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KLF10: A point of convergence in cancer cachexia

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Abstract

Purpose of the review: Cancer associated cachexia is a wasting syndrome entailing loss in body mass and a shortened life expectancy. There is currently no effective treatment to abrogate this syndrome which leads to 20–30% of deaths in patients with cancer. While there have been advancements in defining signaling factors/pathways in cancer induced muscle wasting, targeting the same in the clinic has not been as successful. Krüppel-like Factor 10 (KLF10), a transcription factor implicated in muscle regulation is regulated by the TGF-β signaling pathway. This review proposes KLF10 as a potential convergence point of diverse signaling pathways involved in muscle wasting.

Recent Findings: KLF10 was discovered as a target of TGF-β decades ago but more recently it has been shown that deletion of KLF10 rescues cancer-induced muscle wasting. Moreover, KLF10 has also been shown to bind key atrophy genes associated with muscle atrophy *in vitro*.

Summary: There is an elevated need to explore targets in cachexia, which will successfully translate into the clinic. Investigating a convergence point downstream of multiple signaling pathways might hold promise in developing effective therapies for cachexia.

Keywords/phrases:

Krüppel-like factor 10; Pancreatic Ductal Adenocarcinoma; Cancer associated Cachexia

2. Introduction

Cancer associated cachexia is a multifactorial wasting syndrome that leads to loss of body weight, including skeletal muscle and adipose tissue, and is irreversible by dietary intervention alone(1). There are three defined stages of cachexia: I) Precachexia II) Cachexia, and II) Refractory cachexia, with most patients being diagnosed at the cachexia stage(2). Pancreatic and gastro-esophageal cancers have the highest prevalence with 60–70% of patients diagnosed with cachexia. Lung, hematological, and colorectal cancers are more heterogeneous, with approximately 40–50% of patients developing cachexia while breast cancer and prostate cancer patients experience the lowest cachexia incidence at roughly 20%(3). Adding another layer to the complex biology of cancer cachexia are reports documenting sex differences in cancer cachexia(4). In one study of cancer patients over

Conflicts of Interest

There are no conflicts of interest.

the age of 60, up to 60% of males are diagnosed with cachexia while up to 50% of female patients are cachectic(3) . Further, males also tend to exhibit more severe skeletal loss of muscle compared to females(5) Cancer cachexia contributes up to 20% of all cancer deaths(6). The reasons underlying this contribution are varied and include the fact that cachexia can lead to refractory responses to conventional therapies (e.g. chemotherapy, immunotherapy, radiation) and thus shorter overall survival (7). Cachexia incidence rates vary across the spectrum of human cancers. Diagnosing cachexia is difficult as there are currently no specific biomarkers or diagnostic tests in widespread use. Further, the weight loss criteria defined above can be difficult for providers to use for diagnosis as many patients do not keep accurate track of their weight.

Numerous overlapping and context-dependent signaling pathways contribute to cachexia etiology. Despite the heterogeneity of upstream cachexia drivers/pathways, there is consensus that cachexia-associated signals converge on cellular processes involved in protein and energy homeostasis(8). In this review, we illustrate the possibility of KLF10 being such a convergence point for cachexia signaling pathways.

3. Signaling Pathways in Cancer Cachexia

Cancer cachexia associated signaling is complex and is expertly reviewed elsewhere(6, 9–11). Here we highlight key aspects of Transforming Growth Factor beta (TGF-β) signaling and selected cytokine involvement in cancer cachexia to contextualize discussion of KLF10.

TGF-β signaling pathway

Multiple TGF-β superfamily members – including TGF-β, Myostatin, and Activin – are associated with elevated protein degradation as well as altered mitochondria function and are thus linked to muscle wasting and cancer cachexia(12). Additionally, Myostatin and Activin are known negative regulators of muscle development and growth(13),(14). Studies show that patients with increased circulation of Activin A have shorter overall survival rates and increased weight loss compared to those with lower levels of Activin A(15).

