PKP
PUBLIC KNOWLEDGE PROJECT

Journal of Biological Studies
ISSN 2209-2560

JBS
An Open Access Peer Reviewed Journal

Review Full-Text Paper

Effect of IL6 on the cancer-associated cachexia: a mini review

Zahra Taheri*

Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran

Received: January 25, 2023; **Accepted:** February 10, 2023; **Published online:** May 10, 2023

Abstract: More than 20% of tumor patients die because of cancer-associated cachexia (CAC) which is considered a multifactorial syndrome that is characterized by loss of weight, adipose tissue, and skeletal muscle, as well as anemia, accompanied by systemic inflammation. CAC is associated with various agents including cytokines. IL-6 is one of the major proinflammatory and pleiotropic cytokines produced by several cell types which induces and blocks diverse signaling pathways related to cancers and their disorders. For instance, tumor-secreted IL6 is the main cytokine that dilapidated the adipocyte in CAC. IL-6 also plays an essential role in skeletal muscle loss. The involvement of IL-6 in cancer progression and metastasis emerges the hypothesis of its role as a prognostic factor or a treatment agent in CAC. So, with regard to the importance of CAC and its high incidence, it seems that a comprehensive study on the role and mechanism of action of IL-6 in CAC can fill the scientific gap in death resulting from CAC.

Keywords: IL6, Cancer-associated cachexia, Pancreatic cancer, Prognosis, Treatment

1 Introduction

More than 20% of cancer patients die from Cancer-associated cachexia which is a multifactorial syndrome that is characterized by loss of weight, adipose tissue, and skeletal muscle, as well as anemia, accompanied by systemic inflammation, leading to poor quality of life, chemoresistant, and short survival (Barton, 2001; Tisdale, 2000). There is no unique definition for cachexia but an unwanted loss of 5-10% of the pre-patience weight or skeletal muscle loss (less than 7.26 kg/m^2 for males and 5.45 kg/m^2 for females) during less than six months can be considered a cachexia indicator (Eskiler et al., 2019; Kotler, 2000; Pfitzenmaier et al., 2003; Tisdale, 2001). It seems that cancer cachexia occurs to long-term feeding suppression and metabolic deregulations as consequences of tumor byproducts and cytokine release

*e-mail: Zahra_taheri_2005@yahoo.com

(Kuroda et al., 2007). Cancer cachexia has been reported in around 80% of cancer patients in advanced stages (Han et al., 2019). Approximately, 33% of cancer patients are suffering from cancer cachexia but weight loss is associated with the tumor site. For instance, the greatest weight loss occurred in patients suffering from solid tumors such as head and neck, lung, and colorectal (50%), as well as pancreatic and gastric (85%) whereas only 30% of patients recognized with acute leukemia or breast cancer showed weight loss (Daou, 2020).

CAC is associated with various agents including cytokines. IL-6 is one of the major pleiotropic cytokines which controls various signaling pathways related to cancers and their disorders. For example, tumor-secreted IL6 is the main cytokine that dilapidated the adipocyte in CAC and plays a key role in skeletal muscle loss. The involvement of IL-6 in cancer progression and metastasis emerges the hypothesis of its role as a prognostic factor or a treatment agent in CAC. So, with regard to the importance of CAC and its high incidence, it seems that a comprehensive study on the role and mechanism of action of IL-6 in CAC can fill the scientific gap in death resulting from CAC.

2 IL6 as an inflammatory cytokines

Cytokines belong to a large family of pleiotropic polypeptides (Opal and DePalo, 2000) because of driving multiple cell types and various effects according to the target cells. Just after secretion, they control local or systemic intercellular communication in a paracrine, autocrine, or endocrine behavior. They also adjust the function of other cytokines and related receptors. Various cell types in different situations synthesize cytokines rapidly and transport them via systemic circulation. For example, IL-6 is one of the major proinflammatory and pleiotropic cytokines produced by multiple cell types which induces and blocks diverse signaling pathways (Daou, 2020; Pal et al., 2014).

3 The key role of IL-6-mediated signal transduction in skeletal muscles and CAC

IL-6 was considered an important proinflammatory cytokine in cancer because of its roles in tumor progression and metastasis (Fisher et al., 2011). Furthermore, IL-6 works as a protumorigenic agent in CAC. Based on a lot of investigations, systemic inflammation induced CAC (Evans et al., 2008) and skeletal muscle loss (Chen et al., 2016). CD4 regulatory T cells (Treg), neutrophils, tumor-associated macrophages (TAM), and myeloid-derived suppressor cells (MDSCs) (Schreiber et al., 2011; Swartz et al., 2012) secret IL-6 which leads to neoplastic progression (Naugler and Karin, 2008; Rose-John, 2012). Muscles and other tissues can also release IL-6 in a quick response to injuries as well as infections (Kishimoto, 2006).

