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A New Study Uncovering the Cause of Health Deterioration and Mortality in Late-stage Cancer Patients

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Commentary

Cachexia [Greek origin, Etymology: *kakos* (bad) and *hexes* (condition)] is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle mass with or without loss of body fat. This syndrome can be linked to anorexia, inflammation, insulin resistance, and raised protein turnover [1]. Cachexia is typically found to be associated with severe disorders such as chronic heart/renal failure, cancer, and autoimmune diseases. This condition results in deprived nutrition and decreased skeletal muscle mass [2,3]. Cachexia, a prevalent disorder in Western countries, mostly eventuates in cancer patients (30%) [4]. Moreover, the international consensus defines cancer-associated cachexia (CAC) as a complex condition characterized by a continuous loss of muscle mass (sometimes fat), which cannot be reversed entirely with standard nutrition support. It results from a combination of reduced food intake and altered metabolism [5].

Systemic inflammation is a crucial characteristic of CAC. Although several non-steroidal anti-inflammatory drugs (NSAIDs) have been proposed as potential therapy for CAC, none of them have consistently demonstrated efficacy [6]. We conducted a research study published as "R-ketorolac ameliorates cancer-associated cachexia and prolongs survival of tumor-bearing mice," which explored the effects of the R-enantiomer of ketorolac (RK), a non-steroidal anti-inflammatory drug (NSAID), on CAC and survival rates in tumor-bearing mice. CAC is a chronic condition that causes muscle and fat loss, systemic inflammation, and a significant reduction in the quality of life and life expectancy of cancer patients. This study included 10- to 11-week-old mice inoculated with C26 or CHX207 cancer cells to induce CAC or vehicle control (phosphate buffered saline, PBS). The onset of cachexia was confirmed when body weight loss of ≥ 5% was achieved within 2–3 consecutive days (mild cachexia). Upon induction of cachexia, mice were administered either 2 mg/kg of RK or 12 gm/kg of anamorelin/PBS (vehicle) as control daily by oral gavage. The body weight, food intake, and tumor size were monitored throughout the study. Blood samples were withdrawn at the end of the study, and tissues were collected for further analysis. Immune cell abundance, COX activity, muscle tissues, and muscle fiber size were analyzed with a flow cytometer, fluorometric kit, RT-PCR/western blotting, and hematoxylin/eosin staining, respectively.

The result of this study demonstrated significant improvement in survival rates in mice treated with RK compared to untreated mice. The 10-day survival rate for C26 tumor-bearing mice was 10% in untreated mice, whereas it was found to be a 100% survival rate ($P = 0.0009$) in the RK-treated mice. Similarly, chemotherapy alone led to a 10% survival rate 14 days after treatment initiation. However, when RK and cyclophosphamide were administered together, all mice survived ($P = 0.0001$). RK-treated tumor-bearing mice demonstrated less body weight loss than untreated tumor-bearing mice. Moreover, a protective effect against muscle and fat wasting was observed in RK-treated tumor-bearing mice. RK was found to significantly reduce systemic levels of interleukin-6 (IL-6), a pro-inflammatory cytokine associated with CAC, in both C26 and CHX207 tumor-bearing mice. Additionally, RK protects against cancer-induced T-lymphopenia, further supporting its role in modulating the immune response in CAC. The beneficial effects of RK in ameliorating CAC appeared to depend on the presence of T-cells, as the treatment was ineffective in thymus-deficient nude mice. The study emphasizes that RK's beneficial effects

operate independently of COX inhibition, setting it apart from other NSAIDs with similar anti-inflammatory functions but possessing significant side effects. The study concludes that RK significantly enhances survival and alleviates CAC-associated symptoms in tumor-bearing mice. RK benefits by reducing systemic IL-6 levels and preventing T-lymphopenia. These findings indicate that RK could be considered a promising therapeutic option in managing CAC, thereby warranting further investigation and potential clinical trials to explore the underlying mechanisms further.

