Review Article

Deciphering molecular crosstalk mechanisms between skeletal muscle atrophy and KRAS-mutant pancreatic cancer: a literature review

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Background and Objective: Cachexia-induced skeletal muscle atrophy is a critical manifestation in Kirsten rat sarcoma viral oncogene homologue (KRAS)-mutant pancreatic cancer (PC) patients, predominantly characterized by a shift in metabolic equilibrium towards catabolism that accelerates protein degradation in myofibers and leads to muscle atrophy. This metabolic reprogramming not only supports tumor growth but also precipitates energy depletion in skeletal muscle tissues. Exploring these mechanisms reveals potential therapeutic targets in the metabolic and proteolytic pathways associated with KRAS-mutant PC.

Methods: A comprehensive search for literature was conducted in PubMed, Web of Science, Google Scholar and other search engines up to May 21st, 2024. Studies on PC models and patients were included.

Key Content and Findings: The crosstalk between KRAS-mutant PC and skeletal muscle atrophy can be categorized into four principal domains: (I) KRAS-driven metabolic reprogramming in cancer cells leads to the depletion of muscle energy reserves, thereby influencing the reallocation of myofiber energy towards fueling cancer cell; (II) KRAS-mutant cancer cells rely on nutrient-scavenging pathways, resulting in altered cytokine profiles, increased ubiquitin mRNA expression and autophagy-lysosome pathway, which facilitate myotube degradation and inhibit muscle regeneration, thereby disrupting muscular homeostasis and causing a one-way nutrient flux; (III) tumor-induced oxidative stress inflicts damage on myotubes, highlighting the detrimental effects of reactive oxygen species on muscle structure; (IV) KRAS-mutant cancer cells remodulate immune cell dynamics within the tumor environment, thereby reshaping host immunity. Together, these findings illuminate the intricate interplay between KRAS-mutant PC and skeletal muscle atrophy, mapping the pathophysiological framework that is crucial for understanding sarcopenia and related disorders.

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Conclusions: This comprehensive analysis advances our understanding of the complex etiology of cancer cachexia and stimulates the development of targeted therapeutic strategies.

Keywords: Skeletal muscle atrophy; pancreatic cancer (PC); cachexia; molecular crosstalk; Kirsten rat sarcoma viral oncogene homologue-mutant (KRAS-mutant)

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Introduction

Cachexia, a significant complication in cancer progression, was first characterized by Evans *et al.* (1) as a syndrome of "consuming without gaining weight", primarily manifested by a reduction in skeletal muscle mass. This syndrome is defined by involuntary weight loss due to muscle atrophy, which is non-responsive to nutritional supplementation and resistant to pharmacological treatments. Over the past decade, the impact of cachexia on the efficacy of multidrug chemotherapy regimens has become increasingly evident (2,3). Concurrently, the conceptualization and diagnostic criteria for cachexia have evolved. Initially, the 2011 Fearon criteria focused on weight loss and body mass index (BMI), where the main criterion for cachexia is weight loss >5% over past 6 months (in absence of simple starvation) (4). Subsequent revisions have incorporated physical performance and other measurable indicators (5). The latest definition by the European Society of Medical Oncology (ESMO) in 2021 categorizes cachexia as malnutrition caused by disease-related systemic inflammation (6). This is further refined in the 2020 Global Leadership Initiative on Malnutrition (GLIM) criteria, which require a positive screening result and at least one phenotypic criterion, such as weight loss, low body mass, or diminished muscle mass, for a malnutrition diagnosis (7).

In the realm of pancreatic cancer (PC), cachexia is ubiquitously observed throughout all disease stages (8). Notably, about 80% of individuals diagnosed with pancreatic ductal adenocarcinoma (PDAC) endure cachexia at some phase of their disease, representing the highest incidence among all cancers (9) (*Figure 1*). This underscores the critical need to integrate cachexia management within the therapeutic strategies for PC. Although criteria for weight loss and low body mass have been clearly defined, consensus on defining "reduced muscle mass" continues to be ambiguous. Existing diagnostic metrics, such as the sex-specific L3 vertebrae skeletal muscle index, mid-upper arm muscle area, and appendicular skeletal muscle index, predominantly assess sarcopenia (4,10-14).

Nonetheless, advancing our understanding of the molecular mechanisms underlying muscle wasting in PC may facilitate the development of more targeted biomarkers, thereby improving both diagnosis and treatment of PC-associated cachexia. We present this article in accordance with the Narrative Review reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-24-282/rc).

Methods

We searched for literature with terms "Cachexia/Sarcopenia", "Skeletal Muscle Wasting/Atrophy", "Pancreatic Cancer", and "KRAS Mutation" published in PubMed, Web of Science, Google Scholar and other search engines, encompassing articles in the English language up to May 21st, 2024. Studies on PC models and patients were included. For detailed information, please refer to the search strategy summary in *Table 1*.

Molecular crosstalk mechanisms between skeletal muscle atrophy and Kirsten rat sarcoma viral oncogene homologue (KRAS)-mutant PC

KRAS-mutant PC mediates depletion of muscle energy reserves and energy reallocation

Cachexia, a defining feature of PC, is characterized by a metabolic shift favoring catabolism over anabolism, which fosters a state of chronic inflammation. This metabolic alteration impairs muscle protein synthesis, enhances proteolysis, and accelerates myofiber degradation. Notably, oncogenic modifications in PC, particularly KRAS mutations, drive a systemic metabolic reprogramming that supports both tumor proliferation and cachectic muscle wasting (*Figure 1*).

