

Inflammation and myosteatorsis in pancreatic cancer cachexia

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Impact

Relevance

Cancer cachexia is a multifactorial and devastating syndrome characterized by significant body weight loss including loss of skeletal muscle mass and fat mass that cannot be fully reversed by conventional nutritional approaches. Cancer cachexia is associated with muscle weakness, increased systemic inflammation, loss of appetite, increased therapy toxicity, poor quality of life, and reduced survival. Cachexia affects 50-80% of patients and is directly responsible for 20% of cancer deaths. Given that most pancreatic cancer patients present with locally advanced or metastatic disease already at the time of diagnosis due to a lack of symptoms in the early stages, pancreatic cancer patients have the highest prevalence (up to 80%) of cachexia, and experience loss of more than 10% of body weight on average. Although the clinical management and treatment of cancer have been considerably improved in the past decade, no effective treatment for cancer-associated cachexia has been identified. In addition, the mechanisms behind cancer associated-cachexia remain incompletely understood.

However, catabolic mediators released by cancer cells or immune cells appear to play a key role in the development of cancer cachexia. For instance, pro-inflammatory factors IL-6, TNF- α , and IL-1 β have been reported to induce lipolysis of adipose tissue and muscle atrophy both *in vitro* and *in vivo*. Although genetic deletion or pharmacologic inhibition of these factors ameliorates muscle wasting in mouse models of cancer cachexia, neutralization of single mediators has not been successful in overcoming cancer-associated cachexia in patients. Therefore, there is an urgent need for a better understanding of the underlying mechanisms of cancer cachexia to develop effective cachexia treatment.

Scientific impact

In this thesis, we first studied the association between systemic inflammation and the central complement factors as well as neutrophil activation markers in pancreatic cancer patients with or without cachexia. We revealed that systemic inflammation in patients with cancer cachexia was associated with the activation of key effector complement factors. Furthermore, a positive correlation between neutrophil activation markers and complement factors C3a and

TCC was observed in pancreatic cancer patients. Based on these observations, future studies should work out 1) the source of circulating complement proteins in cachectic patients; 2) systemic inflammation, complement activation and neutrophil activation, cause or consequence? 3) whether complement proteins are increased in skeletal muscle, adipose tissue as well tumor and what's the biological function of complement protein on these tissues. Secondly, no difference in circulating LCN-2 level was observed between cachectic PDAC patients versus non-cachectic PDAC patients, which differs from a previous study showing a significant higher circulating LCN-2 levels in cachectic mouse vs. non-cachectic mouse. Furthermore, LCN-2 levels of patients with normal versus reduced food intake were not different. In exploring the role of LCN-2 in regulation of appetite, these inter species differences deserve validation. Thirdly, nature and distribution of intramyocellular lipid species were assessed in pancreatic cancer patients with or without cachexia by combining LC-MS/MS-based lipidomics and MALDI-MSI. This multimodal approach provide a new approach for intramyocellular lipid metabolism research in the cachexia field, whereby differences in special localization of lipids species can be detected. Furthermore, using patient-derived pancreatic tumor organoids, we also showed that the pancreatic tumor organoid secretome promotes lipid accumulation in mature myotubes. The use of patient-derived organoids in co-culture systems may pave the way for future research on tumor-host communication and tumor immunology in cachexia. For instant, to study the effect of tumor organoids secretome on macrophage polarization.

Target groups

In this thesis, we focused on pancreatic cancer cachexia and showed a close relationship between inflammation, complement activation, neutrophil activation, and myosteatosis. The results as described in here can potentially benefit all types of cancer in which cancer cachexia has been proven to play a role. This would include patients with gastro-oesophageal cancer, head neck cancer, lung cancer, colorectal cancer, haematological cancers, breast cancer, and prostate cancer. Myosteatosis has been associated with insulin resistance, aging, obesity, type 2 diabetes [1] as well as poor prognosis in cancer patients [2], and our findings on the possible contribution of pro-inflammatory cytokines on myosteatosis provides novel insights into the

pathophysiological mechanisms underlying myosteatorsis which potentially also apply to these other fields. It could stimulate pharmaceutical companies to develop new drugs targeting tumor-derived pro-inflammatory cytokines for the treatment of myosteatorsis.

