Cancer Cachexia: The Interplay of Chronic Inflammation and Metabolic Wasting

.

ABSTRACT

|  |
| --- |
| **Background:** Cancer cachexia is a multifactorial syndrome characterized by involuntary weight loss, skeletal muscle wasting, and systemic inflammation. It significantly impairs patient quality of life, reduces tolerance to treatment, and contributes to poor prognosis.  **Objective:** This review explores the role of chronic inflammation in the pathogenesis and progression of cancer cachexia, highlighting its impact on metabolism, appetite regulation, and acute phase responses.  **Methods:** A comprehensive literature analysis was conducted to examine inflammatory mediators such as IL-1, IL-6, TNF-α, and CRP, along with acute phase proteins, tumor-host interactions, and therapeutic strategies.  **Findings:** Inflammation disrupts energy homeostasis and promotes catabolism in muscle and adipose tissues via cytokine signaling and neuroendocrine pathways. Diagnostic tools involving CRP and other inflammatory markers show potential for prognostication. Therapeutic interventions targeting inflammatory pathways, appetite stimulation, and anabolic restoration are under investigation, with combination therapies offering promising results.  **Conclusion:** Understanding the intricate link between inflammation and metabolic wasting in cancer cachexia is crucial for developing effective diagnostics and interventions. Targeting inflammation may represent a pivotal strategy to improve outcomes in patients with cancer cachexia. |

*Keywords: Cachexia, Cancer, Inflammation, Pathogenesis, Metabolism*

1. INTRODUCTION

Cachexia is a complex metabolic condition characterized by significant skeletal muscle wasting, loss of adipose tissue, and unintended weight loss, which is frequently accompanied by anorexia. Unlike starvation-induced malnutrition, it is caused by a complex interaction of metabolic anomalies and systemic inflammation, making it resistant to traditional nutritional supplementation (Argilés *et al.*, 2018). It is associated with chronic illnesses such as cancer, chronic heart failure, chronic renal disease, and autoimmune disorders, as well as a loss in skeletal muscle mass (Nishikawa *et al*., 2021). Cachexia is a prevalent disease in cancer patients, particularly those with pancreatic, esophageal, stomach, lung, head & neck, liver, and bowel malignancies (Zhang *et al*., 2019). These malignancies account for half of all cancer-related fatalities globally. Cachexia is caused by a variety of mediators derived from cancer cells and cells in the tumor microenvironment, including inflammatory and immune cells (Baracos *et al*., 2018), and it significantly impairs quality of life, reduces tolerance to cancer therapies, and contributes to poor prognosis, accounting for up to 30% of cancer-related deaths worldwide (Mariean *et al*., 2023).

Inflammation is a critical feature of cancer cachexia. Pro-inflammatory cytokines including IL-1, IL-6, and TNF-α play a key role in the development of cancer cachexia. These mediators coordinate systemic inflammation, causing metabolic changes that worsen muscle proteolysis and lipolysis while blocking anabolic pathways. Furthermore, the inflammatory environment disrupts appetite control by altering neuropeptide signaling in the hypothalamus, which contributes to anorexia and low food intake (Esper and Harb, 2005). These consequences set off a vicious cycle of inflammation and metabolic dysregulation, accelerating tissue loss.

Cachexia prevalence varies by cancer type, with gastrointestinal and pancreatic malignancies having the greatest incidences (Brown *et al*., 2022). Despite its extensive impact, the pathophysiological processes behind cancer cachexia are poorly understood due to its diverse etiology, providing obstacles to early identification and appropriate therapy. Current data shows that systemic inflammation not only causes cachexia, but also plays an important role in tumor growth and treatment resistance (Setiawan *et al*., 2023; Ruan *et al*., 2024). This highlights the critical need for research into tailored therapies that might modify inflammatory pathways and reduce metabolic abnormalities in cancer cachexia.

This study investigates the complex association between chronic inflammation and cancer cachexia, including pathophysiology, diagnostic criteria, and treatment methods. By knowing how these variables interact, we hope to shed light on potential ways to improve patient outcomes in this severe disorder.

1. **CANCER-RELATED CACHEXIA**

According to Fearon *et al*. (2011), cancer cachexia is "a complex condition characterized by marked muscle tissue loss that is difficult to correct with conventional nutritional support and causes progressive functional impairment with or without the loss of adipose tissue." This term, coupled with the stage categorization, is widely used when discussing cancer cachexia. The mechanism of cancer cachexia development is unknown; however, three phases of cachexia are recognized: pre-cachexia, cachexia, and refractory cachexia (Fearon *et al*., 2011; Nishikawa *et al.*, 2021). Pre-cachexia is the phase before the development of cachexia, characterized by weight loss of 5% or less, malnutrition, modest weight loss, inflammation, and anorexia (Kasvis *et al*., 2019). Pre-cachexia is proposed as the ideal treatment window, providing a chance to act before the progression to cachexia. Early therapy during this stage can improve cancer management and patient outcomes. Cachexia is defined as weight loss of 5% or more within 6 months, a body mass index of less than 20kg/m2 and a continuous weight loss of more than 2%, or weight loss of 2% or more with sarcopenia (Fearon *et al*., 2011, Tisdale, 1997). Cachexia is frequently connected with sarcopenia; however, it is typically regarded as a subsequent illness. Refractory cachexia occurs when the disease becomes clinically resistant owing to preterminal cancer or the existence of a fast advancing malignancy that no longer responds to anticancer treatment. It is characterized by active catabolism and variables that render additional weight loss therapy inefficient or unsuitable. Refractory cachexia is distinguished by significantly impaired physical performance (WHO level 3 or 4) and a life expectancy of fewer than three months. Due to the multifaceted nature of cachexia, research has focused on the possibility of reversing the syndrome, as individuals frequently recover when treated.

Anorexia, combined with digestive and mechanical causes, has been shown to occur in 15%-40% of cancer patients and 80% of patients with end-stage cancer (Fearon *et al*., 2013). Tumors and chemotherapy produce nausea, dysphagia, dysfunction, mucositis, and malabsorption, which reduces body weight and food intake. Cachexia is commonly defined as a reduction in oral intake caused by anorexia, adverse effects, or gastrointestinal transit disruption following cancer treatment (e.g., radiation therapy, chemotherapy, and surgery) (Blum e*t al.*, 2014). There are several reasons of anorexia in cachexia patients. Inflammatory cytokines and tumor-producing substances contribute to anorexia, increased catabolism, and reduced fat and muscle mass. Cachexia mostly affects weight and muscle mass, although in rare situations, it can also be caused by dysphagia or gastrointestinal transit issues (Aapro *et al*. 2014).