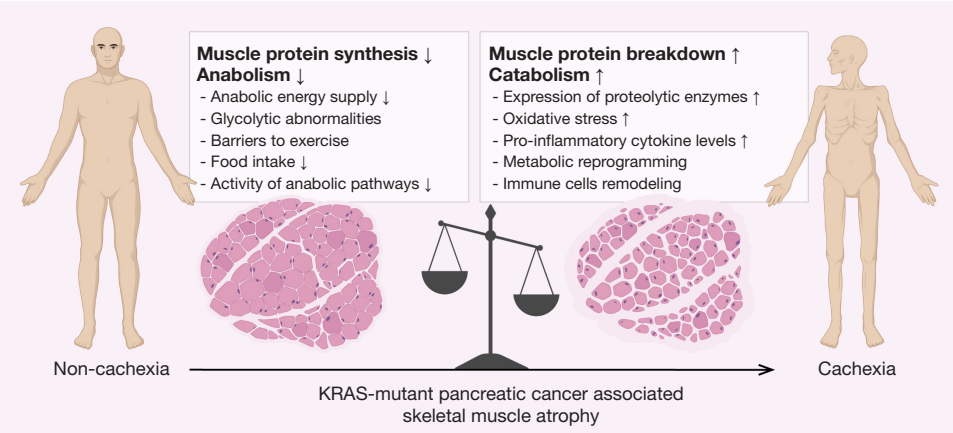

Figure 1 Skeletal muscle atrophy in KRAS-mutant pancreatic cancer due to disruption of anabolic and catabolic balance. KRAS-mutant pancreatic cancer is predominantly characterized by a metabolic shift towards catabolism, with multiple factors collectively accelerating protein degradation in myofibers, ultimately leading to muscle atrophy. KRAS, Kirsten rat sarcoma viral oncogene homologue.

Table 1 The search strategy summary

Items	Specification
Date of search	The literature search was conducted on May 21, 2024
Databases and other sources searched	PubMed, Web of Science, Google Scholar. Additional searches were conducted using relevant search engines to ensure comprehensive coverage
Search terms used	A combination of MeSH terms and free-text keywords was employed, including: “Cachexia/Sarcopenia”, “Skeletal Muscle Wasting/Atrophy”, “Pancreatic Cancer”, and “KRAS Mutation”
Timeframe	The search covered studies published up to May 2024
Inclusion and exclusion criteria	Inclusion: studies involving pancreatic cancer models or patients, with a focus on KRAS mutations
	Exclusion: case reports or studies lacking relevance to the molecular mechanisms linking pancreatic cancer and muscle wasting
Selection process	Two independent reviewers screened the studies, with disagreements resolved by consensus. Only studies meeting the predefined inclusion criteria were selected

KRAS, Kirsten rat sarcoma viral oncogene homologue.

KRAS mutation, in conjunction with metabolic disturbances such as insulin resistance, plays a critical role in PC pathophysiology. Insulin resistance increases the risk of developing PDAC and has been shown to be mitigated by anti-diabetic treatments (15,16). Furthermore, the interaction between KRAS mutation and a hyperglycemic environment creates a self-sustaining cycle conducive to both tumor growth and muscle wasting. This mutation enhances glycolytic flux by upregulating key enzymes, and elevated glucose levels lead to pancreas-specific DNA damage, further accelerating the mutation process (17,18). In cells with KRAS mutations, increased glucose uptake via glucose transporters (GLUTs) and heightened glycolysis provides intermediates essential for biosynthetic pathways (19).

Moreover, the pentose phosphate pathway (PPP) serves a dual role in PC cells by generating nicotinamide adenine dinucleotide phosphate (NADPH) and ribose bases, vital for nucleotide synthesis and maintaining redox balance. PC cells also exhibit the Warburg effect, a metabolic phenomenon where glucose is predominantly converted to pyruvate and lactate in the cytosol under anaerobic conditions. This increased glycolytic activity leads to enhanced glucose uptake and lactate secretion, contributing to the systemic energy depletion characteristic of cancer

Table 2 Overview of potential biomarkers for assessing skeletal muscle atrophy in patients with KRAS-mutant pancreatic cancer

Origin	Potential biomarkers
PC cachexia induction factors	MURF-1, Atrogin-1, myostatin, GDF15, GLUT4, Activin A, PAUF, IRS-1, Ang II, PTHrP, SIRT1/NOX4
Systematic inflammation and immunity factors	PLR, CRP, MyD88
	Activators of NF-κB signaling: TNF-α, IL-1β, IL-6, MCP-1/CCL2, TWEAK, PTX3, OSMR/EDA2R/NIK
	Immune cells and related markers: M2-like macrophages, $Ly6G^+$ neutrophils and granulocytic MDSCs, NLR, LCN2, Cathepsin B
Muscle and lipid wasting products	Fat wasting: ATGL, HSL, UCP1, LCN2, ZAG, C18:C24 ceramide ratio
	Skeletal muscle wasting: CNDP1, β-dystroglycan
Non-coding RNAs	miR-21, miR-155, miR-let-7b-5p, miR-373, miR-30b/c, miR-494-3p, miR-9, miR-338-3p, miR-106b, miR-93, miR-27b
Extra-cellular matrix factors	TIMP-1

KRAS, Kirsten rat sarcoma viral oncogene homologue; PC, pancreatic cancer; MURF-1, muscle RING-finger protein-1; GDF15, growth differentiation factor 15; GLUT4, glucose transporter 4; PAUF, pancreatic adenocarcinoma upregulated factor; IRS-1, insulin receptor substrate 1; Ang II, angiotensin II; PTHrP, parathyroid hormone-related protein; SIRT1, Sirtuin1; PLR, platelet-lymphocyte ratio; CRP, C-reactive protein; MyD88, myeloid differentiation primary response gene 88 protein; NF-κB, nuclear factor kappa B; TNF-α, tumor necrosis factor alpha; IL-1β, interleukin 1 beta; IL-6, interleukin 6; MCP-1, monocyte chemoattractant protein 1; CCL2, CC-motif chemokine ligand 2; TWEAK, TNF-α-like weak inducer of apoptosis; PTX3, pentraxin 3; OSMR, oncostatin M receptor; EDA2R, ectodysplasin A2 receptor; NIK, NF-κB-inducing kinase; MDSCs, myeloid-derived suppressor cells; NLR, neutrocyte-lymphocyte ratio; LCN2, lipocalin 2; ATGL, adipose triglyceride lipase; HSL, hormone-sensitive lipase; UCP1, uncoupling protein-1; ZAG, zinc-α2-glycoprotein; CNDP1, carnosine dipeptidase 1; TIMP-1, tissue inhibitor of metalloproteinases-1.

cachexia (20,21).