IL-6 signal transduction occurs through two paths; classical signaling and trans-signaling. Classical signaling is activated by the membrane-bound IL-6 receptor- (IL-6R) production, principally on the surface of hepatocytes and some leukocytes. Then, the IL-6/IL-6R complex binds to the ubiquitous receptor glycoprotein 130 (gp130) subunit which leads to stimulation of

the Janus kinases (JAK) and the downstream agents STAT1, STAT3, Src homology region 2 (SH2)-containing protein tyrosine phosphatase 2 (SHP2), and PI3-kinase modulating cancer progression (Naugler and Karin, 2008). So, this pathway induces anti-inflammatory and pro-regenerative processes only in IL-6R-expressing cells (Carson and Baltgalvis, 2010; Serrano et al., 2008). But various cells release a soluble form of IL-6R (sIL-6R) which mobilizes the trans-signaling with proinflammatory as well as profibrotic implications (Rose-John, 2012). On the other hand, the trans-signaling pathway expands the IL-6-responsive cells to gp130-producing ones (Daou, 2020).

Moreover, the canonical IL-6/JAK/STAT renews skeletal muscle. Skeletal muscle proximately compromises 30 – 40% of a body mass of a healthy individual. Anabolic, as well as catabolic stimuli, controls muscle mass regulation (growth or wasting) (Serra et al., 2007; Wang et al., 2008). For example, cancer-associated skeletal muscle wasting includes different mechanisms like; diminished related protein synthesis and increased proinflammatory cytokines which elevate muscle proteolysis (Eley et al., 2007; Zoico and Roubenoff, 2002). Moreover, ovarian cancer and gastroesophageal cancer patients with CAC had elevated IL-6 (Daou, 2020).

4 The role of IL-6 in Adipocytes and CAC

Tumor-secreted IL6 is the main cytokine that dilapidated the adipocyte in CAC and is associated with lipid stores lipolysis to support cancer's fast metabolism. Petruzzelli et al. 2014, introduced IL-6 as the key lipolysis factor in white-to-brown transdifferentiation of adipose tissue (WAT browning). Moreover, Wang et al. 2017, reported IL-6 as the merely elevated lipolytic agent in tumor cells following co-culture, though treatment with anti–IL-6 monoclonal antibodies did not block lipolysis (Gyamfi et al., 2018; Han et al., 2019). In general, IL-6 was elevated in breast cancer patients (Gyamfi et al., 2018) and it was higher in non-small-cell lung patients suffering from weight loss than those without weight loss (Zhang et al., 2008). All of these data bold the importance of adipocytes in breast cancer progression as well as IL-6 in CAC (Gyamfi et al., 2018).

As malignant cells-derived IL-6 leads to cachexia, it could represent diagnostic or even therapeutic values for pancreatic ductal adenocarcinoma (PDAC). Rupert et al reported that adipose tissue in comparison to skeletal muscle responds more to PDAC or IL-6 (Rupert et al., 2021).

Adipose and muscle are other resources of IL-6. Muscle wasting could occur after adipose is lost. Because when fat was lost vigorously, lipids accumulated in muscle, mitochondria disordered, and the atrophy of myofiber happened (Rupert et al., 2021).

5 The role of IL-6 in cancer prognosis or treatments

Salgado et al. 2003 studied 96 patients suffering from progressive metastatic breast cancer before the systemic treatments and showed that serum IL-6 was related to a worse prognosis

(Kuroda et al., 2007). Furthermore, increased IL-6 is linked to CAC, angiogenesis, atrophy, enhanced degradation of muscle proteins, and resistance to therapy in advanced breast cancer (White, 2017). Breast cancer individuals with enhanced IL-6 compared to the healthy controls presented cachexia symptoms like weight loss (Liu et al., 2017a; Nariţa et al., 2011). Additionally, IL-6 and STAT3 were significantly higher in breast and gastric cancer individuals with and without cachexia than those in the healthy controls, and especially IL-6 mRNA was up-regulated in cachectic breast cancer. So, IL6- mediated STAT3 signal transduction could be considered an appropriate biomarker in cachectic patients with breast or gastric cancers (Eskiler et al., 2019).

IL-6 overexpression is also related to poor prognosis in various cancers such as prostate, gastric, colon, lung, breast, and brain malignancies through affecting transcription factors as well as cytoplasmic tyrosine kinases (Eskiler et al., 2019).

Based on a valuable investigation, the IL-6 blockade is a helpful strategy in the treatment of various inflammatory diseases (Kang et al., 2019). For example, a humanized anti-IL-6 antibody therapy in non-small-cell lung cancer patients was very safe and well tolerated (Bayliss et al., 2011). CAC therapy with anti-IL-6 antibodies or IL-6R counteracts muscle loss and increases the CAC patient's quality of life (Narsale and Carson, 2014). A blocker of MAPK1 and IL-6 secretion increased muscle weight in cholangio carcinoma patients (Daou, 2020).

