



REVIEW ARTICLE

Pancreatic cancer cachexia: three dimensions of a complex syndrome

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Cancer cachexia is a multifactorial syndrome that is characterised by a loss of skeletal muscle mass, is commonly associated with adipose tissue wasting and malaise, and responds poorly to therapeutic interventions. Although cachexia can affect patients who are severely ill with various malignant or non-malignant conditions, it is particularly common among patients with pancreatic cancer. Pancreatic cancer often leads to the development of cachexia through a combination of distinct factors, which, together, explain its high prevalence and clinical importance in this disease: systemic factors, including metabolic changes and pathogenic signals related to the tumour biology of pancreatic adenocarcinoma; factors resulting from the disruption of the digestive and endocrine functions of the pancreas; and factors related to the close anatomical and functional connection of the pancreas with the gut. In this review, we conceptualise the various insights into the mechanisms underlying pancreatic cancer cachexia according to these three dimensions to expose its particular complexity and the challenges that face clinicians in trying to devise therapeutic interventions.

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BACKGROUND

Cachexia is a multifactorial syndrome defined by a loss of skeletal muscle mass, with or without a loss of fat mass, that cannot be fully reversed by conventional nutritional support and that leads to progressive functional impairment of the entire organism.¹ In humans, cachexia can occur as a consequence of a number of chronic diseases, such as chronic renal failure, AIDS, advanced dementia and cancer. Cachexia associated with cancer has specific tumour-related pathomechanisms that include altered energy metabolism, the presence of pro-inflammatory signals and tumour-derived catabolic factors, sarcopenia, and adipose tissue depletion,² and is therefore distinct from malnutrition, as well as being a prognostic indicator of poor overall survival independent of the initial body mass index (BMI) of the patient.³

Pancreatic cancer has one of the poorest prognoses of all solid tumours, with a 5-year relative survival rate below 8% across all disease stages.⁴ This poor prognosis is a consequence of a number of factors—the disease usually progresses rapidly, has high rates of recurrence after surgery, is commonly resistant to chemotherapy and is especially associated with the development of cachexia. In fact, as many as 63–64% of patients with pancreatic cancer develop cachexia over the course of their disease.^{5–7} At diagnosis, the prevalence varies more markedly, between 21.3 and 63%, which is likely to reflect heterogeneity between the patient cohorts and differences in the definition of cachexia.^{5,6,8,9} Pancreatic cancer patients who develop cachexia commonly suffer from poor appetite with or without concomitant fatigue, depression and cancer pain, lose muscle and fat mass despite nutritional support and frequently show signs of systemic inflammation. Additionally, different degrees of maldigestion with steatorrhea and bloating due to poor pancreatic exocrine function,

impaired glucose tolerance and other gastrointestinal complications due to the interaction of the pancreas with other organs can worsen this clinical picture. For patients with advanced pancreatic cancer, the presence of sarcopenia at diagnosis or the loss of skeletal muscle mass during chemotherapy is clinically extremely relevant and is a stronger prognostic factor of poor overall survival than an Eastern Cooperative Oncology Group (ECOG) performance status of ≥ 2 .⁸ Accordingly, weight loss, digestive problems and loss of appetite significantly increase with disease progression and patients report deterioration in their overall physical quality of life (QoL) at later stages of pancreatic cancer.¹⁰ In addition, the responsibility of caregivers to assist patients with needs related to these symptoms is a major source of stress.¹¹

The high prevalence and clinical importance of cachexia in the context of pancreatic cancer is likely to depend on distinct effects of the tumour on the organism (mediated by tumour-related systemic factors), the role of the pancreas in digestion and nutrient uptake as well as glucose homeostasis (mediated by factors related to alterations in pancreatic function), and its close interaction with other digestive organs (mediated by digestive tract-related factors) (Fig. 1). In this review, we describe insights into the mechanisms underlying pancreatic cancer cachexia in these three dimensions and present the emerging evidence for potential clinical interventions.

PANCREATIC TUMOUR-DERIVED FACTORS ASSOCIATED WITH CACHEXIA

Pancreatic cancer induces metabolic shifts, inflammatory signals and other factors which result in complex interactions with the organism. Together, they are the key mechanisms of the

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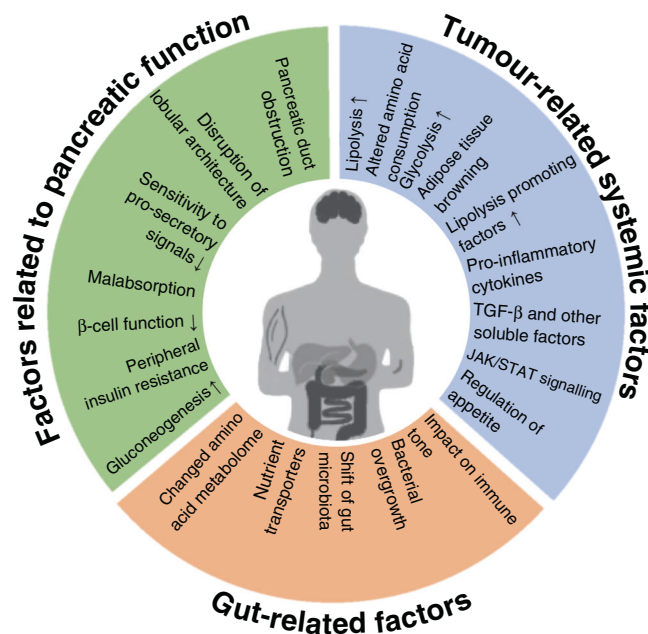


Fig. 1 Conceptualisation of the three dimensions involved in the development of pancreatic cancer cachexia. Pancreatic cancer cachexia is a complex syndrome that integrates three interdependent dimensions: tumour-related systemic factors; factors related to alterations of the pancreatic function; and factors related to the close interaction of the pancreas with other digestive organs. The systemic factors outlined are partly specific for cachexia associated with pancreatic adenocarcinoma, partly generic for that associated with solid malignancies. Factors related to the central function of the pancreas for nutritional uptake and homeostasis, and factors related to other digestive organs are characteristic of pancreatic cancer cachexia.

systemic dimension of the pathophysiology of pancreatic cancer cachexia.

KRAS-dependent metabolic changes related to pancreatic cancer. Activating mutations in the *KRAS* oncogene are found in up to 95% of all human pancreatic adenocarcinomas and the vast majority of these mutations cluster into only three different variants in exon 12: G12D, G12V and G12R.¹² Major insights into tumour-related mechanisms of cachexia in the context of pancreatic cancer have been derived from animal models (Box 1). In mice harbouring the G12D variant, *Kras*-dependent signalling increases glycolysis in pancreatic cancer cells by inducing the expression of the *GLUT1* glucose transporter and transcriptional upregulation of several rate-limiting glycolytic enzymes.¹³ Increased glycolysis is an important adaptive process in hypoxic *Kras*-mutant pancreatic cancer cells and promotes cancer cell survival.¹⁴ Although constituting an energetically inefficient form of glucose metabolism, a high rate of glycolysis and lactate fermentation in the cytosol, known as the Warburg effect, is likely to facilitate the proliferation of pancreatic cancer cells in the absence of oxygen,¹⁵ and heterotopic implantation of pancreatic cancer cell lines with exceptionally high levels of glycolysis has been associated with increased weight loss and the induction of skeletal-muscle proteolysis, adipose tissue lipolysis and hepatic gluconeogenesis, which are catabolic processes characteristic of cachexia (Fig. 2).¹⁶