In addition, PC cells exploit alternative carbon sources to fuel the tricarboxylic acid (TCA) cycle, such as glutamine and aspartate, both of which are integral to maintaining skeletal muscle mass (22). Glutamine importation through solute carrier family 1 member 5 (SLC1A5) and its transformation to glutamate by glutaminase 1 (GLS1) fuel the TCA cycle (23), emphasizing glutamine's role in energy production. Inhibiting glutamine transport by downregulating its transporter SLC1A5 has been shown to attenuate weight loss in PC, albeit without impeding tumor growth (24). Conversely, obstructing aspartate transportation into mitochondria through UCP2 transporter diminishes PDAC cell growth (25). This underscores the versatility of PC in utilizing diverse nutritional sources, often at the expense of body and muscle mass. KRAS mutations further reprogram metabolism by channeling TCA cycle intermediates via malic enzyme 1 (ME1) to produce NADPH and amino acids, enhancing cellular antioxidant capacity and providing synthesis substrates. Simultaneously, KRAS mutations drive fatty acid oxidation (FAO) for energy and NADPH production (26,27), underscoring the metabolic flexibility of cancer cells to meet their energy needs. Collectively, metabolic reprogramming by PC leads to energy extraction from skeletal muscle myotubes. This streamlined overview encapsulates the metabolic intricacies associated with KRAS-driven PC, spotlighting the interplay between tumor growth and host energy metabolism (*Table 2*).

Lipid metabolism in PC

In PC, lipolysis and adipocyte browning are critical phenomena associated with cachexia, serving as energy sources to fuel cancer cell proliferation. Lipolysis, the enzymatic cleavage of triglycerides into fatty acids and glycerol, is enhanced in PC cachexia, primarily catalyzed by enzymes such as adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL), with elevated expressions observed in this condition (28,29). Adipocyte browning, the conversion of white adipocytes to brown-like adipocytes, is characterized by an increase in uncoupling protein-1 (UCP1) activity, which shifts metabolism from energy storage to energy expenditure (30). UCP1, activated by adrenergic stimulation, forms part of a thermoporter complex that includes the mitochondrial calcium uniporter (MCU) and essential MCU regulator (EMRE), facilitating mitochondrial thermogenesis (31). Additionally, lipocalin 2

(LCN2), an adipocytokine secreted by PDAC-induced adipocytes, plays a dual role in enhancing thermogenesis via UCP1 and inducing fat and muscle degradation through ATGL and muscle RING-finger protein-1 (MURF-1) (32).

Zinc-α2-glycoprotein (ZAG), encoded by AZGP1, promotes lipolysis by upregulating UCP1 expression in brown adipose tissue (33) and is found in higher concentrations in PC patients with cachexia (34,35). Intriguingly, ZAG also impedes tumor progression in PDAC by inhibiting epithelial-mesenchymal transition through the transforming growth factor beta/extracellular signal-regulated kinase (TGF-β/ERK) signaling pathway (36).

Ceramides, essential components in lipid metabolism, modulate fatty acid absorption and utilization, prioritizing these processes over glucose metabolism, which can contribute to insulin resistance (37). In muscle cells, *de novo* synthesis of ceramides can trigger apoptosis (38). Furthermore, in PC, the ratio of C18:C24 ceramides serves as a distinguishing marker between cachectic patients and non-cachectic controls, highlighting its potential as a biomarker (39).

Parathyroid hormone-related protein (PTHrP) not only facilitates tumor growth and metastasis in PC but also significantly influences cachexia (40). Elevated levels of PTHrP are associated with weight loss and diminished handgrip strength, indicative of skeletal muscle depletion. The action of PTHrP shifts the energy balance toward a catabolic state, enhancing body fat oxidation and adipose tissue reduction, which are indicative of cachexia alongside skeletal muscle wasting (41).

Disruption of muscular homeostasis by KRAS-mutant PC

Protein synthesis and degradation are crucial determinants of skeletal muscle mass and function. The insulin-like growth factor 1 (IGF-1)/insulin signaling pathway plays a central role in regulating muscle size by enhancing protein synthesis and inhibiting protein breakdown. This pathway predominantly exerts its effects through the phosphoinositide 3 kinase (PI3K)/protein kinase B (Akt) signaling axis (42,43). Activation of Akt leads to the phosphorylation of forkhead box O (Foxo) transcription factors, notably inhibiting the translocation of Foxo3 to the nucleus. This inhibition prevents the transcription of ubiquitin ligases MAFbx/Atrogin-1 and MURF-1, which are integral to protein degradation (44). When the Akt/Foxo3 pathway is suppressed, these ubiquitin ligases become active, leading to the breakdown of key structural and regenerative proteins in skeletal muscle (*Figure 2*).

Additionally, the PI3K/Akt pathway modulates the expression of glucose transporter 4 (GLUT4), essential for insulin-mediated glucose uptake, serving both as a nutritional source for skeletal muscle cells and a systemic regulator of serum glucose levels (45). However, in PC, defects in the PI3K signaling pathway result in compromised glucose utilization in skeletal muscle and disruption of overall glucose metabolism (46).

The nuclear factor kappa B (NF-κB) signaling pathway also plays a significant role in muscle degradation, as NF-κB directly binds with the MURF-1 promoter, thereby promoting muscle catabolism (47). In PDAC patients, NF-κB activation is facilitated by ectodysplasin A2 receptor (EDA2R) through NF-κB-inducing kinase (NIK) activity, enhancing muscle atrophy via upregulated Atrogin-1 and MURF-1 expression. Transcriptional levels of EDA2R are notably higher in cachectic patients compared to non-cachectic individuals and non-cancer controls, and it is upregulated in response to tumor-induced oncostatin M (OSM) binding with its muscle-specific receptor, oncostatin M receptor (OSMR) (48). Targeting the OSMR/EDA2R/NIK signaling axis may thus offer therapeutic potential for mitigating muscle atrophy in cachexia.

Furthermore, in PC, the NF-κB pathway is hyperactivated due to systemic inflammation induced by cytokines from the TGF-β superfamily, which also activates the Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) and SMAD family member 2 and 3 (SMAD2/3) pathways. These pathways collectively suppress myogenesis by downregulating myoblast determination protein (MyoD) (49,50), contributing to the muscle wasting observed in cachexia.

Ubiquitin proteasomal degradation in PC cachexia

Insulin receptor substrate 1 (IRS-1) and MG53

IRS-1 is a crucial element of the insulin receptor signaling pathway, further regulated by MG53, a ubiquitin E3 ligase. Elevated levels of circulating MG53 do not necessarily affect glucose handling or insulin signaling, yet there are conflicting reports regarding its role in glucose metabolism and myogenesis, particularly in PC mouse models (51,52). These discrepancies highlight the necessity for further research into MG53's complex functions in PC cachexia.

