gastrointestinal cancer cachexia with serum CRP concentrations higher than 5 μg/mL.

Other pro-inflammatory molecules involved in inflammation-associated cachexia are leukemia inhibitory factor (LIF) and ciliary neurotrophic factor (CNTF). LIF is a pleiotropic cytokine produced, among others, by embryonic stem cells. LIF acts via STAT3 to induce myotube atrophy in vitro, and a murine model implanted with LIF-secreting neoplasms developed cachexia. On the other hand, CNTF is mostly produced by glioma cells of the peripheral nervous system, and it induces anorexia and body weight loss through the repression of neuropeptide Y (NPY) gene expression in the hypothalamic arcuate nucleus (ARC). Accordingly, it was observed that mice engrafted with glioma cells experienced strong cachectic effects.

In inflammatory environments, local cells express molecules associated with leukocyte trafficking, including P-selectin glycoprotein ligand 1. In fact, myeloid suppressor cells are locally concentrated around the tumor and produce matrix metalloproteinase (MMP)-9, which promotes cancer angiogenesis. Since healthy mammalian cells are located 100-200 μm away from blood vessels due to the diffusion limit of oxygen, when the cell mass grows beyond this limit, it is mandatory to recruit new blood vessels via angiogenesis or the intussusception of pre-existing capillaries or post-capillary venules. Particularly in cancer, a neoplasm can only continue to grow and metastasize with an efficient blood supply; angiogenic signals. such as the metabolic stress induced by local low pH and the pressure promoted by proliferating cells, are provided in the tumor microenvironment to induce the production of vascular endothelial growth factor (VEGF) and angiopoietin factors, which, in turn, induce angiogenesis. Angiogenic promoters are also stimulated with the secretion of prostaglandin E2 (PGE2) by the immune cellular infiltrate enriched with the cyclooxygenase (COX)-2 enzyme, which in breast cancer cells has been shown to bind to G-protein receptors to promote both proliferation and tube formation in endothelial cells via the generation of pro-angiogenic factors, including VEGF. PGE2 is also produced in prostate cancer cells under hypoxic conditions, where it promotes hypoxia-inducible factor (HIF)-1α nuclear accumulation. HIF-1α, a transcription factor responsible for the major transcriptional responses of over 100 genes under hypoxic conditions, is stable under limited oxygen concentrations and dimerizes with its β subunit to regulate neovascularization, intracellular pH regulation, cell survival, tumor growth and energy metabolism, particularly by increasing the expression of transporters and enzymes associated with glycolysis, as will be discussed later.

Conclusions

Cachexia continues to be a health problem that presents, to different degrees, in patients with chronic diseases, such as cancer. There are currently no effective therapeutic schemes to adequately treat cachexia, and our knowledge about the integrative pathogenesis of cachexia, starting from the genetic and biochemical levels, is still insufficient. It is crucial to continue research that systemically evaluates the causes of cachexia, including biochemical and metabolic aberrations as well as new potential treatment targets to reduce the high mortality associated with this syndrome.

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Cite this article: Alfonso Duenas-Gonzalez. Understanding Tumor Anabolism and Patient Catabolism in Cancer-Associated Cachexia. J Diabetes Metab, 2022, 13(6): 942.