Kras^{G12D/+} also promotes the preferential use of glycolytic metabolites in biosynthesis pathways and promotes glutamine as the main carbon source for the tricarboxylic acid (TCA) cycle instead of glucose.^{13,17} In fact, increased glycolysis and glutamine metabolism in *Kras*-mutant pancreatic cancer cells are closely interlinked by some of the downstream anabolic pathways, and depend on each other to promote tumour aggressiveness and survival in the tumour's hypoxic desmoplastic environment.¹⁴ These metabolic changes result in the increased uptake and consumption of glutamine, consistent with the observation that

Box 1 Lessons from mouse models

Most widely used in the study of pancreatic cancer are the *Kras*^{LSL-G12D/+} *Trp53*^{R172H/+} *Pdx1*^{Cre/+} (KPC) and the *Kras*^{LSL-G12D/+} *Ink4a/Arf*^{fl/fl} *Pdx1*^{Cre/+} mouse models, in which tumour development is driven by genetic alterations that reflect frequent equivalent somatic mutations in human pancreatic cancers.^{205,206} These genetically engineered mouse models develop pancreatic carcinomas with a rich desmoplastic stroma and metastatic pattern characteristic of the human disease. Unfortunately, however, the KPC mouse model does not recapitulate the clinical patterns of tissue wasting observed in human patients, and the differential gene expression in skeletal muscle samples from KPC mice was not consistent with that observed in muscle biopsy samples from cachectic pancreatic cancer patients.²⁰⁷ Accordingly, to more fully recapitulate the pattern and pathophysiology of the loss of muscle mass and adipose tissue observed in humans, a new mouse model incorporating tamoxifen-inducible mutant *Kras* and two floxed *Pten*-alleles, the *Kras*^{LSL-G12D/+}; *Ptf1a*^{ER-Cre/+}; *Pten*^{fl/fl} (KPP) mouse, has been engineered.²⁰⁷ Additionally, various orthotopic and heterotopic implantation models of different murine or human pancreatic cancer cell lines and human tumour xenografts in susceptible mice have been used to study cachexia,²⁰⁸ although how well they reflect pancreatic cancer cachexia in humans has not been systematically assessed. Comparison of xenografts of human cancer cell lines within the flank and within the pancreas appears to suggest that certain aspects of cachexia, including the upregulation of genes associated with atrophy in the skeletal muscle, an increase of cachexia-associated cytokines and the development of significant muscle wasting, depend on the presence of the tumour in the pancreas.⁵⁴ Generally, caution should be given to the potential discrepancies between cachexia in mouse models and the human disease.

malignant transformation of precursor lesions in *Kras*^{G12D/+} mice (but not in non-malignant pancreatic pathologies) correlates with a reduction of free circulating glutamine levels.¹⁸ Skeletal muscle is the main reservoir of glutamine in the body, and glutamine is the primary amino acid released by catabolic breakdown of muscle mass.¹⁹ Additionally, pancreatic stellate cells of the tumour microenvironment provide other non-essential amino acids—specifically alanine—through autophagy as an alternative mitochondrial carbon source for tumour cells independent of circulating nutrients.²⁰ This appears to be an important factor for shifting carbon from glucose towards biosynthesis and, more