All three TGF-β superfamily cytokines mentioned above bind to either activin receptor type 2 (ACVR2) or Transformation growth factor beta receptor 2 (TGFBR2) making these receptors intriguing targets for anti-wasting interventions. Canonically, these activated receptors initiate a SMAD signaling cascade that involves SMAD2/3 binding to SMAD4 before translocating into the nucleus and leading to protein degradation(16). Concurrently, there is an upregulation in SMAD7 transcription, a negative regulator of SMAD2/3 phosphorylation which thereby inhibits TGF-β signaling pathway and muscle wasting(17).

Phosphorylation of SMAD2/3 via this pathway always leads to inhibition of AKT/mTOR pathway. In a healthy, homeostatic environment, IGF-1 activates AKT/mTOR pathway via PI3K leading to protein synthesis allowing for the growth of muscle. The phosphorylation of SMAD2/3 via Myostatin or Activin lead to inhibition of AKT, stopping protein synthesis from occurring. AKT itself inhibits Forkhead Box 03 (Foxo3), a protein previously shown to be a key regulator in muscle atrophy induction(18).

Non-canonical TGF-β dependent SMAD-independent signaling involving activation of p38, JNK, MEK/ERK, or mTOR signaling likely further contributes to cancer cachexia, though precise mechanisms of action remain elusive(19).

Additional cytokines implicated in cancer cachexia

Pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), tumor necrosis factor-like weak inducer of apoptosis (TWEAK), Interleukin-1 (IL-1), leukemia inhibitory factor (LIF), and interleukin-6 (IL-6), also referred to as pro-cachectic cytokines, are secreted by tumors as well as by host immune cells and tissues, and have both direct and indirect effects on skeletal muscle wasting(9, 20).

The activation of the previously described pathways leads to protein degradation via the Ubiquitin-Proteosome System (UPS), autophagy-lysosome pathway, and apoptosis(21–23). MuRF1 and Atrogin-1 are two muscle-specific E3 ubiquitin ligases which are heavily implicated in protein degradation(24, 25).

4. Targeting TGF-β Pathway

According to Clinicaltrials.gov, there are/have been over 80 clinical trials focused on ameliorating cachexia, with most falling short of desired outcomes. These clinical trials range from nutritional supplementation to exercise-based programs, to various drug-based/small molecule therapies. While some of the interventions discussed in this section led to some improvement in cachectic patients such as increase in grip strength, decreased fatigue, and increased overall survival(26). None of the trials significantly increased quality of life, muscle mass and/or functionality, or led to an increase in overall survival.

Clinical trials for cancer cachexia utilize a variety of methods including neutralizing antibodies and propeptides targeting previously discussed pro-inflammatory cytokines and TGF-β superfamily cytokines including Myostatin and Activin (A and B). Myostatin binds to the ActRII receptors activating the canonical SMAD2/3 signaling pathway leading to induction of the E3 ligases MuRF1 and Atrogin-1(27). Myostatin has been shown, *in vivo*, to be a negative regulator of myoblast proliferation and differentiation(28). *Mstn* null mice showed a decreased ability to accumulate fat as well as muscle hypertrophy while overexpression of *Mstn* lead to muscle loss (29, 30).In humans, cachectic patients have been shown to have increased circulating myostatin compared to healthy individuals. Myostatin inhibitors showed great success in murine models leading to an increase in muscle mass alongside grip strength(31). Unfortunately, when myostatin inhibitors were brought to clinical trials, they were found to commonly improve muscle mass without actually improving the functionality of the muscle(32). One purposed reason for myostatin's lack of success is that myostatin alone is not sufficient to inhibit muscle atrophy as it is only a part of a complex process.

Activin (A and B) also binds ActRII receptors and is another TGF-β cytokine which is a negative regulator of muscle growth(14). Overexpression of Activin A, *in vivo*, has been shown to induce muscle atrophy while inhibition after muscle injury allowed for increased myogenesis and complete restoration of muscle contraction properties(14).The

phase I clinical trial ended in 2017 and showed there was potential for meaningful clinical results but there have been no study results posted(33).

ActRII receptors have also been the target of a clinical trial as they were shown to be successful in preclinical trials by retaining muscle force and mass(34). One clinical trial was completed using a ActRII antibody but was shown to have 62% of patients receiving the drug having severe adverse effects (SAEs) (https://clinicaltrials.gov/study/NCT01433263).