Societal impact

Pancreatic cancer remains one of the most lethal malignancies, with a five-year survival rate of around 5%. The risk factors for developing pancreatic cancer include aging, diabetes, and chronic pancreatitis. Both the incidence and mortality rate of pancreatic cancer continue to increase due to population growth and aging. According to the data from the Global Cancer Observatory, approximately 844,000 new pancreatic cancer cases will be diagnosed in the world in 2040, and pancreatic cancer will lead to about 801,000 deaths worldwide. To date, surgical resection remains the only curative option for patients with pancreatic cancer. However, only 15-20% of pancreatic cancer patients are initially eligible for surgery, and the five-year survival rate for these patients is poor at around 20% following surgery (in the USA). A study in a larger cohort collected between 2001 to 2010 has revealed that total healthcare costs for patients with pancreatic cancer (n=5,262) were higher than for controls (n=15,786) (person/month, \$15,480 vs. \$1001) [3]. In the same study, the healthcare costs were significantly higher during treatment of the metastatic stage compared to the initial treatment phase of non-metastatic disease (\$21,637 vs. \$10,358, $p < 0.001$) [3]. In general, cachectic patients had a longer hospitalization stay compared to non-cachectic patients (6 vs. 3 days), which also leads to a higher cost per stay (\$4641.30 higher) [4]. Therefore, a better understanding of the mechanisms underlying cancer cachexia as provided in this thesis could help pharmaceutical companies to develop new drugs against cancer-associated cachexia and benefit cachectic patients as well as reduce health care cost.

Anorexia (loss of appetite) is frequently associated with cancer, resulting in progressive weight loss (a key feature of cancer cachexia). A study in both drosophila and mouse tumor models revealed that anorexia could occur earlier than cachexia [5], suggesting that anti-anorexia treatment could be effective against the development of cancer cachexia. Several signals such as GDF-15-GFRAL, Dilp8/IINSL3 (insulin-like 3)-Lgr3/8 (leucine-rich repeat-containing G

protein-coupled receptor 3/8), as well as LCN-2-MC4R have been shown to suppress appetite in patients or experimental models of cancer cachexia. Therefore, the neutralization of these signaling mediators could be a potential therapeutic direction for treating the anorexia-cachexia syndrome. To date, several GDF-15 antibodies including CTL-002, NGM120, and PF-06946860 are tested in clinical trials with cancer patients against the anorexia-cachexia syndrome [6], but there are no approved available treatments for cancer-associated anorexia yet. Our study showed that circulating LCN-2 was not different between PDAC patients with normal and PDAC patients with reduced food intake, which should be noted before pharmaceutical companies develop antibodies to neutralize the LCN-2-MC4R signaling pathway against cachexia-associated anorexia. It is also worth mentioning that a trend toward increasing circulating LCN-2 was observed in malnourished patients. Given that LCN-2 is involved in intestinal and metabolic inflammation, and since gut barrier dysfunction and intestinal inflammation are associated with cachexia progression, it is tempting to speculate that circulating LCN-2 may contribute to development of cachexia by impairing nutritional uptake in the intestine.

One of the underestimated aspects of cancer cachexia is myosteatorsis (also known as fat infiltration in skeletal muscle), which is associated with decreased muscle quality and poor prognosis in cancer patients. Although previous studies have shown that intracellular lipid droplets increase with the development of cancer cachexia, the mechanism behind cancer-associated myosteatorsis remains poorly understood. In cancer patients, myosteatorsis can be assessed by using a CT image at the L3 vertebral level without extra financial burden because CT is commonly used in the clinic for identifying the tumor location in these patients. Therefore, CT-scan-based body composition analysis should be recommended to all cancer patients in the clinic. Patients with myosteatorsis have also been associated with increased risk of hospitalizations [7, 8]. A better understanding of the effect of tumor-derived factors as provided in this thesis could help to identify new therapeutic targets for myosteatorsis in cancer cachexia.

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