Cancer cachexia is highly influenced by lipid mobilizing factor and proteolysis-inducing factor generated by tumors, as well as inflammatory cytokines (Baracos *et al*., 2018). “Lymphocytes, mononuclear cells, and macrophages produce high levels of pro-inflammatory cytokines such IL-1β, IL-6, and TNF-α” (Amitani *et al*., 2013). Inflammatory cytokines act on leptin receptors in the hypothalamus to decrease appetite (Pérez-Pérez *et al.*, 2020). This explains cancer cachexia's reduced food intake as well as metabolic alterations such as increased energy demand and excess catabolism. “Advanced cancer, anticancer therapy, and comorbidities may interfere with anorexia, food intake, and digestive and absorptive function” (Blum *et al*., 2011). “These can worsen anorexia by interfering with both appetite and food intake. Furthermore, patients with cancer cachexia are less sensitive to radiation, chemotherapy, and anticancer treatment, making them more likely to experience postoperative problems” (Murphy, 2009).

The eating status of cancer patients with cachexia is impacted by the kind of tumor and other treatment-induced symptoms such as anorexia, pain, and exhaustion, known as nutritional impact symptoms (NIS). Stomatitis, dysphagia (difficulty swallowing), nausea, vomiting, constipation, and taste changes are among the NIS related with weight loss in cancer patients (Omlin *et al*. 2013). Primary anorexia causes people with cancer to eat less, and additional nutritional problems can exacerbate this. Concurrent hypermetabolism, hypercatabolism, and hypoanabolism exacerbate associated weight loss and are produced by systemic inflammation and catabolic processes that operate partially through the central nervous system. Furthermore, cancer treatments such as chemotherapy and radiation might cause cachexia syndrome (Coletti, 2018).

**2.1 INCIDENCE OF CANCER-RELATED CACHEXIA**

Cancer-related cachexia is accompanied by weight loss and specific loss of skeletal muscle and adipose tissue (Fearon *et al*., 2011; Baracos *et al*., 2018), resulting in lower muscle strength and decreased overall body function and chemotherapy tolerance in patients (Fearon *et al*., 2006). Cancer-related cachexia affects between 50 to 80% of cancer patients (Argilés *et al.*, 2023), accounting for around 11% of patients globally and almost 50% of all cancer patients. It is claimed to be responsible for around 20% of cancer-related mortality (Argilés et al., 2014; von Haehling et al., 2014), however, its prevalence varies depending on the kind of tumor. It has been linked to 25-30% weight loss, which commonly leads to cardiac and respiratory failure (Tisdale 2009; Loberg *et al.*, 2007). “Patients with gastric and pancreatic cancers have an incidence of more than 80%, whereas patients with colon, gastroesophageal, and lung cancers have an incidence of approximately 50% and patients with breast and prostate cancers have an incidence of about 20%” (Gaafer and Zimmers, 2021).

**2.2 DIAGNOSTIC CRITERIA FOR CANCER CACHEXIA**

Cachexia is commonly associated with underlying conditions such as cancer, chronic heart failure, COPD, chronic renal failure, chronic inflammation, septicemia, anorexia, inflammation, insulin resistance, sexual dysfunction, and anaemia. Furthermore, tissue breakdown and muscular exhaustion can cause weight loss, weakness, and weariness. Cachexia is diagnosed by having three or more of the following five items: 1) muscular weakness, 2) weariness, 3) decreased appetite, 4) low lean body mass, and 5) aberrant biochemical data [for example, C-reactive protein (CRP), Hb (hemoglobin), and albumin (Alb) levels] (Fujii *et al*., 2020).

**3.0 INFLAMMATION IN CANCER CACHEXIA**

Inflammation is recognized to be the host's defensive reaction to infection and tissue injury, preventing pathogen spread and promoting tissue regeneration (Sun, 2017). “Pathogen-associated molecular patterns (PAMPs) are recognized by tissue macrophages or mast cells in the early or acute stages of inflammation, causing the secretion of pro-inflammatory cytokines, chemokines, vasoactive amines, and eicosanoids to increase the immune response” (Medzhitov, 2008). “These pro-inflammatory mediators are known to enhance vascular permeability, resulting in a large inflow of plasma-containing antibodies and other soluble components” (Headland and Norling, 2015). As the inflammatory response continues, monocytes and lymphocytes gather at the inflammation sites to neutralize toxic chemicals. As a result, inflammatory cells die and are removed by macrophages. Furthermore, during inflammation resolution, specialized pro-resolving mediators (SPM) biosynthesis has been shown to prevent neutrophil infiltration, reduce pro-inflammatory mediator secretion, stimulate macrophages to phagocytose apoptotic neutrophils, remove bacteria, and restore tissue homeostasis (Serhan, 2011). At the end of the inflammatory cascade, the tissue repair process takes over, reducing inflammation and restoring tissue homeostasis (Rossi *et al.,* 2006). As a result, the inflammatory process involves a variety of cells and mediators that may precisely control cell chemotaxis, migration, and proliferation.

Cachexia is caused by an inflammatory reaction affecting several organs throughout the body. Pro-inflammatory cytokines are significant contributors to cachexia. Cachexia is caused by the activation of inflammatory cytokines such IL1, TNF-α, and IL-6, which contribute to metabolic abnormalities and anorexia. “Inflammatory cytokines not only influence these abnormalities, but they also promote peristaltic dysfunction and edema in the gastrointestinal system, aggravating anorexia and impairing digestive and absorptive activities. It is thought that inflammatory cytokines inhibit the release of corticosteroid-releasing hormone and appetite-stimulating neuropeptide Y, leading to the development of anorexia” (Esper and Harb, 2015).

**3.1 PATHOGENESIS OF INFLAMMATORY RESPONSE AND CANCER-RELATED CACHEXIA**

Systemic inflammation is a major cause of cancer-related cachexia because it disrupts the equilibrium between protein production and degradation (Tan *et al.*, 2011). Tumor cells generating cytokines and other inflammatory mediators, as well as activated immune cells releasing cytokines and chemokines, all contribute to cancer-related systemic inflammation. C-reactive protein (CRP), an acute-phase protein, is one of the most extensively researched systemic inflammatory markers (Fearon *et al.*, 2011). Nasr *et al.* (2018) found that “hepatocytes manufacture this protein in response to inflammatory cytokines such as IL-1, TNF-α, and IL-6”. “Elevated CRP levels are associated with a poor prognosis in both localized and metastatic CRC” (Kersten *et al.*, 2013), as evidenced by previously reported “prognosis predictive scores such as the lymphocyte-to-CRP ratio (LCR), CRP/albumin ratio (CAR), lymphocyte CRP score (LCS), modified Glasgow prognostic score (mGPS), and modified nutritional geriatric risk index (mGNRI), all of which contain CRP. Preoperative LCS can predict the short- and long-term prognoses of patients with gastric cancer” (Okugawa *et al.*, 2020). “The mGNRI is an effective predictor of long-term survival outcomes in cancer patients. Notably, mGPS, LCR, CAR, and CRP levels were shown to be associated with the prognosis of CRC patients” (Yasui *et al.*, 2021; Zhou *et al.*, 2021; Hua *et al*., 2021).

