Molecular Mechanism of Cancer Cachexia

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Cancer cachexia is a condition marked by functional, metabolic, and immunological dysfunctions associated with skeletal muscle (SM) atrophy, adipose tissue loss, fat reduction, systemic inflammation, and anorexia. Generally, the condition is caused by a variety of mediators produced by cancer cells and cells in tumor microenvironments. Myostatin and activin signaling, insulin-like growth factor 1 (IGF-1)/phosphoinositide 3-kinase (PI3K)/AKT signaling, and JAK-STAT signaling are known to play roles in cachexia, and thus, these pathways are considered potential therapeutic targets.

Keywords: cancer cachexia ; skeletal muscle ; inhibitors

1. Introduction

The primary characteristics of cancer cachexia (CC), which accounts for ~22% of cancer deaths, are weakness, weight loss, atrophy, fat reduction, and systemic inflammation [1][2]. Cachexia is strongly associated with cancers involving the lungs, pancreas, esophagus, stomach, and liver, which account for half of all cancer deaths. Furthermore, several malignancy-associated conditions, such as chronic obstructive pulmonary disease (COPD), chronic infections (AIDS and tuberculosis), heart failure, and rheumatoid arthritis, cause inflammation, anorexia, hypogonadism, and other symptoms, all of which lead to muscle wasting and fat loss [3][4]. Earlier, researchers investigated the potential use of SM mass loss as a marker of several diseases, including diabetes, obesity, and aging [5][6][7]. Furthermore, it has been well established that multiple mediators generated by cancer cells are responsible for cachexia [8]. Prostaglandin E2 and pro-inflammatory cytokines such as interleukins (IL-1, IL-6), tumor necrosis factor (TNF), interferon, TNF receptor-associated factor 6, and other tumor-derived catabolic factors like activin and myostatin (MSTN) are examples of such mediators [8][9]. CC and starvation cause weight loss in different ways. Weight loss in cancer patients is due to approximately equal losses of adipose tissue and SM mass, whereas anorexia nervosa-associated weight loss is primarily due to fat loss (muscle loss is only a minor contributor) [10]. In addition, the incidence of CC is dependent on tumor type, for example, its prevalence in gastric/pancreatic, breast, and neck cancer are 80, 40, and 40%, respectively, and in lung, prostate, and colon cancer, its prevalence is around 50%. In some cases, leukemia patients also develop the syndrome. However, CC development is unrelated to tumor size [11][12][13][14].

By regulating glucose, protein, and fat metabolisms, insulin, insulin-like growth factor 1 (IGF-1), and growth hormones (GHs) have significant impacts on body composition. The signals generated by these molecules are disrupted in the presence of muscle wasting or cachexia, and results in an anabolic/catabolic imbalance. In cachexia, insulin receptor, GH, and IGF-1 pathways; peroxisome proliferator-activated receptor gamma (PPARγ) agonists; angiotensin II inhibitors; and testosterone are possible therapeutic targets [15][16]. Transforming growth factor-beta (TGF-β), MSTN, activin, IGF-1/PI3K/AKT, and JAK-STAT signaling pathways are known to underlie muscle atrophy and cachexia [17]. Other potential mediators include testosterone and IGF-1 deficiency and excess MSTN and glucocorticoids [18]. To address the situation posed by limited treatment options, a deeper knowledge of the mechanism responsible for cachexia is required. At present, it appears that drug developments aimed at cachexia management should target anti-inflammatory and appetite-stimulating properties.

2. Cancer Cachexia

Cachexia has been described as an imbalance between energy intake and expenditure leading to severe weight loss [3][8][19]. The condition is subdivided into three stages, precachexia, cachexia, and refractory cachexia. The diagnostic criteria of CC are (1) weight loss of >5% in 6 months in the absence of intended starvation, (2) a body-mass index (BMI) of <20 kg/m^2 and progressive weight loss of >2%, and (3) a low SM index (sarcopenia) with continued weight loss of >2% during a measure of muscularity with fluid retention tumor mass and obesity. During precachexia, some signs like anorexia and impaired glucose tolerance resulting in unexpected weight loss are evident. Refractory cachexia is characterized by two features [19]: (1) a low-performance status, meaning that a patient is capable of only minimal self-care, confined to a bed

or chair for >50% of waking hours, or is completely disabled and incapable of self-care [20]; (2) short life expectancy (less than 3 months) [19]. The key features of cachexia are anorexia, catabolic drivers resulting in muscle wasting, muscle mass and strength loss, and functional and psychosocial effects of cachexia [19][21]. Cachexia was mainly described by clinical experience and/or research vantage points, including weight, skeletal muscle, physical function, food intake, metabolism, inflammation, treatment intensity, quality of life, healthcare utilization, and survival [22].