Clinical trials have not resulted in effective therapy due to a multitude of reasons. Some clinical trials are enrolling patients with varied stages/types of cancer which makes the conclusions difficult to interpret. While there are canonical pathways leading to cachexia, different tumor types and stages lead to variability in progression of cachexia.

Although heterogeneity exists, we propose KLF10, a transcription factor, as a possible convergence point of signaling pathways. This piece discusses how KLF10 might be ideally positioned within atrophy signaling networks with respect to balancing efficacy and specificity outcomes.

5. KLF10 as an anti-cachexia skeletal muscle target

Krüppel-like factors (KLF) are zinc-finger proteins with the ability to bind to DNA elements and act either as transcriptional activators or repressors(35). The word “Krüppel” was derived from a German word meaning “cripple”(36), and *Kruppel* was first identified in Drosophila as a developmental gene that regulated body segmentation in the thorax and the anterior abdomen(37, 38). Interestingly, KLF family members also share homology with Sp1, one of the first mammalian transcription factors to be identified(39). Historically, transcription factors which had zinc-finger motifs homologous to SP1 were annotated to be in the class of Sp1-like/KLF family. To date, 18 KLF family members have been identified and named chronologically based on their discovery(36). KLF family members are responsible for regulating various molecular functions such as proliferation, differentiation, tissue development and survival.

KLFs and skeletal muscle

Since the discovery of KLF factors about two decades ago, several KLFs have been implicated in regulation of various aspects of muscle biology. In one example, KLF3 can bind to muscle creatine kinase promoter thereby influencing muscle differentiation(40). Second, KLF5 regulates skeletal muscle differentiation in concert with the myogenic transcription factors MyoD and Mef2(41). Third, KLF6 is linked to TGF-β-dependent myoblast proliferation(42). Interestingly, KLF6 is not the only KLF family member to respond to TGF-β stimulation. KLF10, formerly called TGF-β-inducible early gene-1 (TIEG1), was first discovered in osteoclasts(43) but is emerging as a critical regulator of muscle biology as well.

The multifaceted role of KLF10 in metabolism and muscle function

In the early 1990s, when TIEG1/KLF10 was discovered in osteoblasts, preliminary studies demonstrated high expression of KLF10 in skeletal muscles, but low to no expression in

the brain, liver, lung, and kidney(43). Since then, KLF10 has been found to be expressed in various tissues and cell types such as pancreas, fibroblasts, smooth and skeletal muscle tissues(44). KLF10 has been reported to be a crucial circadian transcriptional regulator which regulates clock regulation and liver metabolism. In short, KLF10 displayed a clock-like expression pattern in normal wildtype liver but not in *Bmal1* (a clock regulator) knock out mice liver(45). Interestingly, KLF10 regulates hepatic glucose and lipid metabolism in a sex-dependent fashion(46). Conversely, glucose alterations can dictate the expression of KLF10 in hepatocytes.

KLF10 also plays a role in adipogenesis by inhibiting the transcription of CCAAT/enhancer-binding protein (C/EBPα), an anti-proliferation gene, ensuring mitotic clonal division of preadipocytes and avoiding premature differentiation(47).Studies have demonstrated important roles of KLF10 in immune pathways as well. $CD4^+$ T cell (T regulatory cells or Tregs) specific deletion of KLF10 demonstrated a predisposition of these mice to obesity, insulin resistance and fatty liver metabolism due to inability of Tregs to infiltrate liver and adipose tissue reserves(48).

In the last decade, KLF10 has been implicated in muscular dystrophy and has been reported to repress myoblast proliferation(49, 50). Moreover, KLF10 also influences myofiber contractility and is dependent on the type of the muscle(51). Female KLF10 null mice demonstrate several phenotypic changes such as muscle hypertrophy, altered myofiber area distribution, myofiber type switching, and fragile bones(52).A recent study compared mechanical properties of muscles from KLF10 null mice to wildtype littermates at three levels: whole muscle, myofiber and myofibril(53). There were no discernable differences in mechanical properties at the whole muscle of myofibril levels. However, the authors reported differences in passive mechanical properties in the EDL and soleus as compared to the control mice muscles. The authors concluded that the results imply that the alterations are likely arising from the extracellular matrix and not in the sarcomeres themselves(53).