**3.2 INFLAMMATORY MEDIATORS IN CANCER-RELATED CACHEXIA**

Inflammatory reactions are key pathogenic factors in cancer-related cachexia, activating mediators involved in tissue repair. Changes in plasma protein concentrations are part of the acute-phase response (APR), which also includes behavioral, psychological, physiological, and nutritional changes in the body. An acute-phase protein (APP) is a plasma protein whose concentration fluctuates by at least 25% in response to inflammation (Gabay and Kushner, 1999). These proteins are produced in response to inflammation and serve to restore tissue homeostasis and repair by controlling cell proliferation, scar formation, and immune defense activities. Cytokine signaling, specifically IL-6, IL-1, TNF-α, and IFN-γ, initiates APR production. APP concentrations change with cancer and other inflammatory conditions. However, little is known about how these variables affect metabolism, muscle, and fat homeostasis, and the APR-cachexia link is still poorly characterized. Although APR has been proven to raise the patient's resting energy expenditure, which is a sign of increased catabolism (Falconer *et al*., 1994). This lends credence to the idea that APPs play a molecular role in the advancement of cancer and chronic illness-related cachexia.

During the acute phase response, inflammation stimulates protein creation, which necessitates the presence of IL-6 to create a large amount of APP. Cytokines are the major signaling molecules that regulate acute-phase protein levels. Toll-like receptors stimulate innate immune cells, producing IL-1 and TNF-α. These cytokines stimulate the secretion of IL-6 (Gulhar *et al*., 2023). IL-6 binds to IL-6 receptor alpha chain, inducing the dimerization of gp130 and activation of its associated Janus kinases (JAKs), which phosphorylate gp130. These activities activate the mitogen-activated protein kinase (MAPK/ERK) cascade and STAT3. STAT3 activation by tyrosine phosphorylation leads to dimerization and nuclear translocation, DNA binding, and modulation of gene expression (Bonetto *et al*., 2011). IL-6 signaling through STAT3 upregulates acute-phase response protein gene expression in the liver. IL-6 activation of hepatocytes increases positive acute phase reactants such as CRP, serum Amyloid A (SAA), Alpha 1 anti-chymotrypsin, and fibrinogen while decreasing negative acute phase reactants such as albumin, transferrin, and fibronectin (Castell *et al*., 1989). IL-6 has also been demonstrated to directly produce cachexia via a crosstalk pathway between tumor, muscle, and fat that requires IL-6 signaling (Rupert *et al*., 2021). Inflammation is the primary cause of cachexia, as the body strives to maintain a balance between host protection and the detrimental effects of immunological responses on the host (Maccio *et al*., 2021; McGovern *et al*., 2022). CRP and other surrogate indicators can be used to measure the inflammatory response. CRP has been shown to predict both the degree of cachexia and survival in cancer patients (Silva *et al.*, 2020). It is one of numerous APRs that are caused by inflammation and are associated with cachexia. There are several instances of how APR signaling is regulated in cachexia. The next sections explain APR production in extra-hepatic organs, muscles, and tumors.

A diagram of chronic inflammation

Description automatically generated

**3.3 THE MUTUAL RELATIONSHIP BETWEEN INFLAMMATION AND CANCER**

In the mid-nineteenth century, Rudolf Virchow discovered the link between inflammation and cancer, finding that cancer cells are common in sites of chronic inflammation and that inflammatory cells are prevalent in tumor biopsies (Balkwill and Mantovani, 2001). Cancer-related inflammation is now recognized as a major feature of cancer, with a well-established relationship between chronic inflammation and tumor formation (Punt *et al*., 2016). Chronic, dysregulated, chronic, and unresolved inflammation has been linked to not only an elevated risk of cancer, but also a poor prognosis in most cancer types (Elinav *et al*., 2013). Furthermore, accumulating data suggests that “the inflammatory tumor microenvironment (TME) is a critical predictor of the therapeutic success of traditional treatment (e.g., radiation and chemotherapy) and immunotherapy” (Vasan *et al*., 2019). However, “acute inflammation generated by exogenous stimulators has been shown to improve anti-tumor immunity by boosting dendritic cell maturation and activity, as well as the start of effector T cells” (Bray *et al*., 2018).

Patients suffer greatly when cachexia develops as a result of cancer or other chronic conditions. Cachexia is linked to a decreased capacity to tolerate treatments, slower ambulation, worse quality of life, and higher mortality. Cachexia appears to be closely connected to the activation of the acute phase response and a strain on metabolic resources. Interest is growing in the role of acute phase reactants in the immunogenesis of cachexia. Furthermore, increasing research shows that liver, lung, and skeletal muscle cancers have a role in activating the acute phase (Robinson *et al*., 2023). Although the acute phase is increasingly recognized as being involved in cachexia, research into the underlying mechanisms of cachexia associated with the acute phase response remains ongoing, with a lack of a comprehensive understanding and a clear causal relationship. Although most studies to far have been correlative, demonstrating a function for various acute phase reactants might assist bridge the existing knowledge gap.

Given the link between inflammation and tumor (Ma *et al*., 2013), harnessing inflammation looks to be an essential technique for more effective anti-cancer treatment. Numerous clinical investigations have established the potent chemopreventive benefits of nonsteroidal anti-inflammatory medications (NSAIDs), notably aspirin (Cuzick *et al*. 2015). Statins have also been shown to greatly lower the chance of developing a variety of cancers, including breast cancer, colorectal cancer (CRC), and hepatocellular carcinoma (HCC), through anti-inflammatory actions (Bonovas *et al*., 2013). Furthermore, boosting the quantity of specialized pro-resolvin lipid mediators (SPM) and their synthesis pathways has been found to greatly suppress tumor development (Wang et al., 2015). Furthermore, boosting tumor immunity with inhibitory checkpoint blockade or chimeric antigen receptor T-cell (CAR-T) immunotherapy has demonstrated promising results in some cancer types (Gun *et al*., 2019). However, adverse effects including as coagulopathy and "cytokine storm" have hampered their broad applicability to cancer therapy (Bonifant et al., 2016), implying that reducing these undesirable immunotherapy-induced inflammatory processes will benefit cancer patients. In short, tumor-related chronic inflammation has been linked to TME immunosuppression and tumor progression (Ma *et al*., 2013). Thus, a greater knowledge of the link between dysregulated inflammation and tumor formation would be beneficial to the development of novel tactics for battling malignancies and would improve the efficacy of immunotherapy, chemotherapy, or radiotherapy.