3. The Molecular Mechanism Underlying Cancer Cachexia

3.1. Crosstalk between IGF-1 and MSTN Signaling Pathways in Cancer Cachexia

Anabolic and catabolic pathways are regulated by IGF-1, a positive regulator of muscle growth [23]. Under normal circumstances, IGF-1 signaling dominates MSTN signaling, whereas MSTN overexpression inhibits IGF-1 [24][25][26]. IGF-1 stimulates protein synthesis in SM via the PI3K/Akt/mTOR and PI3K/Akt/GSK3 pathways, and the PI3K/Akt pathway inhibits FoxOs and suppresses the transcriptions of E3 ubiquitin ligases, which elicit protein breakdown via the ubiquitin-proteasome system. IGF-1 is also considered to suppress autophagy via a mammalian target of rapamycin (mTOR) and FoxO signaling [27]. Akt is involved in a variety of intracellular metabolic activities, which include hypertrophic responses to insulin and IGF-1. Furthermore, Akt has been identified as a crossing point between the MSTN and IGF-1 pathways [23][28][29]. In cachexia, IGF-1 signaling is impaired, because cachexic muscle cells do not respond to basic IGF-1 stimulation. Two strategies appear to be therapeutic candidates: (1) the utilization of PPAR-agonists to target post-receptor pathways or (2) the exploitation of alternate routes in muscle cells to access the same intracellular targets [15].

When IGF1 binds to its receptor, its intrinsic tyrosine kinase is activated and autophosphorylated, which results in the formation of insulin receptor substrate binding sites (IRSs). Phosphorylated IRSs aid the recruitment and activation of phosphatidylinositol-3-kinase (PI3K), which phosphorylates membrane phospholipids and converts phosphoinositide-4, 5-biphosphate (PIP3, which aids the activation of Akt) to PIP2. Thus, Akt stimulates protein synthesis via mTOR, which promotes protein synthesis and muscle hypertrophy [28].

In cases of chronic heart failure, circulating and local levels of MSTN, which play key roles in myocardial cachexia, are elevated [29]. Activin type-2 receptor (ActRIIB) antagonism and/or MSTN antibodies have emerged as viable therapeutic targets for the treatment of cachexia, although the broad clinical applications of these potential treatment strategies have not been demonstrated [30]. Furthermore, in mouse models, inhibiting ActRIIB reverses cachexia and improves survival [31]. MSTN has been introduced as a major interest in cachexia, sarcopenia, and muscle wasting conditions [32]. MSTN is released primarily by SM and, as mentioned above, negatively regulates muscle mass [33], as demonstrated by the development of cachexia in rodents' systemically administered MSTN [27][34]. MSTN signaling is facilitated by ActRIIB and leads to the phosphorylations of SMAD2 and 3 [35][36]. Congestive heart failure is frequently accompanied by cardiac cachexia, and in rodent models and clinical trials, blocking MSTN appears to improve muscle size and strength significantly [37]. Thus, stimulating IGF-1 and blockading MSTN using natural compounds would promote muscle hypertrophy and provide a possible means of managing cachexia. As a result of these findings, MSTN has emerged as an important developmental target for the treatment of cachexia and muscle wasting disorders. Randomized controlled studies on MSTN antagonists are required [38][39]. By reducing AKT phosphorylation and so boosting the levels of active FoxO1, MSTN signaling reversed the IGF-1/PI3K/AKT hypertrophy pathway, allowing for increased expression of atrophy-related genes. The known atrophy-related genes are Atrogin1 and Glb1 [33]. MSTN expression is increased in the muscle of tumor-induced cachexia [31]. MSTN's role in the development of CC has been little studied in humans, and it is now being studied clinically. A better knowledge of the etiology and heterogeneity of CC might lead to the development of intervention measures to prevent or treat this life-threatening illness.