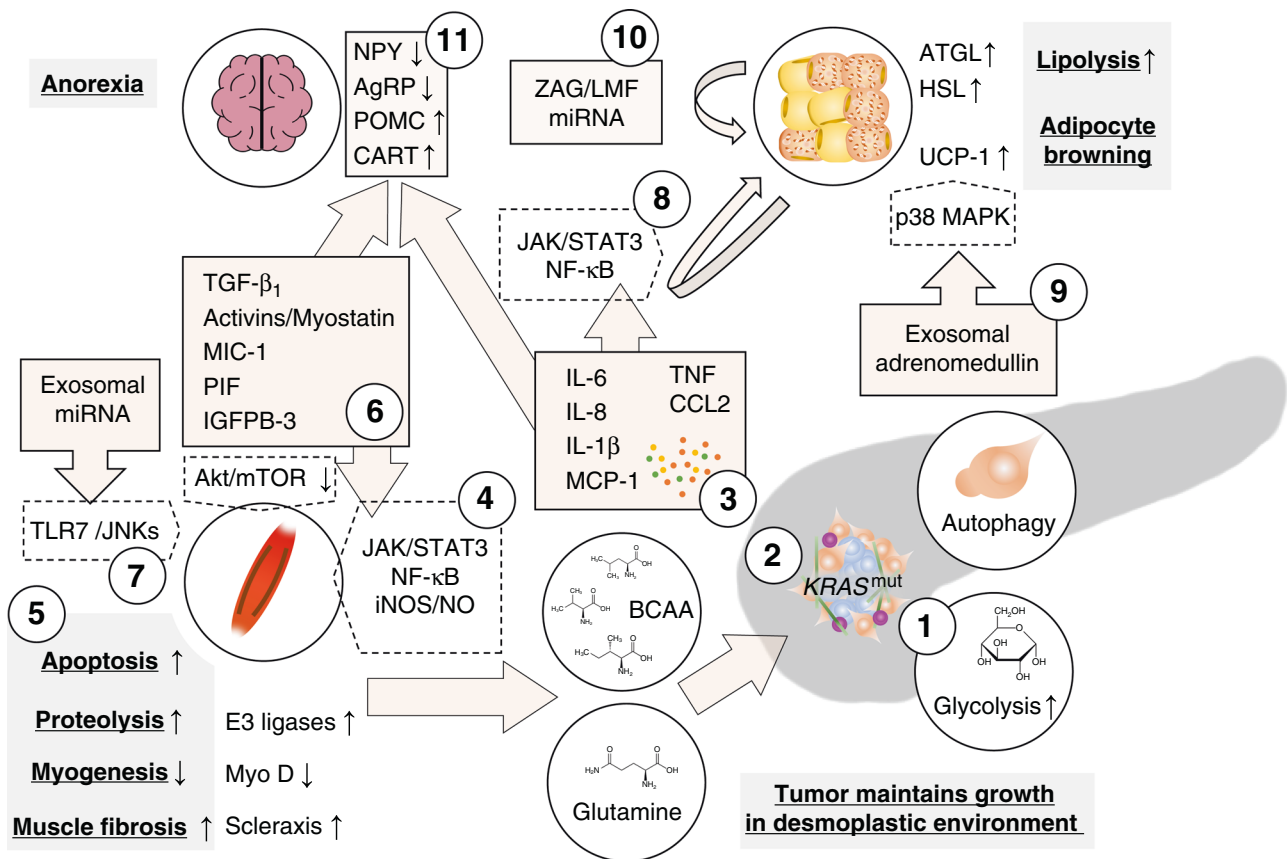


Fig. 2 Tumour-derived factors associated with cachexia in pancreatic adenocarcinoma. Tumours increasingly metabolise glucose through glycolysis which is increased through mutant *KRAS*-dependent upregulation of glycolytic enzymes (1). Other *KRAS*-dependent metabolic changes promote the use of other carbon sources such as glutamine and branched chain amino acids (BCAA) from the breakdown of peripheral tissue, as well as other non-essential amino acids from pancreatic stellate cell autophagy, in the TCA cycle; substrates from the TCA cycle are used for biosynthesis (2). Together, these changes increase survival in a hypoxic and nutrient-deficient environment. Tumour-derived cytokines prompt several catabolic effects in peripheral tissues (3). Interleukin (IL-6, TNF or interferon γ (IFN γ)) induce the breakdown of muscle fibres through the Janus kinase (JAK)/signal transducer and activator of transcription (STAT3) pathway and nuclear factor (NF)- κ B-dependent induction of nitric oxide (4) which leads to decreased myogenesis through downregulation of the myogenic regulatory factor MyoD and increased proteolysis through E3-ligase-dependent ubiquitination (5). Similarly, members of the transforming growth factor (TGF)- β superfamily activate the canonical Smad2/3 pathway which promotes ubiquitin ligase-mediated proteolysis and scleraxis-mediated muscle fibrosis and reduces Akt/mTOR-mediated myogenesis (6). Additionally, microRNAs (miRNAs) in tumour-derived extracellular vesicles induce myoblast apoptosis by Toll-like receptor 7-dependent c-Jun N-terminal kinase (JNK) signalling (7). In white adipose tissue, pro-inflammatory signals, specifically IL-6, promote lipolysis through activation of the JAK/STAT3 pathway and NF- κ B in adipose tissue and induces adipocyte browning through upregulation of uncoupling protein 1 (UCP-1) (8). Lipolysis through hormone-sensitive lipase (HSL) are also mediated by adrenomedullin from tumour-derived exosomes which activates the p38 mitogen-activated protein kinase (MAPK) pathway in adipocytes. Exosomal cargoes (other than adrenomedullin) can also induce adipocyte browning through UCP-1 expression (9). Lipolysis is maintained through paracrine signals in fat tissue like zinc- α 2-glycoprotein (ZAG/LMF) and miRNAs which induce adipose triglyceride lipase (ATGL) and HSL catalyse the hydrolysis of stored triglycerides (10). In the central nervous system, pro-inflammatory cytokines, particularly IL-1 β , and macrophage inhibitory cytokine (MIC)-1 (a member of the TGF- β superfamily), induce anorexia by reducing anabolic neuropeptide Y (NPY)/agouti-related protein (AgRP) and increasing catabolic proopiomelanocortin (POMC) and cocaine-and-amphetamine regulated transcript (CART) signalling (11).

broadly, for supporting the altered energy metabolism related to pancreatic cancer cachexia.

Mouse models with early *Kras*-driven pancreatic cancers show, in addition to decreased glutamine levels, elevated levels of branched-chain amino acids (BCAAs; Fig. 2).^{18,21} BCAAs supply 20% of the TCA cycle carbon input in the healthy pancreas,²² but *Kras*-driven pancreatic cancer cell TCA cycle metabolism becomes independent of BCAA in early carcinogenesis; this contrasts with *Kras*-driven tumours originating in other tissues, which are dependent on the use of BCAAs.^{23,24} Although not crucial for pancreatic cancer cells' energetic requirements, studies in KPC mice found generation of BCAAs through the breakdown of muscle and other body protein and in vitro studies identified them as an important source of carbon for the fatty acid biosynthesis.^{21,25} Detection of BCAAs in clinical samples obtained

before a diagnosis of pancreatic cancer in human patients suggest that similar *KRAS*-dependent processes drive early proteolysis in humans.²¹

Tumour-related changes in adipose tissue physiology

Lipolysis is the main mechanism of adipose tissue wasting in patients with pancreatic cancer. White adipose tissue stores large amounts of energy that can be made available to the organism. In response to fasting or increased physical activity, lipolysis hydrolyses triglycerides into three fatty acids and glycerol, which are released into the blood circulation for β -oxidation into acetyl CoA by other organs and the liver (fatty acids) or for triglyceride synthesis or gluconeogenesis in the liver (glycerol). In a cohort of non-cancer patients and patients with gastrointestinal cancers, the majority of whom had pancreatic cancer, the loss of body fat

significantly correlated with decreased adipocyte size and increased plasma levels of fatty acids and glycerol in the cancer patients. By contrast, other potential causes of fat loss—a decrease in the number of adipocytes, reduced lipogenesis, and inflammation in the adipose tissue—did not differ between cancer patients with or without adipose tissue loss and non-cancer patients.²⁶ Interestingly, the increased level of lipolysis in the fat of patients with gastrointestinal cancer with weight loss does not decrease with glucose infusion, and these patients have a reduced ability to oxidise circulating fatty acids,²⁷ indicating that the primary reason for the upregulation of lipolysis in cachectic pancreatic cancer patients might not be to fulfil the energetic requirements of the tumour. However, the clinical studies that underpin this conclusion are relatively small in size. These results are also difficult to reconcile with the observations that an increased supply of fatty acids triggers fatty acid oxidation, the formation of intracellular lipid droplets, proliferation of MiaPaCa2 human pancreatic cancer cells and the growth of larger tumours in an orthotopic implantation model.²⁸ In the absence of a supply of additional exogenous fatty acids, mice with MiaPaCa2 implants showed a decrease in the size of inguinal and epididymal fat pads along with reduced plasma levels of fatty acids, consistent with increased fatty acid consumption.¹⁶

The results from studies in mouse models of pancreatic and other cancers suggest that upregulation of adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) in white adipose tissue is the major mechanism by which pancreatic cancer increases lipolysis (Fig. 2).^{16,25,29} One well-characterised mediator of increased pancreatic cancer-related lipolysis and weight loss in mice is the zinc- α 2-glycoprotein (ZAG), also termed lipid-mobilising factor (LMF).^{30,31} It is, however, mainly expressed by adipocytes as opposed to originating from pancreatic cancer cells and does not regulate the interaction between the tumour and the adipose tissue.^{32,33} Similarly, overexpression of the micro-RNA 378 in human adipose tissue promotes lipolysis by regulating key lipolytic regulators, including HSL and ATGL, in cachectic patients with pancreatic cancer and other gastrointestinal tumours.³⁴ The direct crosstalk between pancreatic tumour cells and adipocytes might depend on adrenomedullin contained in extracellular vesicles. Results from in vitro studies of human samples and studies in mice suggest that cancer-cell-derived exosomes are internalised by subcutaneous adipocytes into which they release their cargo—a specific ligand that activates the adrenomedullin receptor—leading to activation of the intracellular p38 mitogen-activated protein kinase (MAPK) signalling pathway and ultimately resulting in activation of HSL.³⁵

In addition to increased rates of lipolysis, pancreatic cancer prompts cachexia through increased energy expenditure caused by a phenotypic shift from white adipose tissue to brown adipose tissue, termed adipose tissue browning. Adipose tissue browning occurs as a result of an increased number of mitochondria, the iron content of which confers the brown colour. The metabolic hallmark of adipose tissue browning is the uncoupling of the electron transport chain across the inner mitochondrial membrane of adipocytes mediated by the expression of uncoupling protein 1 (UCP-1; thermogenin), which generates heat by uncoupling oxidative phosphorylation from ATP production.³⁶ In KPC and *Kras^{LSL-G12D/+} Trp53^{fl/fl}* mice, adipose tissue browning linked to increased UCP-1 expression occurs even before the onset of fat wasting.³⁷ Similarly, increased UCP-1 expression and a rise in body temperature occurs in patients with pancreatic cancer before the clinical manifestation of the disease.^{38,39} Interestingly, the mechanisms involved in pancreatic-cancer-induced lipolysis have also been implicated in the induction of adipose tissue browning. ZAG isolated from the urine of pancreatic cancer patients increased the expression of UCP-1 in wild-type mice, and ZAG exposure correlated with increased energy expenditure through increased UCP-1 expression in a dose-dependent

manner.^{31,40} Extracellular vesicles released by the cancer cells have again been identified as intermediaries between the tumour and the adipose tissue; mRNA sequencing of adipocytes exposed to pancreatic cancer-derived exosomes in vitro revealed activation of pathways associated with browning in addition to promotion of lipolysis, fibrosis and acute inflammation.³⁹

Pancreatic-cancer-related systemic inflammation

Systemic inflammation, characterised by increased levels of serum cytokines and acute-phase proteins, is exceedingly common among pancreatic cancer patients and is a well-established independent predictor of poor survival.^{37,41} Pro-inflammatory signals that arise from the interaction between a tumour and the immune system have been implicated in various pathomechanisms of cancer cachexia.² In the context of pancreatic cancer, several of these signals, especially interleukin (IL)-6 and tumour necrosis factor (TNF), have been linked to increased resting energy expenditure and cachexia.⁴¹ The correlation of various serum cytokine and acute-phase protein levels with the occurrence of cachexia is, however, inconsistent across several studies,^{42–48} suggesting that systemic levels of inflammatory markers ineffectively capture the degree to which inflammation contributes to the development of pancreatic cancer cachexia.