6 Role of IL-6 in cancer patients with anemia

Chronic inflammation can lead to anemia via the defection of iron utilization in the erythropoiesis process via Hepcidin which is produced in hepatocytes of patients with inflammation through IL-6 induction. So, as patients with enhanced IL-6 might suffer from hepcidin-induced anemia, anti–IL-6 therapies could recover the anemia through hepcidin suppression in advanced PC patients (Miura et al., 2015).

7 Pancreatic cancer-associated cachexia

Despite a lot of knowledge about pancreatic cancer as the most lethal gastrointestinal one, cachexia reasons, which occurs in approximately 67% of all PC patients, remain unclear (Kitawaki et al., 2006). One of the important mechanisms is the deregulation of neurotensin, which regulates body weight. Another one is the deregulation of a protein and lipid mobilizing factor with an important role in CAC. Both of them occur as a result of cytokines deregulation, especially IL6. Moreover, 5,600 gene chip evaluations of resected human PC tissue showed a significant difference in IL-6 between non-cachectic and cachectic patients (Zhang et al., 2008).

IL-6 production depends on a variety of factors, like genetic factors. It has at least 5 promoter single nucleotide polymorphisms (SNPs); -597 (G/A), -572 (C/G), -174 (G/ C), -634 (C/G), and -190 (C/T) which have associations with some disorders such as lipid abnormalities (Zhang et al., 2008). In addition, the IL-6-634G allele was significantly overexpressed in the cachectic patients and patients with less overall survival. The serum IL-6 in cachectic patients

with PC was significantly higher than in non-cachectic ones. Additionally, resectable pancreatic adenocarcinoma patients with IL-6-634 CG or GG genotype experienced shorter overall survival than those with the CC allele (p = 0.023) (Zhang et al., 2008). IL6 with the role of pro-cachexia cytokines and factors is presented in Table 1.

Table 1. IL6 with the role of Pro-cachexia cytokines and factors

Cell_lines	description	References
Pancreatic adenocarcinoma, KPC cells	PDAC cells extracted adipocyte IL-6 and IL-6 as well as IL-6 receptor (IL6R) in myocytes and circulation. And IL-6 reduction from malignant cells cut adipose wasting and suppressed dysmetabolism, myosteatosis, and atrophy.	(Rupert et al., 2021)
Advanced pancreatic cancer	IL-6-related factors were advanced age ($P < 0.01$), the occurrence of liver metastasis ($P < 0.01$), the large volume of liver metastasis ($P < 0.01$), severe fatigue ($P = 0.02$), high carcinoembryonic antigen ($P = 0.02$), anemia ($P < 0.01$), and high C-reactive protein ($P = 0.02$) in multivariate analyses. Skeletal muscle loss was associated with high IL-6.	(Miura et al., 2015)
Pancreatic cancer	IL-6-634G allele is related to increased susceptibility to cachexia and decreased survival time of Chinese patients with pancreatic cancer.	(Zhang et al., 2008)
Pancreatic cancer	IL-6 represents a prominent cachexia-associated factor in pancreatic cancer. IL-6 overexpression in cachectic patients is associated with the ability of certain tumors to sensitize PBMC and promote cytokine in cachectic PBMC.	(Martignoni et al., 2005)
Advanced Uncertain cancer	IL-6 increases only gradually during the early stages of cachexia, followed by a sudden and steep rise just before death.	(Iwase et al., 2004)
Advanced prostate carcinoma	TNFα, IL-6, and IL-8 were increased significantly in the patients with advanced, cachectic patients compared with patients without cachexia. In the cachectic patients, TNFα was associated positively with IL-8, and there was no correlation between PSA levels and any of the cytokine levels.	(Pfitzenmaier et al., 2003)
Pancreatic cancer	The specificity of serum IL-6 in pancreatic cancer patients was estimated at 93.3%, resulting in acceptable diagnostic accuracy (72.0%) and among them, the detection rates of serum IL-6 elevated significantly with the disease extent ($p < 0.01$)	(Okada et al., 1998)

8 Role of IL-6 in PDAC patients with cachexia

PDAC is also one of the deadliest cancers, with a 5-year survival less than 9% (Siegel et al., 2019). Cachexia affects more than 80% of PDAC patients leading to more death (Hendifar et al., 2019). IL-6 affected PDAC and PDAC-related cachexia, PDAC progression (Ramsey et al., 2019), and its mortality (Babic et al., 2018). Though serum IL-6 is not always detectable in early PDAC nor always associated with cachexia degree (Rupert et al., 2021), IL-6 is enough to produce cachectic mice (Rupert et al., 2021).