3.2. The PI3K/Akt/mTOR Pathway and Cancer Cachexia

SM and cardiac muscle atrophy are considered hallmarks of CC [40], and a variety of agents have been reported to reduce muscle atrophy. In 2001, Bodine et al. reported that a phosphoinositide 3-kinase (PI3K)–protein kinase B (PKB, AKT)–mTOR cascade importantly regulated SM hypertrophy in vivo via the modulations of p70S6K and PHAS-1/4E-BP1 [41]. In CC patients that exhibited weight loss before surgery, PI3K/AKT signaling was diminished and protein synthesis in SM was reduced [42]. The signaling involved was elucidated based on improved understanding of the activities of mTOR [27][43][44], which is a downstream kinase in the IGF-1/PI3K/AKT pathway that acts as a hub for muscle regulation by coordinating the ubiquitin proteasome system and autophagy [45]. mTOR forms mTORC1 and mTORC2 complexes containing RAPTOR and RICTOR, respectively [43][44]. mTORC1 is responsible for protein biosynthesis by 4E-BPs and $p70^{S6K}$ in growing cells and suppresses catabolic autophagy by regulating unc-51-like autophagy-activating kinase 1

(ULK1) and ATG13. Under conditions of nutrient deprivation, mTORC1 is inactivated, which leads to coordinated autophagosome initiation and subsequent lysosomal biogenesis [46].

IGF-1 stimulates the productions of SM proteins via PI3K/Akt/mTOR and PI3K/Akt/GSK3 pathways [27]. A ketogenic diet targets glucose metabolism in cancer cells, inhibits the IGF-1 and PI3K/AKT/mTOR pathways, and suppresses CC, muscular wasting, and tiredness [47]. Growth factors and nutrients activate AKT via PI3K-dependent mechanisms, which, in turn, activate mTOR and enhance muscle cell proliferation and protein synthesis under physiologic conditions. AKT (a serine/threonine kinase) plays a crucial role in myogenic differentiation, and in CC, the phosphorylations of mTOR and its substrates, S6 ribosomal protein, and 4EBP were reduced, irrespective of AKT activation [48][49][50][51]. Furthermore, these alterations in mTOR-related protein signaling pathways were followed by small increases in the protein levels of Beclin1, which is associated with autophagy. In addition, the mTOR signaling system has been shown to regulate myofiber production and development during muscle regeneration through kinase independent and dependent pathways, respectively [52][53].

3.3. Roles of Peroxisome Proliferator-Activated Receptors in Cancer Cachexia

Peroxisome proliferator-activated receptors (PPARs) are well-known transcription factors that belong to the nuclear receptor superfamily and have three isoforms, namely, α, δ, and γ [54][55]. PPARs regulate the transcriptions of a wide range of genes involved in inflammation, metabolism, proliferation, and the differentiation of various cells [56][57], and they are associated with a number of pathologies, including cancer, type 2 diabetes, atherosclerosis, and Alzheimer's disease. Moreover, PPARs are frequently co-expressed to varying degrees in many tissues, including SM and adipose tissue [58][59][60].