A mechanistic explanation for the discrepancy between different clinical observations might be the in vitro finding that some, but not all, pancreatic cancer cells directly express IL-6, which, in turn, triggers additional, local IL-6 expression by tumour-sensitised peripheral blood mononuclear cells (PBMC) in the liver.⁴⁹ Higher serum levels of IL-6 and a correlation with weight loss have also been linked to genetic polymorphisms in the *IL6* gene, which might explain differences between pancreatic cancer patients in terms of cachexia susceptibility.^{45,50}

Pancreatic cancer cells have also been identified as the source of other pro-inflammatory cytokines, including TNF, IL-1 β , IL-8 and the monocyte chemoattractant protein-1 (MCP-1/CCL2).^{51–53} Orthotopic pancreatic cancer xenograft models that lack an adaptive immune response have been used to investigate the association between the tumour secretome and systemic cytokine production. Tumour grafts were seen to alter cytokine production in splenic tissue, and these altered cytokine levels could be linked to the expression of atrophy-associated genes and muscle wasting, but patterns were not consistent between two different studies.^{54,55} Additionally, the expression of TNF and MCP-1 was locally increased in adipose tissue of patients with pancreatic cancer cachexia, highlighting the importance of localised immunopathology in affected peripheral tissues.⁵⁶ In summary, the immune-related mechanisms of pancreatic cachexia are complex and are likely to be heterogeneous across different patients.

Despite this complexity, dysregulation of some canonical intracellular pathways linked to cachexia underlies some of the effects that are mediated by cytokines associated with pancreatic cancer (Fig. 2). In skeletal muscle, pancreatic-cancer-derived IL-6 induces muscle fibre atrophy and exacerbates wasting through activation of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT3) pathway.⁵⁷ When complexed with endogenous soluble IL-6 receptor, IL-6 secreted by tumour cells induces autophagy of differentiated myocytes and, consequently, sarcopenia.⁵⁸ Independent of IL-6, TNF or interferon γ (IFN γ) can activate JAK/STAT3 signalling in myocytes in vitro and in experimental mouse models, which promotes activation of the inducible nitric oxide synthase (iNOS)/nitric oxide (NO) pathway through nuclear factor (NF)- κ B,⁵⁹ leading to sarcopenia. Activation of iNOS reduces myogenesis by general downregulation of protein synthesis and specifically downregulates the transcription of MyoD, a regulator of muscle renewal and maintenance.⁶⁰ Additionally, TNF and IFN γ promote muscle wasting by upregulating the expression of ubiquitin and muscle-specific E3 ligases,

which catalyse ubiquitination of the heavy chain of the muscle motor protein myosin and its breakdown in the proteasome.⁶¹

In white adipose tissue, IL-6 secreted by infiltrating macrophages can trigger browning and moderately increased energy expenditure by inducing UCP-1. This effect is enhanced when IL-6 synergises with β -adrenergic activation, a hallmark of acute or chronic stress, linking inflammation with central stimuli.³⁸ Some of the catabolic effects of IL-6 on white adipose tissue are also mediated through the JAK/STAT3 pathway and NF- κ B, as specifically demonstrated in the *Kras*^{LSL-G12D/+} *Ink4a/Arf*^{fl/fl} *Pdx1*^{Cre/+} mouse model.⁶² Although similar to the signalling pathways involved in muscle wasting and a probable integrator of several inflammatory signals, exactly how STAT3 induces lipolysis is unknown.⁶³

Systemic inflammation is also linked to cancer cachexia through a loss of appetite and reduced caloric intake mediated by downregulation of neuropeptide Y (NPY) and the agouti-related protein (AgRP), important anabolic signals in the central nervous system. Pro-inflammatory cytokines including TNF and IL-1 β are overexpressed in the hypothalamus of cachexia models,^{64,65} in particular, IL-1 β has been implicated in the direct inhibition of NPY expression.⁶⁶ Cytokines also induce proopiomelanocortin (POMC) and cocaine-and-amphetamine regulated transcript (CART), two anorexigenic signals in hypothalamic neurons.⁶⁷ The indirect pathophysiological signals that link inflammation to anorexia are complex and include the effect of cytokines on feedback loops that involve the hormones leptin and ghrelin, which regulate appetite through NPY/AgRP and POMC/CART signalling in the hypothalamus.⁶⁸

Observational studies also suggest that elevated levels of pro-inflammatory cytokines, particularly IL-6, correlate with depression.^{69,70} Speculatively, increased levels of inflammatory signals could therefore provide a mechanism for the occurrence of depression prior to a pancreatic cancer diagnosis.⁷¹ Depression, in turn, is an important risk factor for insufficient nutritional intake and weight loss.⁷²

TGF- β and other tumour-related soluble factors

Transforming growth factor β 1 (TGF- β ₁) has a key regulatory function in the tumour microenvironment of pancreatic cancer and regulates some of the hallmarks of this cellular milieu, including the induction of desmoplasia and immunosuppression through T regulatory cells.^{73,74} High doses of TGF- β ₁ can trigger experimental cachexia and systemic fibrosis in mice.⁷⁵ In skeletal muscle, these effects are mediated by the induction of proteolysis through the E3 ligase atrogin-1 and induction of the transcription factor scleraxis, which stimulates fibroblast proliferation and collagen synthesis (Fig. 2).⁷⁶ Blockade of TGF- β _{1,3} ameliorates muscle wasting in the KPC pancreatic cancer model and, of note, also improves the preservation of adipose tissue and bone density, indicating additional relevant effects of TGF- β signalling in the development of cachexia.⁷⁷

Other members of the TGF- β superfamily, including activins and myostatin, have been implicated in muscle wasting through activation of the canonical Smad2/3 pathway, which decreases Akt/mTOR-mediated protein synthesis in addition to increasing ubiquitin ligase-mediated proteolysis and promoting a fibrotic response.^{78,79} Specific isoforms of activin are overexpressed and secreted by human pancreatic cancer cells and in the KPC pancreatic cancer model, and elevated serum levels and increased expression of activins in peripheral tissues have been found in cachectic KPC mice. Interestingly, the Smad2/3 pathway was dispensable for pancreatic-cancer-related activin-induced muscle wasting, which depended on an alternative p38 MAPK catabolic pathway instead.⁸⁰

Serum levels of MIC-1 (macrophage inhibitory cytokine-1), another member of the TGF- β superfamily, are significantly elevated among patients with pancreatic cancer.⁸¹ MIC-1 triggers

anorexia through the TGF- β receptor II expressed on hypothalamic neurons, as well as dysregulation of NPY/AgRP and POMC/CART using a similar effector mechanism as pro-inflammatory cytokines.⁸²

Additional pancreatic-cancer-derived factors

In addition to pro-inflammatory cytokines and members the TGF- β superfamily, several other pancreatic-cancer-derived factors stimulate protein catabolism. Proteolysis-inducing factor (PIF) is a glycoprotein specifically associated with cancer cachexia.⁸³ PIF activates NF- κ B to upregulate the ubiquitination and proteolysis of skeletal muscle and decreases protein synthesis by phosphorylation of the transcription factor eIF2 α .^{84–86} Serum levels of PIF are significantly increased among pancreatic cancer patients with weight loss independent of the level of inflammation markers.⁸⁷ However, the secretion of PIF by pancreatic cancer cells promotes the production of IL-6, IL-8 and acute phase proteins in the liver in a STAT3- and NF- κ B-dependent fashion, potentially co-operating with the detrimental effects of pancreatic-cancer-related inflammation.⁸⁸