Angiotensin II (Ang II)

Ang II acts as a significant early-stage regulator in cachexia, augmenting the proteolytic activity of ubiquitin-proteasome

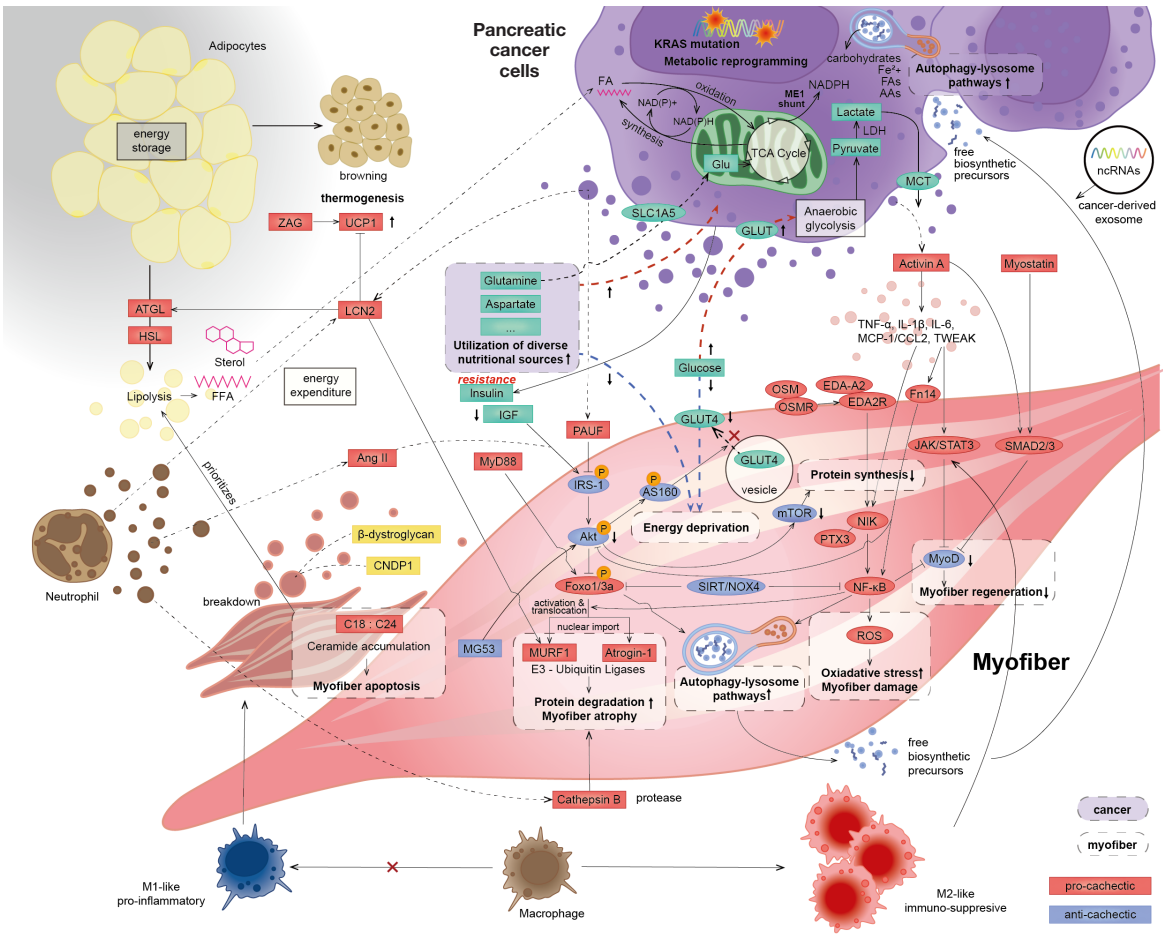

Figure 2 Panoramic view of molecular crosstalk mechanisms between skeletal muscle atrophy and KRAS-mutant pancreatic cancer. Oncogenic KRAS mutations result in increased glucose uptake, redirection of metabolic pathways toward biosynthesis, glutamine reprogramming, and regulation of ROS, also activate distinctive metabolic scavenging pathways, such as macropinocytosis, autophagy, lipid synthesis, and FAO. These processes collectively contribute to skeletal muscle atrophy through various critical interconnected crosstalk mechanisms: (I) KRAS-driven metabolic reprogramming in cancer cells depletes muscle energy reserves, leading to the reallocation of myofiber energy to support cancer cell growth. (II) KRAS-mutant cancer cells rely on nutrient-scavenging pathways, which result in altered inflammatory cytokine profiles, increased degradation of ubiquitin-tagged proteins, and activation of the autophagy-lysosome pathway. These changes facilitate myotube degradation and inhibit muscle regeneration, disrupting muscular homeostasis and creating a unidirectional nutrient flux. (III) Tumor-induced oxidative stress damages myotubes, highlighting the detrimental effects of reactive oxygen species on muscle structure and integrity. (IV) KRAS-mutant cancer cells remodulate immune cell dynamics within the tumor environment. ATGL, adipose triglyceride lipase; HSL, hormone-sensitive lipase; LCN2, lipocalin 2; UCP1, uncoupling protein-1; ZAG, zinc-α2-glycoprotein; FFA, free fatty acids; Ang II, angiotensin II; CNDP1, carnosine dipeptidase 1; MyD88, myeloid differentiation primary response gene 88 protein; IGF, insulin-like growth factor; PAUF, pancreatic adenocarcinoma upregulated factor; IRS-1, insulin receptor substrate 1; Akt, protein kinase B; Foxo, forkhead box O; MURF-1, muscle RING-finger protein-1; AS160, Akt substrate of 160 kDa; SLC1A5, solute carrier family 1 member 5; TCA, tricarboxylic acid; GLUT, glucose transporter; FA, fatty acid; NADPH, nicotinamide adenine dinucleotide phosphate; KRAS, Kirsten rat sarcoma viral oncogene homologue; ME1, malic enzyme 1; LDH, lactate dehydrogenase; AA, amino acid; MCT, monocarboxylate transporter; ncRNA, non-coding RNA; SIRT/NOX4, Sirtuin/NADPH oxidase 4; mTOR, mammalian target of rapamycin; OSM, oncostatin M; OSMR, oncostatin M receptor; EDA-A2, ectodysplasin A2; EDA2R, ectodysplasin A2 receptor, ectodysplasin A2 receptor; Fn14, fibroblast growth factor-inducible 14; JAK/STAT, Janus kinase/signal transduction and transcription activation; SMAD, suppressor of mother against decapentaplegic (protein family); NIK, NF-κB-inducing kinase; PTX3, pentraxin 3; NF-κB, nuclear factor kappa B; MyoD, myoblast determination protein; ROS, reactive oxygen species; FAO, fatty acid oxidation.

pathways, which leads to protein degradation in myotubes. This proteolysis can be mitigated by insulin-like growth factor (IGF) (53). Elevated plasma levels of Ang II are directly linked to skeletal muscle wasting and inversely associated with survival in PC patients (54).