**3.4 THERAPEUTIC IMPLICATIONS**

“Systemic inflammation is currently thought to be the leading cause of muscle wasting in cancer-related cachexia. Functional alterations in brain areas that regulate energy homeostasis lead to anorexia, reduced food intake, and increased muscle and adipose tissue loss” (Ekeoke and Morley, 2015). Consequently, inflammatory indicators are routinely employed as predictors of metabolic problems and clinical consequences (Argiles *et al*., 2014). We investigate developing treatment methods and their potential to reduce the effects of systemic inflammation on cachexia.

**3.4.1 TARGETING INFLAMMATION IN CACHEXIA MANAGEMENT**

“Several in vitro and in vivo investigations have found that pro-inflammatory cytokines have a role in muscle wasting diseases including cancer-related cachexia. High levels of inflammatory cytokines have been linked to muscle wasting in an animal model employing Walker-256 rats (Cella *et al*., 2020) and colon cancer 26 (C-26) (Zhuang *et al*., 2016). “’Administration of creatine or the Zhimu and Huangbai herb pair (ZBHP) reduced muscle” and adipose tissue wasting during cachexia, indicating that modulating inflammatory signaling could be a potential therapeutic target in cancer-related cachexia. A recent study in different mouse models based on the injection of C-26 murine adenocarcinomas or Lewis lung carcinoma (LLC) cells into BALB/c and C57BL/6 or Ager −/− (RAGE-null) mice reported that activation of the receptor for advanced glycation end-products (RAGE) by the S100 calcium-binding protein B (S100B) was able to induce muscle wasting and that the signaling pathway involved was the p38 MAPK/myogenin axis and signal transducer and activator of transcription Furthermore, this study found that muscle atrophy, systemic inflammation, and the release of tumor-derived prokinetic substances were all linked to the persistent activation of RAGE that occurs under cancer circumstances” (Zhao, H., et al., 2021).

C2C12 myotubes treated with TNF-α showed decreased protein production and increased proteolysis. Both treatment of C2C12 myotubes and intraperitoneal injection of TNF-α resulted in upregulation and activation of ERK1/2 and JNK. Inhibiting p38MAPKs lowered the elevation of Atrogin1/MAFbx mRNA, indicating that TNF-α modulates gene expression through p38MAPK signaling (Li *et al*., 2005). A mouse model of the fatal pediatric illness Duchenne muscular dystrophy (DMD) shown that TNF-mediated JNK activation causes conformational changes in the insulin receptor substrate (IRS)-1, affecting downstream pathways following IGF-1/IGF-1 receptor interaction (Grounds *et al*., 2008). As previously noted, IGF-1 regulates muscle-mass homeostasis at numerous levels. Yoshida and Delafontaine's 2020 review found that IGF-1 stimulation activates the PI3K/Akt/mTOR and PI3K/Akt/GSK3β pathways, leading to protein synthesis in skeletal muscle. However, PI3K/Akt may also inhibit E3 ubiquitin ligase, which inhibits FOXOs and so reduces protein breakdown. Interestingly, IGF-1 adversely regulates autophagy through mTOR and FOXO signaling, with Akt playing a prominent role. Yoshida and Delafontaione (2020) believe that IGF-1/Akt inhibits the NF-κB and Smad signaling pathways, which may alleviate muscle atrophy by promoting cytokines and myostatin signaling.

In vitro and in vivo studies have revealed that another member of the tumor necrosis factor superfamily, tumor necrosis factor-like weak inducer of apoptosis (TWEAK), and the receptor factor-inducible 14 (Fn14), may be involved in skeletal muscle regeneration. Chronic administration and muscle-specific transgenic overexpression of TWEAK in mice showed cachectic effects, including low skeletal muscle weight and increased activity of UPS and NF-κB. However, administration of anti-Fn14 monoclonal antibodies reduced tumor growth rate and progression to cachexia (Webster *et al*., 2020).

**3.5 COMPREHENSIVE MANAGEMENT APPROACHES**

Chronic inflammation is thought to be one of the characteristics of tumor initiation and progression (Coussens and Werb, 2002), and therapy-induced chronic inflammation frequently endows residual cancer cells with resistance to subsequent treatments (e.g., chemotherapy resistance and radiotherapy resistance) (Grivennikov *et al*., 2010). Anti-inflammatory medications have been shown to be effective at both tumor prevention and therapy. However, the side effects of Immune Checkpoint Blockade (ICB) and Chimeric Antigen Receptor (CAR)-T therapies, such as coagulopathy and the "cytokine storm" have limited their full application to cancer therapy (Bonifant *et al.*, 2016), indicating that reduction of these pernicious inflammation reactions accompanying immunotherapy will improve therapeutic efficacy. Several treatment techniques for limiting inflammatory cells and their products have recently been effectively tested in clinical or preclinical tumor models. Statins, for example, dramatically lowered the chance of developing a variety of cancers through anti-inflammatory and other mechanisms (Bonovas *et al*., 2013). Similarly, neutralization of IL-17A, IL-11, or IL-22 might prevent colonic carcinogenesis in its early stages (Yang *et al*., 2020), but COXs inhibitors (e.g., celecoxib and aspirin) reduced tumor development and metastasis (Schneider and Pozzi, 2011).

**3.5.1 Targeting Pro-Inflammatory Cytokines**

Pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-6, contribute significantly to cancer cachexia. Therapies that neutralize these cytokines have showed promise:

**IL-6 Inhibition:** Monoclonal antibodies targeting IL-6 or its receptor, such as tocilizumab, have been shown to reduce inflammation and muscle wasting in preclinical experiments (Yi *et al*., 2024).

**TNF-α Blockade:** Infliximab and etanercept have been studied for their ability to reduce muscle breakdown (Sciorati *et al.*, 2020). Clinical investigations indicate that treating TNF-α alone may not be effective in reversing cachexia.

**3.5.2 Modulation of The Acute-Phase Response**

The acute phase response (APR), which is triggered by systemic inflammation, leads to metabolic dysregulation and increased energy consumption in cachexia. Therapies that regulate the APR include:

**C-Reactive Protein (CRP) Modulation:** Modulation of C-Reactive Protein (CRP), a surrogate measure for systemic inflammation. CRP-lowering strategies, such as anti-inflammatory medications or lifestyle changes, may improve metabolic outcomes in cachexia patients.