TGF-β/KLF10 axis in cancer cachexia

Pro-atrophy TGF-β isoforms are increased in the serum of tumor-bearing mice and PDAC patients. These factors are known to derive from bone and immune cells(54), though emerging evidence suggests that they can be secreted by tumors as well. In accordance with this elevation in TGF-β family members, KLF10 was recently found to be increased in skeletal muscles of PDAC patients and in multiple preclinical models of cachexia(55). While KLF10 is an established target of TGF-β, it had previously not been implicated in cachexia etiology. Investigators further found that KLF10 mediated TGF-β–induced expression of atrophy-associated genes(55) and binding studies suggested that KLF10 can directly bind some of these factors including *FoxO1* and *Trim63*. Lastly, KLF10 null mice had preserved muscle mass and myofiber cross section upon tumor implantation, without the perturbation of any cytokine/upstream factors. This implies targeting KLF10 is sufficient in blocking tumor-associated muscle wasting.

6. Conclusion and Future Opportunities

Despite scientific advancements and significant progress understanding the syndrome, cancer cachexia has no FDA-approved therapies in clinic. Past clinical trials have not shown promising results and therefore there is a need to investigate effective targets. One way of doing that is to screen for novel pathways/proteins. Novel proteins/pathways, most of the time, lead to an increase in common downstream targets (FoxO1, MuRF1, Atrogin-1). This implies there might be a common convergence point of multiple stimuli which leads to activation of protein degradation genes. This also might explain why targeting upstream players such as cytokines in the clinic have not been as successful as predicted.

We propose KLF10 being a potential node of convergence, which when targeted, will block the diverse upstream stimuli. In such a circumstance, targeting KLF10 will hypothetically be more successful than antibody neutralization agents against one ligand. Preclinical data has determined that global deletion of KLF10 is not fatal or detrimental in adult mice. Therefore, there are therapeutic opportunities for development of small molecule inhibitors or PROTACS (proteolysis targeting chimera) against KLF10. Moreover, since tumor implantation in KLF10 null mice has shown muscle preservation, anti-KLF10 therapies can also be a pre-emptive measure to delay/block cachexia upon cancer diagnosis.

Even though KLF10 seems like a promising target for cancer cachexia, it has its limitations. KLF10 has been, in some contexts, shown to function as a tumor suppressor. In some instances, KLF10 can act as a tumor suppressor via TGF-β signaling and activates apoptosis and inhibits cell proliferation(56, 57).In hepatocellular carcinoma (HCC), where loss of TGF-β sensitivity is one of the hallmarks, activation of KLF10 inhibits growth and induces apoptosis(58). Furthermore, in pancreatic cancer tissue specimens, KLF10 expression was negatively correlated with cancer stage(59).In lung cancer cells, KLF10 can suppress TGF-β induced epithelial to mesenchymal transition by repressing the SNAI2 promoter(60). These examples and more provide a possible barrier to developing anti-KLF10 therapeutics for clinical use, since it has a possibility of exacerbating tumor growth. However, with the advent of tissue-specific nanodrug delivery, there is opportunity for exploration of KLF10 as a possible muscle target.

Furthermore, KLF10 is not only upregulated in cachectic muscles, but also in other atrophy datasets such as chronic infection and dexamethasone-induced muscle atrophy(61, 62).Therefore, this target holds a promise for targeted therapy, not just for cancer-induced muscle atrophy but for muscle atrophy in general.

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Summary

- Cancer associated cachexia effects up to 80% of cancer patients (dependent on cancer type) and leads to 20–30% of cancer related deaths
- Despite great efforts and due to the complexity of the syndrome, there are currently no FDA approved treatments for the syndrome showing a need for novel targets
- Krüppel-like Factor 10 (KLF10) has been implicated in manifestation of cancer cachexia, and is regulated by TGF-β signaling, a key pathway involved in cancer associated cachexia.
- KLF10 has the potential of being a convergence point of multiple signaling pathways.