Rethinking CAC: An Immune Disorder Beyond Metabolism

CAC is a multifactorial complex syndrome defined by the loss of skeletal muscle mass, often accompanied by fat loss, which eventually leads to reduced functionality and quality of life. This condition manifests due to elevated systemic inflammation and catabolic signals, suppressing protein synthesis and promoting muscle breakdown [7]. Despite the crucial role of inflammation-driven involvement of immunoregulation in cachexia, the immunological aspect extensively involved in the cachectic progression remains poorly explored [8]. The data focusing on the impact of the immune system on cachexia initiation are currently limited. However, while we do not understand the mechanisms of cachexia fully as yet, it is quite clear that its onset is driven by the inflammatory processes initiated by the underlying illness.

Cancer is characterized by malfunctioning of the immune system and inflammation. This disruption of immune tolerance is a crucial feature of cancer cells, and failure of this homeostasis state may result in autoimmunity. Overproduction of cytokines and autoantibodies against different organs is a common feature of advanced malignancy and autoimmune disorders. These cytokines, overproduced in the tumor microenvironment, interact with muscle cells and result in muscle wasting. Notably, IL-1β, IL-6, and TNF-α cytokines have been associated with CAC (summarized in **Table 1**) [9].

Both immune and non-immune cells exhibit abundant expression of these inflammatory mediators once their pattern-recognition receptors are activated by damage-associated molecular patterns and/or pathogen-associated molecular patterns [8,10,11]. Cytokines activate JAK-STAT (Janus kinase/signal transducer and activator of transcription) and NF-κB signaling pathways as well as downstream transcriptional regulation can induce several catabolic pathways in muscles and adipose tissue including mitochondrial dysfunction, a

Table 1. Glimpses of a few inflammatory mediators associated with CAC.

Cytokine	Produced by	Organs affected by cancer	Model (Trials)	Effects in cachexia	Reference
IL-1α	Macrophages and endothelial cells	Pancreas, breast, colorectal	Mice and rats	Lipolysis, anorexia, weight loss, suppression of hunger	[54-56]
IL-1β	Macrophages	Gastric, breast, lung, and several other	Mice and human	Anorexia, weight loss, sarcopenia, weakness, impaired mitochondrial metabolism	[57-59]
IL6	Activated macrophages	Colorectal, pancreas, and several others	Mice and human	Adipose wasting, skeletal muscle loss, affects gut and liver tissue, impaired mitochondrial metabolism	[55,56,59]
TNFα	Activated macrophages, CD4+, neutrophils, mast cells, eosinophils and neurons	Pancreas, lungs, colon, and several other	Mice and human	Anorexia, muscle and adipose wasting, insulin resistance, increased energy expenditure, impaired mitochondrial metabolism	[60-62]
GDF15	Adipocytes, Macrophages, Endothelial cells, Vascular smooth muscle cells, Cardiomyocytes, and Trophoblastic cells	Lungs, pancreas, colorectal, prostate, and several others	Mice	energy metabolism, anorexia, muscle atrophy, adipose tissue depletion, bone loss, anemia	[56,63,64]
IFNγ	Activated T and NK cells	Pancreas, lung, colon, prostate	Mice and rats	Loss of body weight, reduced appetite, atrophy of adipose tissue	[56,65,66]

IL-1α: Interleukin-1 Alpha; IL-1β: Interleukin-1 Beta; IL-6: Interleukin-6; TNFα: Tumour Necrosis Factor Alpha; GDF15: Growth Differentiation Factor 15; INFγ: Interferon Gamma

burst of reactive oxygen species (ROS), and pathways like NLRP3 (nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3), JNK (Jun N-terminal kinase), MAPK (mitogen-activated protein kinase), PI3K (phosphatidylinositol-3 kinase) and NF-κB leading to inflammation [8,10,12-14]. According to a study conducted by Lima *et al.*, in patients with colorectal CAC, the tumors exhibited elevated levels of inflammatory cytokines (IFN-α and IL-8), growth factors (such as granulocyte-macrophage colony-stimulating factor and epidermal growth factor), and deposits of actin and collagen [15]. Another study reported elevated levels of growth differentiation factor 15 (GDF15) in several malignant tumors and was found to be associated with cachexia-inducing weight loss [16]. Several cytokines are induced in a context-dependent manner in cachexia and may contribute to its development. However, further research is imperative to elucidate the role of pro and anti-inflammatory cytokines in the pathophysiology of cachexia [5].

