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Viewpoint

Challenges in Targeting the "Crosstalks" in Cancer Cachexia

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Abstract

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Cancer cachexia syndrome is characterized by involuntary weight loss which usually occurs in advanced malignancies. The pathogenicity of this syndrome is multifactorial, due to a complex interaction of tumor and host factors. The syndrome is closely related to the prognostication of malignancies. Several research works are in progress to target the major effectors of cancer cachexia syndrome. This letter is a nutshell on the current status of the cancer cachexia syndrome—the crosstalks and potential therapeutic targets.

Keywords

- adipose tissue
- cancer cachexia
- central nervous system
- skeletal muscle
- tumor environment

Introduction

Cancer cachexia syndrome (CCS) is a syndrome which leads to involuntary weight loss in patients with advanced malignancies. It can also develop early in the course of some malignancies like pancreatic cancers. It is a well-known fact that cancer cachexia cycle correlates closely with the prognosis and treatment responses. CCS is commonly misunderstood as a nutritional disorder, but it has wider pathophysiological spectrum. The syndrome in itself has been a topic of interest for a long time, but there were some recent published articles which looked into identification of novel targets in tumor environments (both micro- and macroenvironment) to help in tailoring "adjuvant" therapies.

Mechanisms in Cancer Cachexia

Initial works had already proposed that dysregulated macroenvironment is due to high demand of glucose due to increased demands of tumor cells. This is achieved through the activation of various metabolic pathways like glycogenolysis, Cori's cycle, lipolysis, etc. All these catabolic processes overrun the anabolic ones which lead to energy loss and thereby weakness and fatigue.[1] In this manner, the cycle progresses from precachexia to refractory cachexia based on the changes in weight (►Fig. 1).

Almost all organ systems are affected in CCS. Skeletal muscle atrophy and loss of adipose tissue are the frontrunners

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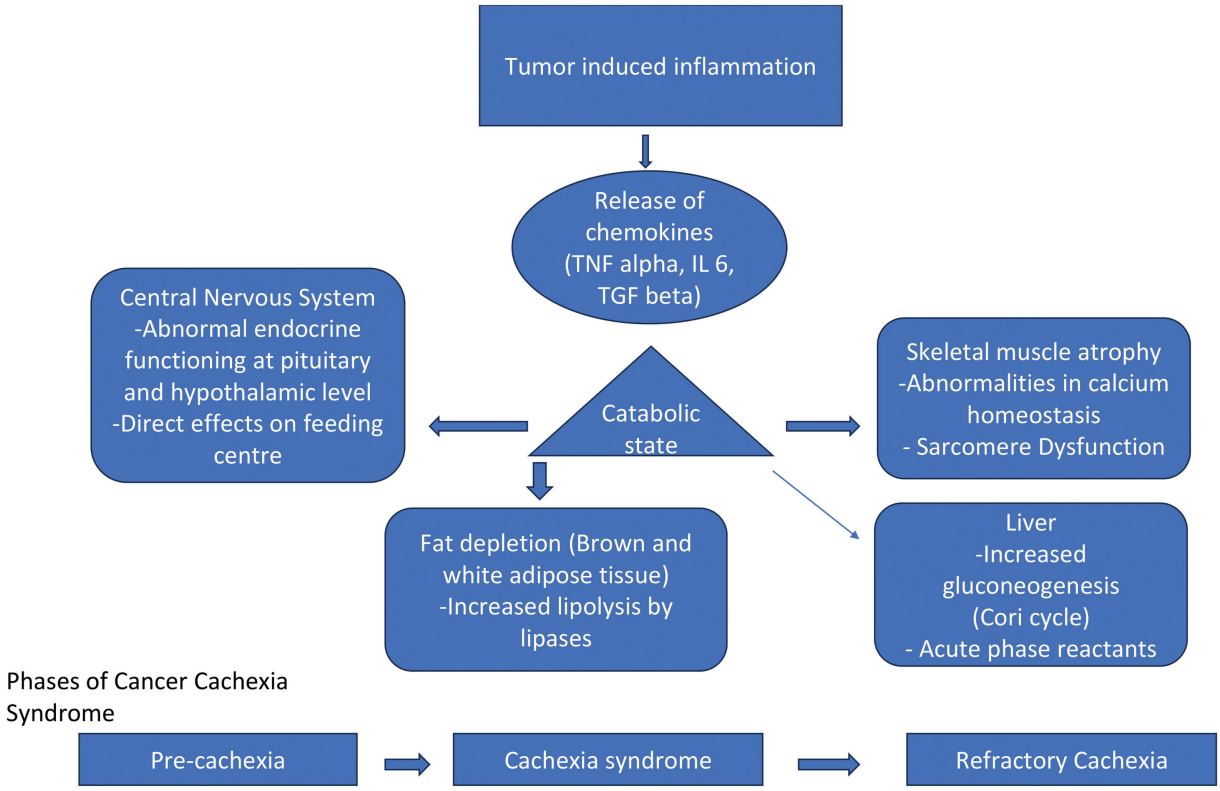

Fig. 1 Vicious cycle of Cancer Cachexia syndrome.

of CCS. The liver is one of the major organs which is involved in the metabolic changes during CCS. The researchers have dwelled into molecular mechanisms of each of these entities and there have been some recent findings which has created more inquisitiveness into the topic.