**Specialized Pro-Resolving Mediators (SPMs):** Lipoxins and resolvins, are lipid-based mediators that promote inflammation resolution and tissue healing (Serhan *et al*., 2008). Increasing SPM levels has been proven to reduce chronic inflammation in cancer cachexia.

**3.5.3 Anabolic and Nutritional Interventions**

While inflammation is crucial to cachexia, restoring anabolic pathways and improving nutrition are just as important:

**Anabolic steroids:** Anabolic steroids, such as oxandrolone and testosterone, have been used to increase muscular growth and strength (McCullough *et al.*, 2021). However, their effectiveness in cachexia is still being studied.

**Nutritional Support:** Supplementing with omega-3 fatty acids, which have anti-inflammatory effects, can enhance weight growth and muscular function in cachexia patients (de Castro *et al*., 2022). Protein-rich meals and amino acid supplements (such as leucine) also aid in muscle protein synthesis (Ely *et al*., 2023).

**3.5.4 Targeting Energy Homeostasis**

Hypothalamic pathway dysregulation relates to anorexia and decreased food intake in cachexia. Treatments for restoring appetite and energy balance include:

**Appetite Stimulants:** Megestrol acetate and dronabinol have been used to enhance hunger and calorie intake, with varying results (Ceolin *et al*., 2024).

**Modulation of neuroinflammatory pathways:** Targeting neuropeptide signaling pathways in the hypothalamus may help restore appetite and treat cachexia-related anorexia (Krasnow *et al.*, 2010).

**3.5.5 Combination Therapies**

Given the multifaceted nature of cancer cachexia, combination therapy that address inflammation, metabolism, and appetite control are likely to be the most successful. Emerging therapies include

**Multimodal Approaches:** multimodal approaches, which combine anti-inflammatory medicines with dietary assistance and physical rehabilitation to improve results (Shiaraishi *et al*., 2024).

**Personalized Medicine:** Tailoring therapies based on individual patient profiles, including inflammatory markers and genetic predispositions, may enhance treatment efficacy.

4.0 Conclusion

Acute Inflammation is the first reaction to damaging stimuli, with the persistence of inflammatory components possibly producing chronic inflammation. Innate immune cells (endothelial cells, neutrophils, macrophages, mast cells, NK cells, and dendritic cells) and adaptive immune cells (T cells and B cells), as well as proinflammatory factors (vasoactive amines, vasoactive peptides, complement fragments, and some cytokines, such as IL-1, IL-6, IL-15, IL-17, IL-23, TNF-α, and IFN-γ) are important for the initiation of inflammation. In addition, chemokines (CCL2, CXCL12) are required for the recruitment of inflammatory cells in the inflammatory region. Anti-inflammatory cells (M2 macrophages, Th2, Tregs, and MDSCs), cytokines (IL-4, IL-10, IL-13, and TGF-β), and SPMs (LTA4, LXA4, LXB4, lipoxins, RvE, RvD, MaR1, MaR2, DHPA, PCTR1, and protectin D1) play a role in inflammation resolution. The influence of inflammation on most malignancies is two-edged, with cancer affecting the inflammatory response. Typically, the immune system detects and destroys infections and tumor cells, therefore preventing tumor growth. However, during chronic inflammation, inflammatory cells and cytokines may operate as tumor promoters, influencing cell survival, proliferation, invasion, and angiogenesis. Given the tight association between inflammation and tumors, reducing inflammation is a significant strategy to enhance anti-cancer treatment. There are two components to treating inflammation for cancer therapy. Activating anti-cancer immunity cells (such as DCs, NK cells, NKT cells, CTLs, Th1 cells, and B cells) can boost the immune system's ability to destroy cancer. In addition, inhibiting pro-cancer immune cells (e.g., mast cells, TAMs, MDSCs, TANs, eosinophils, Th2 cells, Th17 cells, Treg cells, and Breg cells) or converting their polarization to an anti-tumor type by targeting key signal pathways can impede the immunosuppressive effect and cancer progression. For example, inhibiting the unfolded protein response mediator PERK in MDSC can reverse their pro-tumor function and induce anti-tumor T cells. In summary, the inflammatory response in cancer cachexia can cause muscular and adipose tissue loss, which is increased as cachexia advances. This dual role highlights the intricate relationship between inflammation and the development of cachexia in cancer patients.

**Disclaimer (Artificial intelligence)**

Authors hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, manuscript) were used in the generation of facts presented in this review article.