PPARα is expressed in the liver, SM, heart, adipose tissue, kidney, and other tissues, and it plays crucial roles in fatty acid catabolism, glucose metabolism, and the regulation of energy consumption and inflammation. PPARα agonists, notably fibrates (e.g., clofibrate, fenofibrate, ciprofibrate, bezafibrate), are used to improve lipid metabolism and insulin sensitivity in metabolic syndrome [61]. Fenofibrate, a selective PPARα activator used to treat dyslipidemia in humans, has been shown to reduce inflammation in rheumatoid arthritis patients [62]. It prevents the development of CC in mice [63]. Fenofibrate treatment restored muscle mass and body weight loss in a non-small cell lung cancer mouse model exhibiting muscle wasting and mimicking human CC [63]. PPARβ/δ is expressed at varying levels in several tissues, most notably in SM, but is also expressed in the heart, skin, and gut, and it has a wider range of functions than PPARα [58]. PPARβ plays a critical regulatory role in intermediate metabolic processes and is also involved in differentiation, apoptosis, inflammation, and other cancer-related processes [64]. PPARβ agonists (e.g., GW501516) activate PPARβ and provide functional improvements in Duchenne muscular dystrophy (DMD) patients by increasing utrophin A (an autosomal homolog of dystrophin) expression [65]. DMD is a serious, progressive muscle-wasting ailment that causes movement problems and premature death. Mutations in DMD (encoding dystrophin) cause the ailment by preventing dystrophin synthesis in the muscle. Muscles lacking dystrophin are more vulnerable to injury, resulting in a gradual loss of muscle structure and function [66][67].

PPARγ is expressed in the SM, placenta, lung, spleen, heart, liver, ovary, and other tissues but is most abundant in adipose tissue. PPARγ regulates whole-body glucose homeostasis and insulin sensitivity, and currently, studies have focused on its involvements in inflammation, lipid metabolism, and tumor development, particularly in the context of CC. [68][69]. PPARγ activation has an anti-inflammatory effect caused by attenuation of the NF-κB signaling pathway, and thus, it inhibits the productions of IL-6 and other pro-inflammatory factors by regulating the STAT3 pathway [70]. It was recently reported that alpinetin (a plant-derived flavonoid) retards CC progression and protects against muscle atrophy by activating PPARγ, thus suppressing the phosphorylations of NF-κB and STAT3 [71], and alantolactone was found to inhibit the STAT3 pathway to improve the muscular atrophy in a CC [72]. STAT3 is a transcription factor that promotes cancer growth and muscular cachexia. The deletion of the gene producing the STAT3 protein lowers the expression of muscle differentiation factors like MyoD and myogenin in vitro. In vivo investigations show that STAT3 deletion impairs post-traumatic muscle regeneration, which is consistent with previous findings [73]. STAT3 is the most important component of the IL-6 and JAK2 signaling pathways, controlling SM mass, growth, repair, and regeneration [74]. The STAT3 pathway has been demonstrated to cause muscle atrophy in DMD, Merosin-negative congenital muscular dystrophy (MDC1A), sepsis, and cancers [75]. The key molecular mechanism leading to CC is thought to be permanent stimulation of the acute phase protein response. In experimental cachexia models, the IL-6/STAT3 6 signaling pathway causes muscle mass loss [76]. A variety of STAT3-interacting peptides, such as PY*LKTK [77] and Y*LPQTV [78], are now being explored in preclinical trials. These peptides bind to the SH2 domain and hence inhibit STAT3 dimerization. Another STAT3 inhibitor, galiellalactone [79], binds to the DNA-binding domain responsible for STAT3 binding to DNA, preventing transcriptional activation of STAT3-

targeted genes [80]. STAT3 activity is required for muscle tissue formation and maintains homeostasis, whereas STAT3 inhibitors appear to be potential components in illnesses involving muscle atrophy.

PPARγ activation induces preadipocyte to adipocyte differentiation and promotes triglyceride accumulation. Furthermore, PPARγ is an important transcription factor, and its inactivation explains the downregulations of multiple adipogenic genes. The expression and role of MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) in adipocytes was recently studied by a microarray analysis, and MALAT1 knockdown was found to reduce adipogenesis by regulating PPARγ gene expression at the transcriptional level [81]. MALAT1 is a widely expressed lncRNA, and it participates in a variety of physiological and pathological processes, such as myogenesis, cancer, and aortic aneurysm [82]. Like some well-known proteins, such as hormone-sensitive lipases, adipose triglyceride lipases, and uncoupling protein-1, and lncRNAs (e.g., CAAlnc1), they are promising unique regulators of adipose tissue loss in CC [83]. In one study, PPARγ expression was markedly enhanced in the SM of tumor-bearing mice, which demonstrated the significance of the effect of PPARγ on muscle wasting. In addition, the administration of GW1929 (a PPARγ agonist) resulted in the restoration of muscle loss [84].

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