Pancreatic adenocarcinoma upregulated factors (PAUFs)

PAUFs, secreted by PC cells, not only promotes tumor progression and metastasis (55) but also contributes to cachexia. Administration of PAUFs has been shown to induce body weight loss and muscle atrophy through mechanisms including the upregulation of Atrogin-1 via rapid deactivation of the IRS-1/Akt/Foxo3 signaling pathway (56).

Sirtuin1 (SIRT1)/NADPH oxidase 4 (NOX4) pathway

SIRT1, part of the silent information regulator 2 (SIR2) family, functions as an NAD^+-dependent protein deacylase, regulating Foxo transcription factors (57). In PC, secreted factors reduce SIRT1 expression, activating Foxo and leading to increased levels of Atrogin-1 and MURF-1. Reduced SIRT1 activity also enhances NF-κB signaling, inducing oxidative stress through NOX4 (58). Inhibition of both SIRT1 and NOX4 has proven effective in reducing body weight loss and muscle atrophy, positioning the SIRT1/NOX4 pathway as a potential therapeutic target for cachexia in PC.

Toll-like receptor (TLR)/myeloid differentiation primary response gene 88 protein (MyD88)/XBP1 signaling

The MyD88 acts as a crucial adaptor for TLRs, excluding TLR3 and the type-1 interleukin receptor (IL-1R) family. In PDAC, MyD88 is associated with poor survival outcomes, primarily due to its role in systemic inflammation. Crucially, MyD88 is essential for PDAC cachexia progression, mediating the upregulation of Foxo1, Atrogin-1, and MURF-1 (59), suggesting its utility as a biomarker for this condition.

These interacting factors collectively promote skeletal muscle degradation over regeneration, contributing to the progressive decline of skeletal muscle in cachexia.

Autophagy-lysosome pathway

KRAS-mutant cells rely on nutrient-scavenging pathways, including macropinocytosis and autophagy-lysosome pathway, to release free biosynthetic precursors for cancer cell utilization. Consequently, autophagy emerges as the main catalyst of skeletal muscle proteolysis in PC under catabolic conditions. PDAC features an upregulation of autophagy, or enhanced macropinocytosis to offset autophagy blockade (60,61). In PC patients, systematic interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) induce muscular autophagy via inhibitory kappa B kinase alpha (IKKα)/NF-κB and AMP-activated protein kinase/mammalian target of rapamycin (AMPK/mTOR) signaling, leading to skeletal muscle wasting (62,63). KRAS-mutant PC cells transport extracellular protein macropinocytosis to meet their metabolic demands (64), causing a one-way nutrient flux from skeletal muscle cells to PC cells.

PC-induced oxidative stress damages myotubes

NF-κB signaling

PC is often accompanied by chronic inflammation, which inflicts oxidative stress on skeletal muscle cells and results in cell damage directly. This oxidative damage is significantly influenced by the TGF-β superfamily. Key members, including myostatin, Atrogin-1 and growth differentiation factor 15 (GDF15), induce the production of pro-cachectic cytokines TNF-α, interleukin 1 beta (IL-1β), IL-6, monocyte chemoattractant protein 1/CC-motif chemokine ligand 2 (MCP-1/CCL2) and TNF-α-like weak inducer of apoptosis (TWEAK) (65-67). These cytokines activate the NF-κB signaling pathway, which contributes to skeletal muscle wasting by inducing oxidative stress, which is a known facilitator of muscle atrophy (68). While MCP-1/CCL2 levels upon diagnosis correlate with future skeletal muscle wasting (67), the reliability of these cytokines as biomarkers of cancer cachexia is yet to be established, warranting further investigation (*Figure 2*).

Activin A, another TGF-β superfamily member expressed by PDAC cells, promotes both tumor growth and cachexia, with variations based on sex (69). PDAC cells release soluble factors, triggering Activin A secretion from both tumor tissue and distant organs, correlating with increased cachexia severity and myotube atrophy. Notably, cachexia presents less severely in females, potentially due to estradiol's influence (65). Targeting Activin A signaling appears to inhibit tumor progression and muscle wasting, thus extending survival (70,71), indicating its significant prognostic and therapeutic potential.

The pentraxin 3 (*PTX3*) gene, with NF-κB binding sites (72,73), encodes a humoral pattern recognition protein elevated in PC patients (72). Serum PTX3 levels have been identified as a risk factor for skeletal muscle and correlate

with inflammatory markers as well as disease severity (74), suggesting its utility as a biomarker for PC and related cachexia.

Biomarkers for assessing skeletal muscle atrophy in KRAS-mutant PC

Myofiber components

Detection of altered levels of skeletal muscle cell components in the serum, particularly during muscle wasting, is a key diagnostic indicator in PC. β-dystroglycan, a central component of the dystroglycan complex, plays a pivotal role in skeletal muscle cells by linking the intracellular actin cytoskeleton to the extracellular matrix (75). In PC patients, β-dystroglycan undergoes aberrant glycosylation and shows significant upregulation. These changes have led to its adoption as a marker for cachexia in clinical settings (76,77).

Carnosine, predominantly located in the muscle tissue, is metabolized by carnosine dipeptidase 1 (CNDP1). Intriguingly, circulating levels of CNDP1 show a positive correlation with survival rates, BMI and fat mass in PC patients. Conversely, these levels inversely associate with percentage of weight loss and other cachexia-related factors (78).