References

1. Aapro, M., Arends, J., Bozzetti, F., Fearon, K., Grunberg, S. M., Herrstedt, J., Hopkinson, J., Jacquelin-Ravel, N., Jatoi, A., Kaasa, S. & Strasser, F. (2014). Early recognition of malnutrition and cachexia in the cancer patients: a position paper of a European School of Oncology Task Force. Annals of Oncology, 25:1492–1499.
2. Algiles, J. M., Busquest, S., Stemmler, B. & Lopez-Soriano F. J. (2014). Cancer cachexia: understanding the molecular basis. Nature Reviews Cancer, 14:754–762.
3. Amitani, M., Asakawa, A., Amitani, H. & Inui, A. (2013). Control of food intake and muscle wasting in cachexia. International Journal of Biochemistry and Cell Biology, 45:2179–2185.
4. Argiles, J. M., Stemmler, B., Lopez-Soriano, F. J. & Busquets, S. (2018). Inter-tissue communication in cancer cachexia. Nature Reviews Endocrinology, 15:9–20.
5. Argilés, J.M., López-Soriano, F.J., Stemmler, B. Busquets S. (2023). Cancer-associated cachexia — understanding the tumour macroenvironment and microenvironment to improve management. Nature Reviews of Clinical Oncology 20(4):250–264 (2023). <https://doi.org/10.1038/s41571-023-00734-5>
6. Balkwill, F. & Mantovani, A. (2001). Inflammation and cancer: Back to virchow? Lancet, 357:539–45.
7. Baracos, V. E., Martin, L., Korc, M., Guttridge, D. C., Fearon, K. C. H. (2018). Cancer-associated cachexia. Nature Reviews Disease Primers, 4:17105. doi: 10.1038/nrdp.2017.105. PMID: 29345251.
8. Blum, D., Omlin, A., Baracos, V. E., Solheim, T. S., Tan, B. H. L., Stone, P., Kaasa, S., Fearon, K. & Strasser, F. (2011). Cancer cachexia: a systematic literature review of items and domains associated with involuntary weight loss in cancer. Critical Reviews in Oncology-Hematology, 80:114–144.
9. Blum, D., Stene, G. B., Solheim, T. S., Fayers, P., Hjermstad, M. J., Baracos, V. E., Fearon, K., Strasser, F., Kaasa, S. (2014). Validation of the consensus-definition for cancer cachexia and evaluation of a classification model–a study based on data from an international multicentre project (EPCRC-CSA). Annals of Oncology, 25:1635–1642.
10. Bonetto A, Aydogdu T, Kunzevitzky N, Guttridge DC, Khuri S, Koniaris LG, et al. (2011) STAT3 Activation in Skeletal Muscle Links Muscle Wasting and the Acute Phase Response in Cancer Cachexia. PLoS ONE 6(7): e22538. https://doi.org/10.1371/journal.pone.0022538
11. Bonifant, C. L., Jackson, H. J., Brentjens, R. J. & Curran, K. J. (2016). Toxicity and management in CAR T-cell therapy. Moecular Therapy Oncolytics, 3:16011.
12. Bonovas, S., Nikolopoulos, G. & Sitaras, N. M. (2013). Statins and reduced risk of hepatocellular carcinoma in patients with hepatitis C virus infection: further evidence is warranted. Journal of Clinical Oncology, 31:4160.
13. Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A. & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, 68:394–424.
14. Brown LR, Laird BJA, Wigmore SJ, Skipworth RJE. Understanding Cancer Cachexia and Its Implications in Upper Gastrointestinal Cancers. Curr Treat Options Oncol. 2022 Dec;23(12):1732-1747. doi: 10.1007/s11864-022-01028-1. Epub 2022 Oct 21.
15. Castell, J. V., Gómez-Lechón, M. J., David, M., Andus, T., Geiger, T., Trullenque, R., Fabra, R. & Heinrich, P. C. (1989). Interleukin-6 is the major regulator of acute phase protein synthesis in adult human hepatocytes. FEBS Letters, 242(2):237–239.
16. Cella, P. S., Marinello, P. C., Borges, F. H., Ribeiro, D. F., Chimin, P., Testa, M. T. J., Guirro, P. B., Duarte, J. A., Cecchini, R., Guarnier, F. A. & Deminice, R. (2020). Creatine supplementation in Walker-256 tumor-bearing rats prevents skeletal muscle atrophy by attenuating systemic inflammation and protein degradation signaling. European Journal of Nutrition, 59:661–669.
17. Chiappalupi, S., Sorci, G., Vukasinovic, A., Salvadori, L., Sagheddu, R., Coletti, D., Renga, G., Romani, L., Donato, R. & Riuzzi, F. (2020). Targeting RAGE prevents muscle wasting and prolongs survival in cancer cachexia. Journal of Cachexia, Sarcopenia and Muscle, 11:929–946.
18. Coletti, D. (2018). Chemotherapy-induced muscle wasting: an update. European Journal of Translational Myology, 28:7587.
19. Coussens, L. M. & Werb, Z. (2002). Inflammation and cancer. Nature, 420:860–867.
20. Cuzick, J., Thorat, M. A., Bosetti, C., Brown, P. H., Burn, J., Cook, N. R., Ford, L. G., Jacobs, E. J., Jankowki, J. A., La Vecchia, C., Law, M., Meyskens, F., Rothwell, P. M., Senn, H. J. & Umar A. (2015). Estimates of benefits and harms of prophylactic use of aspirin in the general population. Annals of Oncology, 26:47–57.
21. Elinav, E., Norwarski, R., Christoph, A., Thaiss, B. H., Chengcheng, J. & Richard, A. F. (2013). Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. Nature Reviews Cancer, 13:759–771.
22. Esper, D. H. & Harb, W. A. (2005). The cancer cachexia syndrome: a review of metabolic and clinical manifestations. Nutrition in Clinical Practice, 20:369–376.
23. Ezeoke, C. C. & Morley, J. E. (2015). Pathophysiology of anorexia in the cancer cachexia syndrome. Journal of Cachexia, Sarcopenia and Muscle, 6:287–302.
24. Falconer, J. S., Fearon, K. C., Plester, C. E., Ross, J. A. & Carter, D. C. (1994). Cytokines, the acutephase response, and resting energy expenditure in cachectic patients with pancreatic cancer. Annals of Surgery, 219(4):325–31.
25. Fearon, K. C., Voss, A. C. & Hustead, D. S. (2006). Cancer Cachexia Study G. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. American Journal of Clinical Nutrition, 83:1345–1350.
26. Fearon, K., Arends, J. & Baracos, V. (2013). Understanding the mechanisms and treatment options in cancer cachexia. Nature Reviews Clinical Oncology. 10:90–99.