Studies on the association between immune cell function and cachexia are limited. However, recent studies have suggested the involvement of multiple immune cell types, such as macrophages, neutrophils, T cells, and myeloid-derived suppressor cells (MDSCs), in the initiation and progression of cachexia [5]. The pancreatic ductal adenocarcinoma (PDAC) mouse model of CAC demonstrated that the increased number of microglial cells in the brain caused the depletion of neutrophils (the number of neutrophils is directly proportional to the degree of cachexia), thereby giving protection against severe cachexia [17]. Further, macrophages are involved in protection against lipolysis in adipose tissue, whereas in muscle tissue, an increased number of macrophages leads to a higher degree of atrophy, which is primarily affected by polarization of macrophages [18,19]. The number of MDSCs in the spleen and bone marrow positively correlates with cachexia [20,21]. A negative correlation was observed between the abundance of CD4+FOXP3+ T cells and cachexia, while CD8+ T cells exhibited a negative correlation with cachexia [22,23].

Immunometabolism plays a pivotal role in cachexia, as the condition depletes the body's energy reserves, thereby potentially triggering systemic inflammation, immune cell activation, and metabolic disturbances [5,8]. Cancer cells can induce metabolic reprogramming of immune cells, resulting in systemic changes in metabolism, further inducing the transition from pro-inflammatory to immunosuppressive responses [24,25]. Recent studies suggest that activated immune cells mediate the activity of several signaling molecules, such as p38 MAPK, STAT3, etc., resulting in the promotion of cancer cachexia [26-30]. Several preclinical studies have suggested overexpression of cytokines (IL-6 and IL8), increased NLR, and changes in the TGFβ pathway during CAC progression, indicating that immune disorders are associated with CAC [9,31-34].

Research shows that immune responses in cachexia usually trigger tissue catabolism. Immunometabolic crosstalk during cachexia induces adipose tissue and muscle catabolism, producing fatty acids and amino acids, respectively [5]. Adipose tissue lipolysis increases levels of NEFAs (nonesterified fatty acids) and glycerol, which are utilized by other organs [35,36]. *In vitro* studies have shown that treating adipocyte and hepatocyte cell lines with saturated fatty acids activates Toll-like receptor 4 (TLR4) signaling, further activating NF-κB and resulting in increased TNF and IL-6 production [37]. The studies suggest that adipose tissue lipolysis and NEFA release carry out activation of TLR4, further aggravating tissue catabolism [38,39]. Further, alterations in amino acid profiles have also been observed in the tumor microenvironment. Immune cells and tumor cells compete for available amino acids to support their high anabolic demands, which modulates the activation status of immune cells [40]. For example, glutamine is primarily taken up by tumor cells, limiting its availability for T cells [41]. Comprehensive profiling and dissection of systemic and local amino acid levels in cachexia will contribute to a better understanding of their pathophysiological effect on inflammation, metabolism, and disease outcomes [5].

As stated earlier, cachexia is characterized by muscle atrophy and adipose tissue depletion. The depletion of skeletal and cardiac muscle mass is due to three cellular processes downstream of FOXO (forkhead box O) and NF-κB (nuclear factor kappa B) signaling, viz., proteasomal degradation, autophagy, and reduced myocyte regeneration [42-45]. Cachexia is responsible for increased lipolysis with suppression of liquid uptake and lipogenesis causing depletion of lipid droplets of adipose tissue [46,47]. The changes in the adipose tissue are known to occur through either transcriptional modulation or ATGL-mediated and HSL-mediated lipolysis [47].