Extracellular matrix

Tissue inhibitor of metalloproteinases-1 (TIMP-1) have emerged as a crucial regulator of matrix metalloproteinase (MMP) activity. In PC, TIMP-1, along with intercellular adhesion molecule 1 (ICAM1), has been identified as a biomarker superior to carbohydrate antigen 19-9 (CA19-9) in global quantitative proteomics profiling (79). Additionally, TIMP-1 upregulation positively correlates with weight loss and serves as a prognostic indicator in cachectic PDAC patients without jaundice (80).

Non-coding RNAs (ncRNAs)

ncRNAs, particularly microRNAs (miRNAs), are emerging cachexia mediators in PC cachexia. MiR-21, secreted by micro-vesicles, activates the toll-like receptor 7/c-Jun N-terminal kinase (TLR7/JNK) pathway, inducing myoblast apoptosis (81). Serum miR-155 levels correlate with the severity of PC cachexia, influencing TNF-α signaling and regulatory T cell (Treg) function, as well as TLR signaling via suppressor of cytokine signalling 1 (SOCS1), forkhead box P3 (Foxp3) and TGF-β-activated kinase 1 binding protein 2 (TAB2) (82-85). Both miR-21 and miR-155 are overexpressed in intraductal papillary mucinous neoplasms (IPMNs) lesions, precursors of PC, suggesting their potential as predictive biomarkers for both PC and associated cachexia (86).

MiR-let-7b-5p, a PC-derived exosomal miRNA, targets RNF20, an E3 ubiquitin ligase. This interaction alleviates insulin resistance in myotube cells by deactivating the STAT3/Foxo1/GLUT4 axis (87). In PC, ZIP4 activates the cyclic adenosine monophosphate (cAMP) response element binding protein (CREB)-miR-373-PH domain and leucine-rich repeat protein phosphatase 2 (PHLPP2) feed-forward loop, where the suppression of PHLPP2 promotes both tumor growth and cachexia by dephosphorylating Akt and inhibiting downstream CyclinD1 and STAT5-TGF-β signaling (88). CircANAPC7, a long non-coding circular RNA, functions as a miR-373 sponge, counteracting the suppression of PHLPP2, and inhibiting skeletal muscle wasting (89). In the adipose tissue of PC patients, ncRNAs modulates lipid metabolism and thermogenesis. MiRNAs such as miR-30b/c, miR-494-3p, miR-9, miR-338-3p, miR-106b, miR-93, and miR-27b are implicated in the regulation of UCP1 and other thermogenic proteins (90-94).

Immune cell remodeling in PC-induced sarcopenia and cachexia

The orchestration of immune responses plays a pivotal role in skeletal muscle regulation, where a delicate equilibrium is maintained between the removal of damaged muscle fibers and the promotion of myogenesis. This balance is disrupted in the immunosuppressive milieu of PC, dominated by an abundance of M2-like macrophages, myeloid-derived suppressor cells (MDSCs), and Tregs, overshadowing the roles of M1-like macrophages and effector T cells (95,96) (*Figure 3*).

Macrophages are central to the repair and remodeling of skeletal muscle. Initially, circulating monocytes are recruited to the site of injury, differentiating into M1-like macrophages that facilitate the clearance of necrotic tissue and support satellite cell proliferation (97). Subsequently, a phenotypic transition to M2-like macrophages occurs, favoring myogenesis (98). In the context of PC, however, M2-like macrophages synergize with tumor cells, promoting muscle wasting via STAT3 signaling (99) and crosstalk. PC cells overexpress CCL2, which upregulates CC-motif chemokine ligand 5 (CCL5) secreted by M2 macrophages, stimulating PC cells to release TWEAK via CCL5/TNF receptor associated factor 6 (TRAF6)/NF-

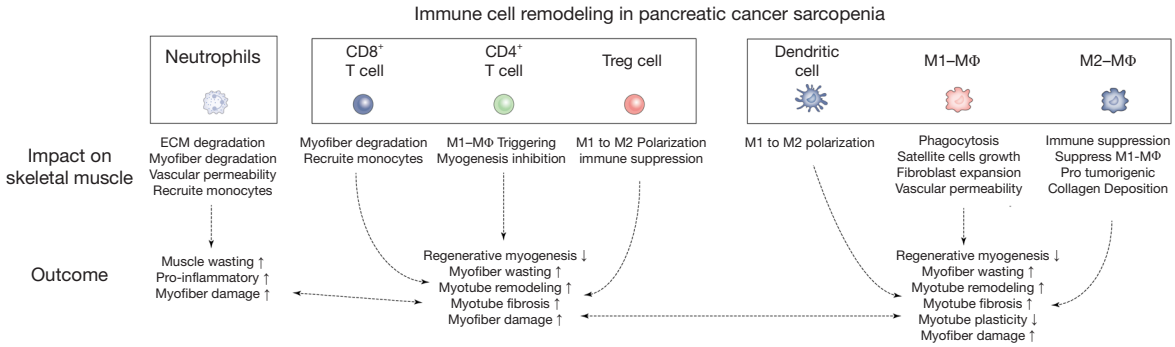

Figure 3 Mechanisms of immune cell remodeling in KRAS-mutant pancreatic cancer sarcopenia. The orchestration of immune responses is critical for skeletal muscle regulation, maintaining a delicate balance between the removal of damaged muscle fibers and the promotion of myogenesis. This equilibrium is disrupted in the immunosuppressive environment of KRAS-mutant pancreatic cancer, which is characterized by an abundance of M2-like macrophages, MDSCs, neutrophils, and Tregs. This altered immune landscape leads to myotube damage, muscle wasting, and a loss of regenerative myogenesis and plasticity. ECM, extracellular matrix; Tregs, regulatory T cells; KRAS, Kirsten rat sarcoma viral oncogene homologue; MDSCs, myeloid-derived suppressor cells.

κB signaling, leading to skeletal muscle wasting through MURF-1 activation (100).

Furthermore, Kupffer cells, liver-resident macrophages, exhibit a correlation with both nutritional decline and tumor proliferation in PC (101).