Skeletal Muscle Atrophy

Biomarkers that have been identified for skeletal muscle atrophy include:

(1) E3 ubiquitin ligases, MuRF1/TRIM63, and Atrogin-1/MAFBx/FBX32 and more recent discoveries include TRIM32, MUSA/FBXO30, SMART/FBXO21, and FBXO31.
(2) Hyperactivation of the autophagy system like E3 ubiquitin proteasome pathway.
(3) Mitochondrial dysfunction which leads to decrease in the levels of the peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) and defects in mitochondrial dynamics.

The skeletal muscle loss has been tried to be targeted through the molecular pathway involved which is the JAK/STAT (Janus kinase/signal transducer and activator of transcription) pathway. Ruxolitinib, which antagonizes this pathway, has been shown to reduce the progression CCS in stage 4 nonsmall cell lung cancer. Nutrient signaling with supplements like omega 3 fatty acids and branched chain amino acids have also shown some efficacy. Lastly, but not the least, physical exercise is one of the nonpharmacological mainstays in CCS management. A review by Mavropalias et al summarized the evidence from exercise training trials involving patients with cancer cachexia and noted several studies reporting improved outcomes of maintaining body-weight and lean mass even though a Cochrane Review in 2021 on the same topic showed negative results.[1–3]

Lipolysis

Adipose tissue is divided into white adipose tissue which stores lipids and secretes endocrine factors, classical brown adipose tissue which executes nonshivering thermogenesis, and beige/brite adipose tissue (BeAT) participates in adaptive thermogenesis. The metabolic reprogramming of these adipose tissues occurs mainly via lipolysis which is regulated by adipocyte triglyceride lipase, hormone sensitive lipase (HSL), and monoacylglycerol lipase. Lipolysis usually precedes skeletal muscle atrophy. There is evidence that high levels of HSL are strongly correlated with CCS. Tumor factors that promote lipolysis include zinc-alpha 2 glycoprotein (ZAG) and interleukin (IL)-6. There is a close interplay between skeletal muscle wasting and adipose tissue breakdown during CCS.

Newer Targets

Even though the skeletal muscle and adipose tissue are the main organs involved, recent studies have expanded the macroenvironment to include the central nervous system (CNS), bone, and gut microbiota.[1]

The CNS, through multiple mechanisms including hypothalamic and neuroendocrine alterations, can accelerate

anorexia and peripheral tissue catabolism. These changes can promote the release of inflammatory mediators like IL-6, IL-1β, tumor necrosis factor (TNF) alpha, transforming growth factor (TGF)-β, etc. which proceeds into a vicious cycle. Some medicines like melanocortin type 4 receptor antagonists and ghrelin receptor antagonists have been found to be useful to some extent. Newer targets like glial-derived factor 15 (which acts on the feeding center of the brainstem leading to anorexia) are being tried in preclinical and clinical trials.[1,2]

Bone metastasis in malignancy leads to increased TGF-β signaling and triggers an imbalance in $Ca++$ homeostasis that is essential in sarcomere functioning. Along with TGF-β, the tumor RANK ligand also promotes bone resorption, thereby accentuating the CCS cycle by the aforementioned mechanism. In this regard, antibone resorption agents like bisphosphonates have been indirectly linked to preservation of skeletal muscle function.[1,4]

Microbiome has been long linked to various mechanistic and therapeutic areas of cancer. There is evidence that gut microbiota has been linked to skeletal muscle physiology. This occurs in the form of several of its secreted metabolites like the short-chain and branched-chain fatty acids, bile acids, and amino acids. Preclinical research shows that addition of prebiotics and probiotics reduces muscle and adipose loss and increases survival. However, investigations are still needed to understand the regulation of microbiota by tumor factors and its impact on specific signaling axes in CCS.[1]

Tumor Microenvironment and CCS

The tumor microenvironment in CCS in itself is a separate topic. Macrophages represent one of the most abundant immune cell types in the immune microenvironment and are associated with cancer progression and metastasis. Emerging evidence suggests that macrophages play key roles in both muscle wasting and muscle regeneration, and CCL2/MCP1 is a central cytokine in regulating the infiltration and polarization of macrophages. Recently, a new marker, cancer cell-derived TWEAK (TNF-like weak inducer of apoptosis) secretion, which may contribute to CCL2-driven muscle wasting was studied in pancreatic cancers and may prove to be a promising target.[5]

Conclusion

Targeting the factors involved in CCS is challenging as it requires a multifaceted approach. As elucidated, the complexity is huge and it is increasing with newer research being done in the field. Nevertheless, the importance of CCS should not be buried as it definitely has a significant role in prognostication of malignancies. Hence, more focused research in this area is necessary

Conflict of Interest
None declared.

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