Another tumour-derived factor that contributes to pancreatic cancer cachexia is the insulin-like growth factor (IGF)-binding protein-3 (IGFBP-3). IGFBP-3 targets myoblast renewal by inhibiting the expression of MyoD and another promyogenic transcription factor, myogenin, and enhances muscle proteolysis by suppressing the PI3K/AKT pathway.⁸⁹

Tumour-derived extracellular vesicles are increasingly recognised as vehicles of molecular cargo that induce skeletal muscle wasting, similar to their role in the upregulation of lipolysis. Extracellular vesicles from pancreatic cancer cells promote apoptosis in myoblasts by the intracellular delivery of miRNAs that stimulate Toll-like receptor (TLR) 7 to activate c-Jun N-terminal kinase activity.⁹⁰ Tumour-derived extracellular vesicles also promote muscle catabolism by releasing Hsp70 and Hsp90 extracellularly, which activate TLR4 and promote muscle wasting in a mouse model, although the relevance of this mechanism in pancreatic cancer cachexia is unknown.⁹¹

ALTERATIONS OF PANCREATIC FUNCTION

The pancreas has a dual exocrine and endocrine function. It secretes lipases, proteases and amylase, which are crucial for the breakdown of macromolecules and nutrient uptake in the gut, and controls glucose homeostasis through the hormone's insulin and glucagon. Pancreatic exocrine insufficiency (PEI), in which insufficient levels of pancreatic enzymes are produced, affects two-thirds of patients with pancreatic head tumours at diagnosis, and over the course of the disease this number increases to more than nine out of ten patients.⁹² Patients with PEI can develop malnutrition owing to insufficient caloric uptake and different deficiencies of essential amino acids and various micronutrients including lipophilic vitamins, iron and folic acid. Similarly, three-quarters of patients with pancreatic cancer have compromised endocrine function at diagnosis, characterised by impaired glucose tolerance or overt diabetes.⁹³ Tumour surgery, especially pancreatoduodenectomy, is also an important cause of iatrogenic PEI among pancreatic cancer patients.^{94–96} However, in contrast to exocrine function, endocrine function frequently improves after tumour resection if the patient had poor glucose control prior to surgery.^{97–99}

Pancreatic cancer, PEI and cachexia

Pancreatic cancer can induce PEI directly by affecting the pancreatic tissue as well as indirectly by undermining the physiological regulation of pancreatic secretion.¹⁰⁰ Pancreatic head tumours commonly obstruct the pancreatic duct, thereby blocking the secretion of pancreatic enzymes necessary to break down nutrients in the intestine. Pancreatic cancer also induces a

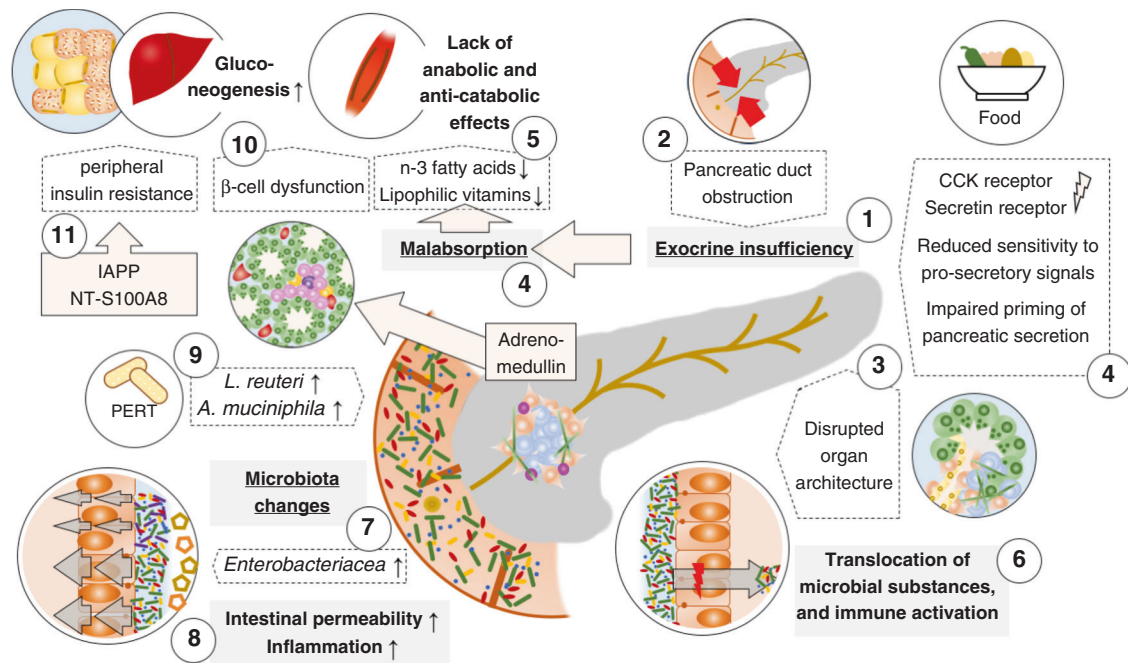


Fig. 3 Impaired pancreatic exocrine and endocrine function interact with alterations in the digestive tract to promote pancreatic cancer cachexia. Pancreatic cancer induces pancreatic exocrine insufficiency (PEI) (1) through obstruction of the pancreatic duct (2) or disruption of the organ architecture (3) as well as an altered physiological function, i.e. a reduced sensitivity to the pro-secretory signals secretin and cholecystikinin (CCK) resulting in an impaired priming of the pancreatic (4). PEI results in malabsorption of nutrients including lipophilic vitamins and n-3 fatty acids which results in insufficient caloric uptake and a lack of anabolic or anti-catabolic signals (5). PEI, in combination with changes of the histological architecture of the pancreas, also leads to excess bacterial growth in the duodenum and the translocation of bacteria and bacterial components into the tumour with implications for the immune tone (6). Pancreatic cancer is associated with specific changes of the gut microbiota and outgrowth of *Enterobacteriaceae* (7), particularly *Klebsiella*, is associated with increased intestinal permeability and systemic inflammation linked to the development of cachexia (8). Pancreatic enzyme replacement therapy (PERT) counteracts cancer-related dysbiosis and promotes the abundance of *Lactobacillus reuteri* and *Akkermansia muciniphila* which potentially reduce muscle wasting and increase the anti-tumoural immune response, respectively (9). Changes of the endocrine function of the pancreas comprise tumour-derived local adreno-medullin that reduces the Insulin secretion from islet cells in the pancreas (10) and an increase of peripheral insulin resistance through pancreatic-cancer-induced secretion of the islet amyloid polypeptide (IAPP) from β -cells and likely an increase of the S-100A8 N-terminal peptide (11). Endocrine dysregulation is also associated with increased gluconeogenesis (12), which depletes peripheral tissues to maintain the altered glucose utilisation.

characteristic intra- and peri-tumoural stroma that is enriched in extracellular matrix and deficient in cells and blood vessels that are able to replace functional pancreatic tissue.¹⁰¹ Moreover, the microscopic architecture of the pancreatic lobules is often disrupted, especially in pancreases with tumours that arise from precursor lesions (Fig. 3).¹⁰²

Pancreatic secretion is initiated through the parasympathetic nervous system during food intake.¹⁰³ Following food intake, distention of the duodenal wall and the passage of nutrients into the duodenal lumen trigger the release of secretin and cholecystikinin (CCK), which stimulate the secretion of alkali from pancreatic ducts and enzymes from pancreatic acinar cells.^{104,105} Perineural invasion is a histopathological hallmark of pancreatic cancer, and invasion of sympathetic nervous fibres by tumour tissue is central to cancer pain.¹⁰⁶ Analogously, parasympathetic denervation due to tumour infiltration could contribute to PEI through disruption of the physiological priming of the pancreas. Histological studies of healthy pancreatic tissue and specimens from patients with pancreatic cancer, however, showed that parasympathetic innervation was largely unchanged despite severe a reduction in the number of sympathetic fibres.¹⁰⁷ This suggests a minor role for neural remodelling as a result of tumour infiltration in tumour-associated PEI.