Neutrophils, as initial responders to muscle injury, primarily focus on clearing debris. However, their prolonged presence can hinder muscle regeneration (102). PC cachexia is characterized by increased neutrophil counts and the upregulation of neutrophil-derived proteases, such as Cathepsin B (54), with neutrophils also being a significant source of LCN2, a mediator of both metabolic regulation and anorexia (103,104). Moreover, the presence of $Ly6G^+$ neutrophils and granulocytic MDSCs (gMDSCs) has been linked to muscle wasting in PC (105), with the neutrophil/lymphocyte ratio serving as a biomarker for cachexia-related inflammation (54).

T lymphocytes, particularly $CD8^+$ cells, exert control over muscle mass independently and through modulation of macrophage function (106-108). Cachexia in early-stage PDAC is associated with diminished levels of tumor-infiltrating $CD8^+$ T cells (109), where the activation of TLR7 on $CD8^+$ T cells has been shown to counteract cachexia and limit tumor growth (110,111), underscoring a crucial inverse relationship between $CD8^+$ T cell presence and cachexia. Conversely, the roles of $CD4^+$ T helper cells and Tregs appear unchanged in cachexia, though a decrease in liver IL-4 mRNA has been observed, indicating a potential area for further exploration regarding $CD4^+$ T cells' involvement in cachexia (98).

Current therapeutic interventions for PC-associated cachexia

Current therapeutic strategies against cachexia focus on restoring the balance between skeletal muscle degeneration and regeneration. Efforts to promote muscle regeneration include countering anorexia, nutritional supplementation, and encouraging physical activity, while strategies to discourage muscle degeneration involve suppressing inflammation and other catabolic signaling pathways (*Table 3*).

Prophagic therapy

In PC cachexia, the central nervous system is an integral and complex regulator of appetite. Inflammation in the PC milieu suppresses prophagic responses and enhances anorexigenic responses in the hypothalamus by endocrine hormones leptin and ghrelin (117). Growth hormone secretagogue receptor (GHS-R) functions as ghrelin's receptor and controls the release of growth hormone as well, the latter an upstream regulator of IGF-1 in the muscle tissue. GHS-R delivers outstanding performance as a therapeutic target. Its antagonists, anamorelin and macimorelin are rising stars in the field of cachexia therapy. Anamorelin for PC associated cachexia treatment made its debut with the ONO-7643 trial and landed

Table 3 Current therapeutic targets for pancreatic cancer-associated sarcopenia and cachexia

Pharmaceutical therapy	Therapeutical target or biochemical feature	Compound	Clinical trial No.	Phase and design	Population	N	Primary outcomes	Cachexia/ sarcopenia	Study start and completion dates	Results
Prophagic therapy	GHS-R	Anamorelin	NCT04844970	II, randomized, double blind, placebo-controlled	US, unresectable or metastatic PDAC	100	Weight change	Cachexia	April 01, 2023 to NP	Recruiting
		Macimorelin	NCT01614990	II, randomized, triple blind, placebo-controlled	US, incurable solid tumor	15	Change in body weight, IGF-1 plasma levels and QoL score	Cachexia	May 2012 to December 2012	Published (112)
	GDF15	Ponsegromab	NCT05546476	II, randomized, double blind, placebo-controlled	US, NSCLC, pancreatic, colorectal cancer	187	Weight change	Cachexia	November 21, 2022 to March 13, 2024	Active, not recruiting
Progestogens	Progesterone	Megestrol acetate	NCT00637728	III, randomized, double blind, placebo-controlled	US, stage II, III, or IV lung or pancreatic cancer	5	Caloric intake	Cachexia	June 2006 to September 2006	Completed (not published)
	Androgen	Decanoate	NCT03263520	Not applicable, randomized, double-blind, *vs.* dexamethasone	Brazil, palliative high gastro-intestinal, hepatobiliary and pancreatic cancer	60	BMI, body weight, body composition, QoL score	Cachexia, sarcopenia	February 2016 to October 31, 2017	Completed (not published)
Pro-myogenesis	TNF-α	Infliximab	NCT00060502	II, randomized, double blind, placebo-controlled	US, newly diagnosed pancreatic cancer	73	Change in lean body mass	Sarcopenia	April 2003 to February 2006	Completed (113)
		Thalidomide	NCT06017284	III, randomized, double blind, placebo-controlled	China, metastatic PDAC	100	Rate of nausea/vomiting	Cachexia	November 01, 2023 to NP	Recruiting
	IL-1α	Xilonix	NCT03207724	I, open-label, single group assignment	US, advanced or locally advanced pancreatic cancer	16	Maximum tolerated dose of Xilonix and onivyde, 5-fluorouracil/folinic acid in combination with Xilonix	Neither	October 16, 2017 to October 27, 2020	Completed (114)
	Activin type 2 receptors	Bimagrumab	NCT01433263	II, randomized, double blind, placebo-controlled	Lithuania, Romania, Switzerland, UK, US, stage IV NSCLC or stage III/IV pancreatic adenocarcinoma	57	Thigh muscle volume change	Sarcopenia	August 2011 to April 2014	Completed (not published)
	Myostatin	LY2495655	NCT01505530	II, randomized, triple blind, placebo-controlled	US, unresectable or metastatic pancreas cancer	125	Overall survival	Neither	December 2011 to January 2016	Completed (not published)
Anti-inflammation	Nutrients	EPA and DHA	NCT02681601	II, randomized, open-label *vs.* standard dietary intervention	US, unresectable PDAC	2	Body weight and body composition	Cachexia, sarcopenia	July 19, 2016 to October 01, 2021	Terminated
	NSAIDs	Ibuprofen	Unknown	Unknown	Pancreatic cancer	16	Resting energy expenditure, serum CRP level	Cachexia	Unknown	Completed (115)
		Celecoxib	IRCT201407222027N4	III, randomized, triple blind, placebo-controlled	Iran, esophageal, gastric, colorectal and pancreatic cancer	90	Quality of life, body weight	Cachexia	October 2015 to NP	Completed (116)
	NSAIDs	Ketorolac acid	NCT05336266	Early I, open-label, single group assignment	US, advanced and refractory PDAC	20	Patient compliance	Neither	July 01, 2022 to NP	Recruiting
Corticosteroids	Prednisolone and dexamethasone	–	–	–	–	–	–	–	–	–