27. Fearon, K., Strasser, F., Anker, S. D., Bosaeus, I., Bruera, E., Fainsinger, R. L., Jatoi, A., Loprinzi, C., MacDonald, N., Mantovani, G., Davis, M., Muscaritoli, M., Ottery, F., Radbruch, L., Ravasco, P., Walsh, D., Wilcock, A., Kaasa, S. & Baracos V. E. (2011). Definition and classification of cancer cachexia: an international consensus. Lancet Oncology, 12:489–495.
28. Fujii, H, Makiyama, A., Iihara, H., Okumura, N., Yamamoto, S., Imai, T., Arakawa, S., Kobayashi, R., Tanaka, Y., Yoshida, K. & Suzuki, A. (2020). Cancer cachexia reduces the efficacy of nivolumab treatment in patients with advanced gastric cancer. Anticancer Research, 40(12):7067-7075.
29. Gaafer OU, Zimmers TA. Nutrition challenges of cancer cachexia. JPEN J Parenter Enteral Nutr. 2021; 45: S16–S25. <https://doi.org/10.1002/jpen.2287>
30. Gabay, C. & Kushner, I. (1999). Acute-phase proteins and other systemic responses to inflammation. New England Journal of Medicine, 340(6):448–54.
31. Grivennikov, S. I., Greten, F. R. & Karin, M. (2010). Immunity, inflammation, and cancer. Cell, 140, 883–899.
32. Grounds, M. D., Radley, H.G., Gebski, B.L., Bogoyevitch, M. A. & Shavlakadze, T. (2008). Implications of cross-talk between tumour necrosis factor and insulin-like growth factor-1 signalling in skeletal muscle. Clinical and Experimental Pharmacology and Physiology, 35:846–851.
33. Gulhar, R., Ashraf, M. A. & Jialal, I. (2023). Physiology, acute phase reactants. Treasure Island, FL: StatPearls.
34. Gun, S. Y., Lee, S. W. L., Sieow, J. L. & Wong, S. C. (2019). Targeting immune cells for cancer therapy. Redox Biology, 25:101174.
35. Headland, S. E. & Norling, L. V. (2015). The resolution of inflammation: Principles and challenges. Seminars in Immunology, 27:149–160.
36. Hua, X., Kratz, M., Malen, R. C., Dai, J. Y., Lindstrom, S., Zheng, Y. & Newcomb, P. A. (2021). Association between post-treatment circulating biomarkers of inflammation and survival among stage II-III colorectal cancer patients. British Journal of Cancer, 125:806–815
37. Kasvis P., Vigano M., Vigano A. Health-related quality of life across cancer cachexia stages. Ann. Palliat. Med. 2019;8:33–42. doi: 10.21037/apm.2018.08.04.
38. Kersten, C., Louhimo, J., Algars, A., Lahdesmaki, A., Cvancerova, M., Stenstedt, K., Haglund, C. & Gunnarsson, U. (2013). Increased C-reactive protein implies a poorer stage-specific prognosis in colon cancer. Acta Oncologica, 52:1691–1698.
39. Li, Y. P., Chen, Y., John, J., Moylan, J., Jin, B., Mann, D. L. & Reid, M. B. (2005). TNF-alpha acts via p38 MAPK to stimulate expression of the ubiquitin ligase atrogin1/MAFbx in skeletal muscle. FASEB Journal, 19:362–370.
40. Lin, Y., Rajala, M. W., Berger, J. P., Moller, D. E., Barzilai, N. & Scherer, P. E. (2001). Hyperglycemia-induced production of acute phase reactants in adipose tissue. Journal Biological Chemistry, 276(45):42077–83.
41. Loberg, R. D., Bradley, D. A., Tomlins, S. A., Chinnaiyan, A. M. & Pienta, K. J. (2007). The lethal phenotype of cancer: the molecular basis of death due to malignancy. CA:A Cancer Journal for Clinicians, 57:225–241.
42. Ma, Y., Adjemian, S., Mattarollo, S. R., Yamazaki, T., Aymeric, L., Yang, H., Catani, J. P. P., Dalil, H. D., Duret, H., Steegh, K., Martins, I., Schlemmer, F., Michaud, M., Kepp, O., Sukkurwala, A. Q., Menger, L., Vacchelli, E., Droin, N., Galluzzi, L., Krzysiek, R., Gordon, S., Taylor, P. R., Van Endert, P., Solary, E., Smyth, M. J., Zitvogel, L. & Kroemer, G. (2013). Anticancer chemotherapy-induced intratumoral recruitment and differentiation of antigen-presenting cells. Immunity, 38, 729–741.
43. Maccio, A., Sanna, E., Neri, M., Oppi, S. & Madeddu, C. (2021). Cachexia as evidence of the mechanisms of resistance and tolerance during the evolution of cancer disease. International Journal of Molecular Sciences, 22(6):2890.
44. Mariean CR, Tiucă OM, Mariean A, Cotoi OS. Cancer Cachexia: New Insights and Future Directions. Cancers (Basel). 2023 Nov 26;15(23):5590. doi: 10.3390/cancers15235590.
45. McGovern, J., Dolan, R. D., Skipworth, R. J., Laird, B. J. & McMillan, D. C. (2022). Cancer cachexia: a nutritional or a systemic inflammatory syndrome? British Journal of Cancer, 127(3):379–82.
46. Medzhitov, R. (2008). Origin and physiological roles of inflammation. Nature, 454, 428–435.
47. Murphy, K. T. & Lynch, G. S. (2009). Update on emerging drugs for cancer cachexia. Expert Opinion on Emerging Drugs, 14:619–632.
48. Narasimhan, A., Zhong, X., Au, E. P., Ceppa, E. P., Nakeeb, A. & House, M. G. (2021). Profiling of adipose and skeletal muscle in human pancreatic cancer cachexia reveals distinct gene profiles with convergent pathways. Cancers (Basel), 13(8):1975.
49. Nasr, R., Salim, H. M., Nassar, F., Mukherji, D., Shamseddine, A. & Temraz, S. (2018). Inflammatory markers and microRNAs: the backstage actors influencing prognosis in colorectal cancer patients. International Journal of Molecular Science, 19:19.
50. Nishikawa H, Goto M, Fukunishi S, Asai A, Nishiguchi S, Higuchi K. Cancer Cachexia: Its Mechanism and Clinical Significance. Int J Mol Sci. 2021 Aug 6;22(16):8491. doi: 10.3390/ijms22168491. PMID: 34445197; PMCID: PMC8395185.
51. Okugawa, Y., Toiyama, Y., Yamamoto, A., Shigemori, T., Ide, S., Kitajima, T., Fujikawa, H., Yasuda, H., Hiro, J., Yoshiyama, S., Yokoe, T., Saigusa, S., Tanaka, K., Shirai, Y., Kobayashi, M., Ohi, M., Araki, T., McMillan, D. C., Miki, C., Goel, A. & Kusunoki, M. (2020). Lymphocyte-C-reactive protein ratio as promising new marker for predicting surgical and oncological outcomes in colorectal cancer. Annals of Surgery, 272:342–351.
52. Omlin, A., Blum, D., Wierecky, J., Haile, S. R., Ottery, F. D. & Strasser, F. (2013). Nutrition impact symptoms in advanced cancer patients: frequency and specific interventions, a casecontrol study. Journal of Cachexia Sarcopenia and Muscle, 4:55–61.
53. Pérez-Pérez A, Sánchez-Jiménez F, Vilariño-García T, Sánchez-Margalet V. Role of Leptin in Inflammation and Vice Versa. Int J Mol Sci. 2020 Aug 16;21(16):5887. doi: 10.3390/ijms21165887.