In contrast to the relatively minor impact of pancreatic tumours on parasympathetic innervation and, consequently, pancreatic secretion, disruption of hormonal regulation appears to affect pancreatic secretion, and patients with pancreatic ductal

adenocarcinoma express alternatively spliced secretin receptor isoforms with reduced secretin-binding capacity.¹⁰⁸ Similarly, plasma levels of CCK are comparable between patients with pancreatic cancer and non-cancer patients but CCK receptors are differentially expressed in the healthy pancreas and pancreatic cancer.^{109,110} Although the functional activity of CCK signalling in healthy humans is controversial,¹¹¹ these differences suggest that reduced tissue sensitivity to pro-secretory signals rather than altered hormone levels due to anatomical alterations of the GI-tract contribute to cancer-associated PEI (Fig. 3).

Regardless of the underlying mechanisms of PEI, compromised pancreatic exocrine function in the context of pancreatic cancer is associated with a significantly increased loss of muscle mass. In a prospective radiological cohort study of 132 patients with pancreatic disease, of whom 59 had pancreatic cancer, sarcopenia was strongly associated with PEI.¹¹² A similar effect exists in mice, which is dependent on the presence of the tumour in the pancreas, and heterotopic tumour transplants failed to initiate cachexia. In this model, tissue wasting could be attenuated by pancreatic enzyme replacement, which indicates a direct link between the pancreatic tumour, decreased exocrine function and cachexia.¹¹³

A lack of digestive enzymes causes malabsorption, thereby reducing the uptake of macronutrients to provide energy, and is characterised by bloating and diarrhoea, which further reduce appetite and oral intake.¹¹⁴ Moreover, among the nutrients that are taken up—the extent of the uptake of which is determined by

the exocrine pancreatic function—essential fatty acids and lipophilic vitamins have additional significance for pancreatic cancer cachexia.¹⁰⁰ In a small cross-sectional study, the levels of several essential n-3 polyunsaturated fatty acids in the plasma of patients with newly diagnosed pancreatic cancer were reduced compared with those in patients with gastro-oesophageal or non-small cell lung cancer, unless these patients had weight loss.¹¹⁵ In accordance with this observation and the early occurrence of other metabolic changes, altered plasma levels of n-3 polyunsaturated fatty acids were identified as potential predictors of the risk of developing pancreatic cancer.¹¹⁶ In addition, n-3 polyunsaturated fatty acids also appear to have direct anabolic and anti-catabolic effects on peripheral tissues, including improved insulin sensitivity as well as a reduced acute-phase response and inhibition of the ubiquitin-proteasome proteolytic pathway, which counteracts skeletal muscle wasting.¹¹⁷ Thus, the reduced levels of n-3 polyunsaturated fatty acids in the plasma of patients with newly diagnosed pancreatic cancer might be expected to bring about catabolic and anti-anabolic effects. These effects have, however, not been studied in detail in the context of pancreatic cancer and results from Phase 3 clinical trials call into question whether or not n-3 polyunsaturated fatty acids are relevant for the survival of cancer patients.¹¹⁸

Observational studies of patients with chronic pancreatitis have shown associations between PEI and decreased serum levels of α -tocopherol, the main component of vitamin E, and of vitamin D metabolites.^{119,120} However, the underlying cause of PEI might be relevant here because patients with pancreatic cancer showed altered serum levels of only vitamin D, not of vitamin E.¹²¹ Unfortunately, the 103 patients in this cohort study were heterogeneous across various disease stages, which might have confounded the results. Moreover, vitamin D deficiency is highly prevalent among cachectic patients with other primary tumours.¹²² Therefore, it is unclear whether or not some of the mechanisms that contribute to dysregulation of lipophilic vitamin homeostasis are specific for pancreatic cancer. Reduced levels of vitamin D have been implicated in reduced muscle strength with underlying mechanisms that might promote cachexia in rodents.¹²³ Briefly, reduced vitamin D levels are likely to trigger the overexpression of the vitamin D receptor (VDR) on muscle cells, which is associated with compromised muscle regeneration.¹²⁴ However, relatively little is known about the regulation of this process and it has not been studied specifically for pancreatic cancer. Vitamin E has been implicated in the pathogenesis of cachexia because of its antioxidative properties, which limit inflammation, but the evidence is generally weak.¹²⁵

Alterations of pancreatic endocrine function

The development of diabetes mellitus, accompanied by weight loss, often precedes pancreatic cancer by months to years.¹²⁶ Analogous to Type 2 diabetes, pancreatic-cancer-induced diabetes develops as a consequence of impaired β -cell function and peripheral insulin resistance.¹²⁷ These effects are considered to be mediated by tumour-cell-secreted paraneoplastic factors. The ensuing metabolic changes associated with pancreatic cancer promote weight loss, but this weight loss is not associated with the improvement in glucose control that usually occurs in Type 2 diabetes patients who lose weight.¹²⁷ The underlying mechanisms of this observation are likely to be complex, but paradoxical weight loss might at least be partially mediated by tumour-secreted adrenomedullin, which both stimulates lipolysis and induces β -cell dysfunction (Fig. 3).^{128,129}

Peripheral insulin resistance has been suggested to be mediated by the S-100A8 N-terminal peptide, which was identified in the plasma proteome of pancreatic cancer patients with diabetes.^{130,131} In vitro, this peptide reduced glucose catabolism in myoblasts but its exact connection to peripheral insulin resistance is still unclear.¹³² Pancreatic-cancer-induced secretion of the islet

amyloid polypeptide (IAPP) from β -cells is another potential mediator of peripheral insulin resistance,^{133,134} reducing insulin sensitivity in vivo and glycogen synthesis in vitro. Irrespective of the particular factor that mediates pancreatic-cancer-induced peripheral insulin resistance, the mechanisms associated with it involve altered gene expression downstream of the insulin receptor, which decreases glycogen synthesis and storage despite a normal expression of glucose transporters.¹³⁵ In the liver, lack of insulin from β -cells and insulin resistance, in addition to depletion of glycogen storage, also lead to a reduced inhibition of gluconeogenesis which, through the Cori cycle, consumes pyruvate from increased fat oxidation and depletion of adipose tissue.¹³⁶

DIGESTIVE-TRACT-RELATED FACTORS

The pancreas is located anatomically close to the gastrointestinal tract and linked to it through an essential role for digestion. Pancreatic cancer can affect the structure of other digestive organs or indirectly alter the physiology of the gut—factors that are increasingly recognised to contribute to pancreatic cancer cachexia.

Gastric outlet obstruction

The development of a pancreatic tumour can affect adjacent digestive organs through infiltrative growth or external compression. Some studies investigating surgical and interventional strategies to manage gastric outlet obstruction, usually of the duodenum, have estimated a prevalence of 5–10% in patients with newly diagnosed pancreatic cancer. Gastric outlet obstruction can cause nausea and vomiting and other consequences of impaired oral intake including dehydration, malnutrition and weight loss.^{137,138} In a proportion of patients, these effects might contribute to the cachexia phenotype through poor nutrition.