The intricate link between immune responses and cachexia remains unexplored and yet to be unraveled. Therefore, future studies on cachexia should integrate immunology and the use of tools and knowledge from evolutionary medicine and systems biology [48]. Moreover, clinical studies encompassing both animal models and human trials are also crucial for further validation. Immunomodulation in cachexia, specifically in the context of CAC, has been largely overlooked in research. Therefore, more rigorous studies on immune cell function will substantially enhance our understanding of the role of immunomodulation in tissue metabolism during cachexia [5]. Though numerous pre-clinical studies have indicated that tumor-induced immune disorder promotes the development of CAC, direct evidence demonstrating immunomodulation to the onset of CAC symptoms is still lacking [9]. However, research indicates that inhibiting cytokines and immunomodulation can reduce CAC progression, suggesting that these pathways may be considered an effective strategy for treating CAC [9].

Similarly, our study revealed that RK-mediated immunomodulation in a mouse model improved T-lymphopenia and decreased systemic IL-6 concentrations, thereby ameliorating cachexia and increasing the survival

rate in cachexigenic tumor-bearing mice undergoing chemotherapy. Hence, our study highlights and emphasizes the benefit of RK in patients suffering from CAC [49].

Immune Disorder may be the Root Cause of Cancer Death

Cancer cachexia, generally an overlooked condition in cancer patients, is often associated with immune system disturbances. In response to cancer, immune cells release inflammatory molecules in CAC, including interleukins, members of the growth factor family, and tumor necrosis factor [50]. Particularly in cancer cachexia, substances secreted by the tumor and tumor-induced immune responses followed by an altered metabolic state have been suggested to be deeply involved in its pathogenesis [30]. The study by Riccardi *et al.*, compared plasma profiles of CAC and weight-stable cancer (WSC) patients. The study demonstrated alterations in plasma concentrations of markers of systemic inflammation in cancer cachexia patients. Higher levels of pro-inflammatory cytokines like IL-6, tumor necrosis factor-alpha (TNF-α), and IL-8 were reported [51]. In another study by Mangano *et al.* [52], TNF-α directly leads to muscle wasting by activating the ubiquitin-proteasome system. In cancer cachexia, it disrupts carbohydrate, protein, and fat metabolism. TNF-α also increases gluconeogenesis, breaks down fat and proteins, and reduces the synthesis of proteins, lipids, and glycogen. Another study by Shukla *et al.* [19], highlighted the role of macrophages in muscle wasting in preclinical trials. It demonstrated that reducing macrophages lessened systemic inflammation and muscle wasting in mice with pancreatic tumors. Inhibiting macrophage-driven STAT3 activation or macrophage-derived interleukin-1 alpha or interleukin-6 reduced muscle fiber atrophy.

Pre-clinical and clinical studies have confirmed increased levels of proinflammatory cytokines like IL-6, IL-8, and TNFα, as well as immune markers (NLR) in patients with CAC. Hence, immunomodulatory mechanisms involved in cachexia may impact the anti-neoplastic immune response [9]. Immunomodulation could be a potential anti-cancer therapy to constrain CAC mechanisms. RK, a new immunomodulator, was found to reverse the cachexia weight loss and substantially elevated the survival rate in CAC mice. This immunomodulator opens new avenues for research in immunomodulation and may hold an answer to long pending questions, i.e., why do patients with cancer die? [53]. Our study provides an answer that late-stage cancer patients could die from immune disorder-induced implications like cachexia, multiple organ failure, etc. This study revealed that RK-mediated immunomodulation can significantly reverse cancer cachexia and enhance the survival rate. Hence, the study proposes using RK in treating patients suffering from CAC [49]. If the role of this new immunomodulator, i.e., RK, holds true in clinical trials, it would change the paradigm of late-stage cancer care. Our ongoing trials (NCT05336266) support the role of RK in treating patients with CAC.

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