54. Philip, M., Rowley, D. A. & Schreiber, H. (2004). Inflammation as a tumor promoter in cancer induction. Seminars in Cancer Biology, 14:433–9.
55. Punt, S., Dronkers, E. A. C., Welters, M. J. P., Goedemans, R., Koljenović, S., Bloemena, E., Snijders, P. J. F., Gorter, A., van der Burg, S. H., de Jong, R. J. B. & Jordanova, E. S. (2016). A beneficial tumor microenvironment in oropharyngeal squamous cell carcinoma is characterized by a high T cell and low IL-17(+) cell frequency. Cancer Immunology, Immunotherapy, 65, 393–403.
56. Robinson, T. P., Hamidi, T., Counts, B., Guttridge, D. C., Ostrowski, M. C., Zimmers, T. A. & Koniaris, L. G. (2023). The impact of inflammation and acute phase activation in cancer cachexia. Frontiers in Immunology, 14:1207746
57. Rossi, A. G., Sawatzky, D. A., Walker, A., Ward, C., Sheldrake, T. A., Riley, N. A., Caldicott, A., Martinez-Losa, M., Walker, T. R., Duffin, R., Gray, M., Crescenzi, E., Martin, M. C., Brady, H. J., Savill, J. S., Dransfield, I. & Haslett, C. (2006). Cyclin-dependent kinase inhibitors enhance the resolution of inflammation by promoting inflammatory cell apoptosis. Nature Medicine, 12:1056–1064.
58. Ruan GT, Deng L, Xie HL, Shi JY, Liu XY, Zheng X, Chen Y, Lin SQ, Zhang HY, Liu CA, Ge YZ, Song MM, Hu CL, Zhang XW, Yang M, Hu W, Cong MH, Zhu LC, Wang KH, Shi HP. Systemic inflammation and insulin resistance-related indicator predicts poor outcome in patients with cancer cachexia. Cancer Metab. 2024 Jan 25;12(1):3.
59. Rupert, J. E., Narasimhan, A., Jengelley, D. H. A., Jiang, Y., Liu, J., Au, E., Silverman, L. M., Sandusky, G., Bonetto, A., Cao, S., Lu, X., O'Connell, T. M., Liu, Y., Koniaris, L. G. & Zimmers, T. A. (2021). Tumor-derived IL-6 and trans-signaling among tumor, fat, and muscle mediate pancreatic cancer cachexia. Journal of Experimental Medicine, 218(6).
60. Schneider, C. & Pozzi, A. (2011). Cyclooxygenases and lipoxygenases in cancer. Cancer Metastasis Review, 30:277–294.
61. Serhan, C. N. (2011). The resolution of inflammation: the devil in the flask and in the details. Faseb Journal, 25:1441–1448.
62. Setiawan T, Sari IN, Wijaya YT, Julianto NM, Muhammad JA, Lee H, Chae JH, Kwon HY. Cancer cachexia: molecular mechanisms and treatment strategies. J Hematol Oncol. 2023 May 22;16(1):54.
63. Silva, G. A. D., Wiegert, E. V. M., Calixto-Lima, L. & Oliveira, L. C. (2020). Clinical utility of the modified Glasgow Prognostic Score to classify cachexia in patients with advanced cancer in palliative care. Clinical Nutrition, 39(5):1587–92.
64. Sun, S. C. (2017).The non-canonical NF-kappaB pathway in immunity and inflammation. Nature Reviews Immunology, 17:545–558.
65. Tan, B. H., Ross, J. A., Kaasa, S., Skorpen, F. & Fearon, K. C. (2011). European Palliative Care Research C. Identification of possible genetic polymor phisms involved in cancer cachexia: a systematic review. Journal of Genetics, 90:165–177.
66. Tavares, P., Gonçalves, D. M., Santos, L. L. & Ferreira, R. (2021). Revisiting the clinical usefulness of C-reactive protein in the set of cancer cachexia. Porto Biomedical Journal, 6(1):e123.
67. Tisdale M. J. (1997). Biology of cachexia. Journal of the National Cancer Institute, 89:1763–1773.
68. Tisdale M. J. (2009). Mechanisms of cancer cachexia. Physiological Reviews, 89:381–410.
69. Vasan, N., Baselga, J. & Hyman, D. M. (2019). A view on drug resistance in cancer. Nature, 575:299–309.
70. Von Haehling, S. & Anker, S. D. (2014). Prevalence, incidence and clinical impact of cachexia: facts and numbers-update 2014. Journal of Cachexia, Sarcopenia and Muscle. 5:129–133.
71. Wang, Z., Cheng, Q., Tang, K., Sun, Y., Zhang, K., Zhang, Y., Luo, S., Zhang, H., Ye, D. & Huang, B. (2015). Lipid mediator lipoxin A4 inhibits tumor growth by targeting IL10-producing regulatory B (Breg) cells. Cancer Letters, 364:118–124.
72. Webster, J. M., Kempen, L. J. A. P., Hardy, R. S. & Langen, R. C. J. (2020). Inflammation and skeletal muscle wasting during cachexia. Frontiers in Physiology, 11:597–675.
73. Yang, W., Yu, T., Huang, X., Bilotta, A. J., Xu, L., Lu, Y., Sun, J., Pan, F., Zhou, J., Zhang, W., Yao, S., Maynard, C. L., Singh, N., Dann, S. M., Liu, Z. & Cong, Y. (2020). Intestinal microbiota-derived short-chain fatty acids regulation of immune cell IL-22 production and gut immunity. Nature Communications, 11:4457.
74. Yasui, K., Shida, D., Nakamura, Y., Ahiko, Y., Tsukamoto, S. & Kanemitsu, Y. (2021). Postoperative, but not preoperative, inflammation-based prognostic markers are prognostic factors in stage III colorectal cancer patients. British Journal of Cancer, 124:933–941.
75. Yoshida, T. & Delafontaine, P. (2020). Mechanisms of IGF-1-mediated regulation of skeletal muscle hypertrophy and atrophy. Cells, 9:1970.
76. Zhang R., Li J., Assaker G., Camirand A., Sabri S., Karaplis A.C., Kremer R. Parathyroid Hormone-Related Protein (PTHrP): An Emerging Target in Cancer Progression and Metastasis. Adv. Exp. Med. Biol. 2019;1164:161–178. doi: 10.1007/978-3-030-22254-3\_13.
77. Zhou, J., Wei, W., Hou, H., Ning, S., Li, J., Huang, B., Liu, K. & Zhang, L. (2021). Prognostic value of C-reactive protein, Glasgow prognostic score, and Creactive protein-to-albumin ratio in colorectal cancer. Frontiers in Cell and Developmental Biology, 9:637650.
78. Zhuang, P., Zhang, J., Wang, Y., Zhang, M., Song, L., Lu, Z., Zhang, L., Zhang, F., Wang, J., Zhang, Y., Wei, H. & Li, H. (2016). Reversal of muscle atrophy by Zhimu and Huangbai herb pair via activation of IGF-1/Akt and autophagy signal in cancer cachexia. Support Care Cancer, 24:1189–1198.
79. Zhao, H., Wu, L., Yan, G., Chen, Y., Zhou, M., Wu, Y., & Li, Y. (2021). Inflammation and tumor progression: signaling pathways and targeted intervention. Signal transduction and targeted therapy, 6(1), 263.