Microbiota and pancreatic cancer cachexia

The pancreas and gastrointestinal tract reciprocally influence each other even without direct tumour involvement, and major changes in the systemic metabolism result from this cross-talk. The microbiota is a central mediator of this interaction and its role in cancer and has been studied extensively in various tumour types.¹³⁹ The pancreas is located at the point at which the oral microbiota and the gut microbiota meet, and dysbiosis in either microbial population has been implicated in the development of pancreatic cancer.^{140–142} Significantly increased differential abundance of the genus *Klebsiella* and other *Enterobacteriaceae* characterises certain patterns of the human gut microbiome that are associated with pancreatic cancer and favour its progression.^{142,143} Enteric bacteria can also translocate into the pancreas and are present in healthy pancreatic tissue, pancreatic cysts and tumours,^{144,145} albeit as different populations of different species—accordingly, characterisation of bacterial 16S ribosomal DNA identified distinct microbial patterns that distinguished cancer from healthy tissue.¹⁴⁴ *Enterobacteriaceae* and other bacteria of the phylum *Proteobacteria* are also major constituents of the intratumoural microbiome in human pancreatic tumours, although substantial variation does exist between individuals.^{142,144} Inflammation that results from the outgrowth of the Gram-negative *Enterobacteriaceae* family in the gut (particularly *Klebsiella oxytoca*), has been associated with increased intestinal permeability, bacterial translocation to mesenteric lymph nodes, increased systemic inflammation markers and the development of cachexia in mice.^{146,147} However, in KPC mice with metastatic tumours, the increased abundance of likely resistant *Enterobacteriaceae* occurring after treatment with broad-spectrum antibiotics was associated with a polarisation of the tumour microenvironment towards helper T (T_H 1) cells/cytotoxic (T_C 1) cells and attenuation of tumour growth.¹⁴³

Moreover, *Enterobacteriaceae* also appear to be characteristic of the gut microbiome of naturally slow-progressing cases of pancreatic cancer in KPC mice.¹⁴² Therefore, the exact significance of the microbiome changes for pancreatic cancer cachexia in the context of overall disease progression as well as related immune mechanisms are still unclear.

The way in which pancreatic cancer influences the gut microbiome largely involves the exocrine function of the pancreas. PEI is associated with small intestinal bacterial overgrowth, a syndrome that comprises excess bacterial growth in the duodenum, jejunum and ileum, microbial imbalance and the translocation of bacteria into the pancreas.¹⁴⁸ In mice, supplementation of pancreatic enzymes alters the composition of the intestinal microbiome and promotes the abundance of *Lactobacillus reuteri* and *Akkermansia muciniphila*.¹⁴⁹ *L. reuteri* attenuates muscle wasting when fed to *Apc*^{Min/+} mice that are prone to cancer cachexia (albeit not a pancreatic cancer model) and *A. muciniphila* is linked to the systemic immune tone in cancer patients by inducing, educating and tuning the immunological balance between responsiveness and sustained tolerance towards increased effectiveness of programmed cell death protein (PD)-1/programmed death-ligand (PD-L)-1 through increased recruitment of T_H1 cells to the tumour.^{150,151} Other evidence suggests that antibacterial peptides secreted from the acini, rather than pancreatic enzymes, are involved in shaping the gut microbiome and limiting bacterial outgrowth; loss of acini function leads to gut inflammation, problems with weight gain and death (Fig. 3).¹⁵²

Notably, nonspecific disruption of the gut microbiota of cancer-free mice can result in decreased physical endurance.¹⁵³ However, the animals show no morphological signs of muscle loss and the phenomenon appears to involve impaired expression of intestinal nutrient transporters and reduced glycogen availability in the muscle.¹⁵³ Alterations of the gut microbiota also broadly affect the blood metabolome, especially amino acid metabolites.¹⁵⁴ Although not well-characterised in the context of weight loss, microbiomes from obese donors differed from those of lean donors specifically in the abundance of genes related to glutamine/glutamate transport and BCAA degradation, which corresponded to reduced serum glutamine levels and higher serum concentrations of BCAA. In addition, gavage of mice with *Bacteroides thetaiotaomicron* (which is dominant in the human gut microbiota but decreased in obese individuals) increased the expression of genes involved in lipolysis and fatty acid oxidation of white adipose tissue in the host.¹⁵⁵ Conclusions for cancer cachexia should only be made with great care, but the knowledge that pathogenic microbiomes can directly affect fat tissue through metabolic pathways that are also crucial to the pathophysiology of the pancreatic-cancer-associated loss of body mass is exciting.

IMPLICATIONS FOR CLINICAL INTERVENTIONS

A large spectrum of therapeutic approaches that target various aspects of the different dimensions of pancreatic cancer cachexia have been suggested, some of which are outlined below. Unfortunately, failure of cachexia-directed treatment is common, and amelioration or reversal of pancreatic cancer cachexia remains a major clinical challenge.^{156,157}

Nutritional strategies to counter metabolic changes

Nutritional counselling to ensure adequate energy and protein intake and, if indicated, supplemental or complete artificial nutrition is the mainstay of cancer cachexia therapy.¹⁵⁸ Modifications of volitional nutrition constitute the typical primary interventions against cancer cachexia and the most common class of cachexia treatment in clinical trials.² Although provision of sufficient caloric intake is a generic strategy to address cachexia, several nutritional supplements also target the specific metabolic

changes that are involved in pancreatic cancer cachexia, as outlined below.

A high-fat, low-carbohydrate diet (a ketogenic diet) that generates ketone bodies might act against cancer cachexia by inducing systemic metabolic changes, and treatment with ketone bodies (sodium hydroxybutyrate and lithium acetoacetate) was able to reduce glycolytic flux and glutamine catabolism in a pancreatic cancer model.¹⁵⁹ Supplementation with glutamine together with arginine and β -hydroxy- β -methylbutyrate is likely to shift the metabolic equilibrium away from proteolysis as a source of glutamine and positively support protein synthesis, and this supplementation significantly increased fat-free mass in a cohort of patients with advanced cancers, among them a minority of pancreatic cancer patients.¹⁶⁰ However, supplementation with excess quantities of glutamine is generally not recommended because of concerns regarding potential adverse effects of glutamine on other biochemical pathways such as compromised distribution of other amino acids that use the same transporter and excess glutamate and ammonia production.^{158,161} The ketogenic BCAA leucine and its metabolite β -hydroxy- β -methylbutyrate, which are often used in conjunction with glutamine supplementation, can stimulate muscle protein synthesis through anabolic signalling mediated by the mTOR pathway and inhibition of proteolysis by the reduced expression of proteasome components and ubiquitin ligases.^{162–164} Accordingly, results from several prospective trials indicated that both BCAA and β -hydroxy- β -methylbutyrate improved the protein metabolism of cachectic patients.^{160,165,166} Unfortunately, a Phase 3 trial of β -hydroxyl β -methyl butyrate, glutamine and arginine suffered from poor protocol adherence and failed to reach its primary endpoint of an improvement of lean body mass.¹⁶⁷

Another nutritional intervention that has been extensively investigated is supplementation with n-3 fatty acids, which inhibit proteolytic pathways, preserve protein biosynthesis and inhibit lipolysis.¹⁶⁸ In small non-randomised cohorts of pancreatic cancer patients, n-3 fatty acid supplementation was associated with a moderate but persistent weight gain.^{169,170} This observation was corroborated in a randomised, double-blind trial in which sufficient intake of n-3 fatty acid resulted in weight gain, lean body mass and improved quality of life.¹⁷¹

Targeting of pancreatic cancer cachexia-related inflammatory pathways

Insufficient evidence exists to support the unimodal blockade of inflammatory pathways to alleviate pancreatic cancer cachexia. Nevertheless, an improved understanding of the immunopathology of cachexia as well as studies exploring the combination of immunomodulation in a multimodal approach might warrant re-evaluation.²