GHS-R, growth hormone secretagogue receptor; PDAC, pancreatic ductal adenocarcinoma; NP, not published; IGF-1, insulin-like growth factor 1; QoL, quality of life; GDF15, growth differentiation factor 15; NSCLC, non-small cell lung cancer; BMI, body mass index; TNF-α, tumor necrosis factor alpha; IL-1α, interleukin 1 alpha; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; NSAIDs, non-steroidal anti-inflammatory drugs; CRP, C-reactive protein.

approval in Japan in 2020 (118,119). It significantly improves body weight, lean body mass and appetite (118), whereas responsiveness is associated with higher total protein, albumin, transferrin and prognostic nutritional index, and lower neutrophil/lymphocyte and C-reactive protein (CRP)/albumin ratios (120). Anamorelin is still undergoing phase II clinical trials in PC patients in the US (NCT04844970). Macimorelin awaits further investigation based on its pilot trial (NCT01614990) (112). In the pilot trial, continual daily oral administration of macimorelin lasted one week. Although no statistic difference in body mass, physical function endpoints, appetite, food intake or energy expenditure was observed, body weight and quality of life exhibit numerical improvement (112). Anorexia is also induced by GDF15/GDNF family receptor alpha-like (GFRAL) signaling (121). GFRAL's ligand GDF15 is a potential therapeutical target for PC-associated cachexia. Ponsegromab (PF-06946860), a humanized monoclonal antibody (mAb) against GDF15, is currently under phase II trial (NCT05546476).

Progestogens

Megestrol acetate is a progesterone derivative earliest used for acquired immunodeficiency syndrome (AIDS)-associated cachexia treatment as an appetite stimulant (122). Its anti-cachectic usage has extended to cancer-associated cachexia, effectively improving appetite and body weight in PC patients (NCT00637728) (123,124). Nandrolone decanoate is a minor endogenous androgen that managed to improve body weight, lean body mass and functionality in human immunodeficiency virus (HIV)-afflicted cachexia patients (125,126). A trial has been conducted on nandrolone decanoate's efficacy for treating malnutrition in cancer patients, which included cachectic PC patients (NCT03263520), though no results have been published yet.

Inflammation suppression

In PC-associated cachexia, the integrated JAK/STAT3 and SMAD2/3 signaling aforementioned pathway is activated upon cytokine, activin and myostatin stimulation, which downregulates the expression of MyoD, a pro-myogenesis molecule. Cytokines, especially TNF-α and interleukin 1 alpha (IL-1α) (82), as well as activin and myostatin, are potential therapeutic targets in cachexia treatment. Infliximab and thalidomide are TNF-α suppressants. Infliximab is a chimeric IgG1-κ mAb against TNF-α, while thalidomide is an inhibitor of TNF-α synthesis. However, neither drug resulted in significant improvement in cachexia in PC patients (113,127-129).

Xilonix or bermekimab (MABp1) is a mAb specific to human IL-1α. It is currently under phase I trial (NCT03207724).

Bimagrumab (BYM338) is a human mAb against activin type 2 receptors. LY2495655 is a humanized IgG1 mAb against myostatin. Both studies have completed phase II trials on PC patients but neither exhibited promising results (130) (NCT01433263, NCT01505530).

Anti-inflammatory nutrients

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are ω3 or n-3 polyunsaturated fatty acids (PUFAs) found in cold-water fish. In PC patients, EPA managed to stabilize body weight as well as reduce CRP, IL-6 and cortisol-to-insulin ratio, while improving serum insulin, creating a pro-myogenesis profile (131-133). However, there were controversial results showing EPA failed to outperform placebo in weight stabilization (134,135). EPA plays an anti-cachectic role by inhibiting proteolysis, enhancing protein synthesis and aiding chemotherapy, and is most effective when provided in early stages of cachexia development (136,137).

Non-steroidal anti-inflammatory drug (NSAIDs) and corticosteroids

Ibuprofen and celecoxib are selective COX2 inhibitors. Ibuprofen was shown to reduce resting energy expenditure as well as CRP levels, and celecoxib resulted in weight gain when combined with megestrol acetate in PC patients with cachexia (115,116,138). Ketorolac acid is a COX enzyme inhibitor, also known as a NSAID. In cancer-bearing mice with cachexia, it has shown to prolong survival and ameliorate weight, adipose and muscle loss in a T-cell-dependent manner (139). It is still recruiting candidates for an early phase I trial on advanced and refractory PDAC patients (NCT05336266). Short-term usage of corticosteroids in treating cancer-associated cachexia already acquired moderate strength recommendation (140).

Anti-inflammatory diet

The Mediterranean diet is a balanced, pro-health structure

based on plant-origin foods, delivering a broad spectrum of nutrients and fibers essential to overall health. It also comprises moderate seafood, which is abundant in ω3 or n-3 PUFAs. The food pyramid of the Mediterranean diet includes fruit, vegetables and cereal as its bottom layer. Virgin olive oil is rich in monounsaturated oleic acids and antioxidant compounds, and it serves as the major culinary fat. Other natural sources of lipids include olives, nuts and seeds. Fish, shellfish, white meat and eggs are moderately consumed as the main source of animal protein instead of red meats. In addition to food consumption, culinary and physical activity in a sense of socialization as well as adequate rest is also an essential part of the Mediterranean lifestyle, contributing to an overall health and well-being (141). A study on stage III–IV colorectal cancer patients with cachexia delivered promising results. The Mediterranean diet increased weight, lean body mass, muscle strength, the global health status score and physical performance score while lowering TNF-α, high-sensitive-C-reactive protein (hs-CRP) and IL-6 serum levels (IRCT20211027052884N1) (142). These results may shed light on future applications in PC.

Physical activity

Exercise, according to the 2020 American Society of Clinical Oncology (ASCO) guideline, awaits further evaluation to be approved for effective cancer-associated cachexia treatment (140). It is currently under investigation as a part of multimodal trials on PC patients with cachexia (NCT05420259 and NCT04907864).

These therapeutic interventions represent a multifaceted approach to tackling the complex issue of cachexia in PC, with a mix of pharmacological, nutritional, and lifestyle modifications aimed at improving patient outcome.

Conclusions

Comprehensive evidence updates the intricate crosstalk between KRAS-mutant PC and skeletal muscle atrophy, delineating the pathophysiological context essential for grasping sarcopenia and associated disorders. Thorough analysis enriches our knowledge of the complex causes of PC cachexia and sarcopenia and promotes the development of targeted therapeutic strategies.

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Footnote

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