Through the synthesis of prostanoids, cyclo-oxygenase-2 (COX-2) induces IL-6 and regulates the expression of TNF,^{172,173} and COX-2 metabolites have been directly implicated in the regulation of muscle turnover.¹⁷⁴ In two small Phase 2 trials, cachexia patients with different malignancies, the majority of which were upper gastrointestinal cancers, were treated with the selective COX-2 inhibitor celecoxib, resulting in weight gain and improved QoL scores.^{175,176} Another Phase 2 trial that predominantly included patients with pancreatic cancer with weight loss (49/73) reported that the combination of megestrol acetate, a synthetic derivative of progesterone, to stimulate appetite, and the nonselective COX-inhibitor ibuprofen reduced weight loss and improved QoL.¹⁷⁷ Megestrol acetate alone has been extensively studied as an appetite stimulant to counter anorexia in patients with hormone-insensitive tumours but has not been shown to affect body weight in patients with gastrointestinal cancer.¹⁷⁸ Analogous to COX-2 inhibition, thalidomide, an inhibitor of TNF synthesis, has been shown to reduce weight loss and loss of lean body mass in patients with cachexia and advanced pancreatic

cancer.¹⁷⁹ By contrast, however, a placebo-controlled Phase 2 trial of infliximab, a monoclonal antibody against TNF, did not demonstrate any significant improvements in lean body mass, endurance or survival.¹⁸⁰ Similarly, an exploratory analysis of body weight and QoL in two randomised trials of the JAK1/JAK2 inhibitor ruxolitinib were terminated after interim analyses failed to uncover any clinically relevant benefits in the inhibition of the JAK/STAT pathway.¹⁸¹

In a multimodal feasibility study of patients with pancreatic cancer cachexia, supplementation with n-3 polyunsaturated fatty acids plus celecoxib, together with exercise, was associated with a trend towards better preservation of body mass, and this approach is currently being tested in an adequately powered Phase 3 trial.^{182,183} Physical exercise alone has previously been shown to improve muscle strength in patients with pancreatic cancer but appears to have little effect on body weight without additional interventions.¹⁸⁴

Targeting other mediators of pancreatic cancer cachexia

Anamorelin, an agonist of the ghrelin receptor, improves anorexia and addresses the hypothalamic effects of systemic inflammation, and was found to improve appetite, lean body mass and body weight in patients with gastrointestinal cancer in a small non-randomised trial.¹⁸⁵ Similarly, cannabinoids paradoxically activate hypothalamic POMC neurons through cannabinoid receptor 1 (CB₁R), which results in a selective increase in the expression and release of β -endorphin and an appetite-stimulating effect.¹⁸⁶ The orally active cannabinoid Δ -9-tetrahydrocannabinol (dronabinol) was shown to mitigate anorexia in a randomised Phase 3 trial of a mixed population of cachectic cancer patients containing a substantial proportion of individuals with gastrointestinal cancers. However, the effects of dronabinol were inferior to those of megestrol acetate, and dronabinol did not confer an additional benefit when both drugs were combined.¹⁸⁷

Similarly, targeting members of the TGF- β superfamily has not been effective. In a Phase 2 trial of patients with advanced pancreatic cancer, the combination of a myostatin antibody with standard-of-care chemotherapy for advanced pancreatic cancer failed to confer additional clinical benefits (the primary endpoint was overall survival).¹⁸⁸

To address the potential significance of altered neurosignalling or depression for pancreatic cancer cachexia, different classes of antidepressants could hypothetically be considered but have, to our knowledge, not been systematically evaluated. Mirtazapine, an atypical tetracyclic antidepressant, has been evaluated exclusively because of its capability to improve appetite with some signs of efficacy to stabilise weight in a small non-randomised trial of nondepressed patients with pancreatic cancer.¹⁸⁹

Pancreatic enzyme replacement therapy for PEI

Pancreatic enzyme replacement therapy (PERT) is the oral substitution of pancreatic enzymes to mitigate malabsorption and ensuing symptoms related to PEI. However, in a New Zealand retrospective study of 129 patients with metastatic pancreatic cancer who had symptoms that could be attributed to malabsorption, only 21% of patients were found to have received pancreatic enzyme replacement therapy.¹⁹⁰ A lack of adequate management of PEI and resulting dietary issues adversely affected the QoL of patients with pancreatic cancer, with a lack of routine dietary consultation, a perceived unwillingness of clinicians to prescribe enzyme therapy and insufficient clarity of dosing instructions being reported.¹¹⁴

This lack of clinical awareness is concerning, as several placebo-controlled studies have demonstrated that PERT improves parameters such as fat absorption and the frequency of bowel movements and supports weight stabilisation of patients with advanced pancreatic cancer.^{191–193} Moreover, PERT has also been

associated with prolonged survival.¹⁹⁴ Accordingly, UK multi-society guidelines for the management of patients with pancreatic cancer periampullary and ampullary carcinomas,¹⁹⁵ US NCCN guidelines on pancreatic adenocarcinoma,¹⁹⁶ the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on nutrition in cancer patients¹⁵⁸ and the United European Gastroenterology (UEG) recommendations for PEI¹⁹⁷ support the use of PERT for pancreatic cancer patients.

Management of endocrine insufficiency

Patients with pancreatic-cancer-related diabetes commonly require insulin therapy, and concomitant metformin therapy is encouraged to address peripheral insulin resistance.¹⁹⁸ In the liver, metformin also reduces hepatic gluconeogenesis through inhibition of mitochondrial glycerophosphate dehydrogenase, which limits the conversion of lactate and glycerol into glucose.¹⁹⁹ This effect might mitigate tumour-induced peripheral tissue wasting and metformin was able, in fact, to reverse sarcopenia in an experimental cancer cachexia model.²⁰⁰ It is therefore surprising that metformin treatment was associated with a trend towards a slightly more prevalent weight loss (12 versus 8%) and anorexia (37 versus 20%) and had no effect on overall survival in a double-blind placebo-controlled Phase 2 trial of 121 patients with advanced pancreatic cancer.²⁰¹

Microbiome

The microbiota has not been the target of strategies in clinical trials to modulate pancreatic cancer cachexia, although experimental approaches to minimise the overall gut microbiome with antibiotics¹⁴³ or to modulate its composition or diversity with probiotics²⁰² or faecal transplants²⁰³ to target pancreatic cancer exist. In a clinical setting, a more targeted elimination of detrimental bacteria than broad-spectrum antibiotics would likely be necessary to counter harmful effects of a broad depletion of the microbiota which has frequently been associated with poorer response of various cancers to treatment and shorter patient survival. Based on the available preclinical evidence supplementation of probiotics, especially *Lactobacillus*, might be an interesting approach to ameliorate pancreatic cancer cachexia but well-planned prospective trials would be needed to inform clinical practice.²⁰⁴

CONCLUSION

Pancreatic cancer cachexia is an exceedingly common problem that arises independent of the stage of pancreatic cancer. Reflecting the particular systemic effects of pancreatic cancer and the central role of the pancreas in the digestive tract, pancreatic cancer cachexia has three interacting dimensions that make up a complex syndrome: systemic metabolic changes and signals, often associated with *KRAS*-mutations; an impaired exocrine and endocrine pancreatic function; and alterations of the intestinal tract with a particular impact on the microbiome. A number of approaches to target some aspects of the different dimensions of pancreatic cancer cachexia, such as nutritional strategies, targeting inflammatory and other mediators of pancreatic cancer cachexia, and PERT, have been or are being studied. The interdependent nature of these dimensions also needs to be considered in the clinical management of patients with pancreatic cancer cachexia. There are several points of convergence between the three different dimensions—for example, immune state and exocrine insufficiency—that are attractive targets for development of therapeutic strategies and future research. Addressing these links—as exemplified by substituting exocrine pancreatic function with PERT—has significant potential to ameliorate cachexia and consequently improve the quality of life and prognosis of patients with pancreatic cancer.

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