9 Discussion and future perspective

Cancer cachexia is usually associated with systemic inflammatory response and adipose

degradation. Based on various studies, IL-6 was mainly linked with CAC. Furthermore, fat loss might accompany by CAC progress (Tsoli et al., 2016). Plasma Apolipoprotein E (ApoE) which significantly decreased in CAC patients is a component of very low-density lipoproteins (VLDL), chylomicrons (CM), and the remnants as well as β-VLDL. ApoE correlated with plasma triglyceride positively (Tao et al., 2014). ApoE is associated with lung cancer and is considered an appropriate biomarker for NSCLC patients suffering from lymph node metastasis (An et al., 2019). ApoE was also considered a novel PC marker without association with PC risk (Liu et al., 2017b). In Han et al study, plasma ApoE was under-expressed in CAC patients compared to non-CAC ones irrespective of gender and tumor kind, emphasizing its key role in the CAC process (Han et al., 2019).

Free fatty acid (FFA) considers a key agent in skeletal muscle, heart, liver, and pancreas as the primary fuel, hormone precursors, or non-hormonal signaling molecules. Analyzing CAC according to gender showed that FFA only enhanced significantly in women while serum IL-6 was significantly increased in both CAC men and women. So, a significant positive association between serum IL-6 and FFA only in CAC women was reported (not in men). This suggests that IL-6 as a primary agent in lipolysis induction in females with CAC, resulting in enhanced FFA (Han et al., 2019).

In this study, we generally found a central role for cancer–derived IL-6 in CAC with emphasis on PDAC and PC cachexia, cancer-tissue crosstalk via IL-6 and sIL6R signal transduction, cachexia mechanisms, as well as crosstalk between IL-6, fat, and muscle (Figure 1).

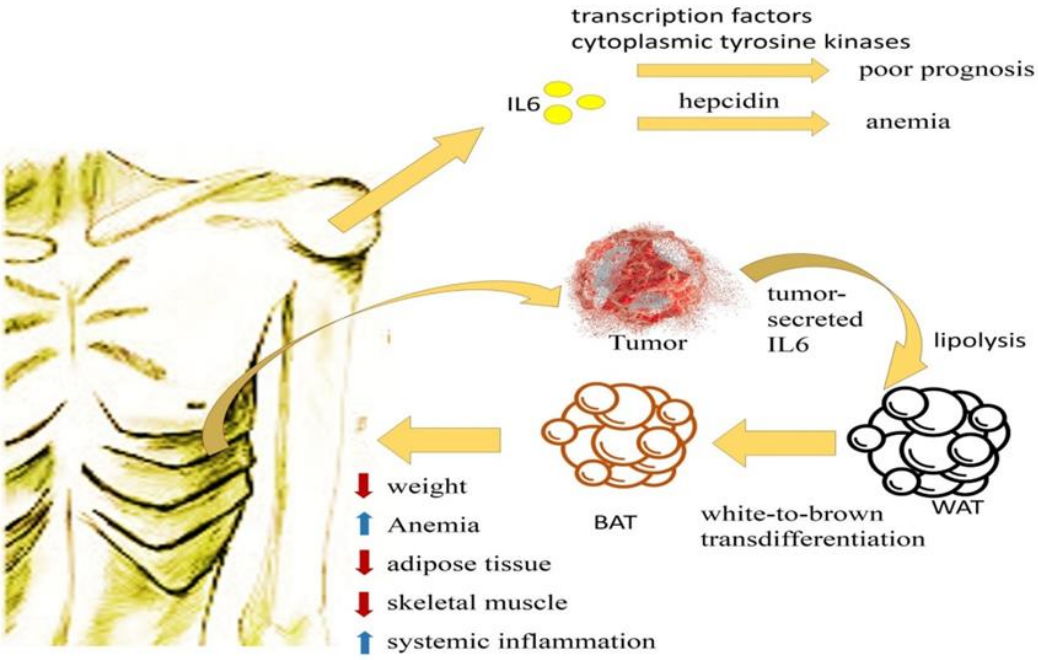

Figure 1. Mood of IL-6 in CAC

Indeed, IL-6 activity is associated with cachexia severity in PDAC patients. Alternatively, tissue IL-6 and its signaling agents might be more relevant as markers and more essential for

wasting onset. Moreover, cell-type synthesis of IL-6 might determine cachexia phenotypes. IL-6 secretion by myeloid cells and fibroblasts in the cancer microenvironment involves PDAC development, progression, metastasis, chemoresistance, as well as immunosuppression process. Because of the important role of inflammatory cytokines in chronic diseases, demonstrating their mechanism of action in future studies seems necessary.

Acknowledgments

Declared none.

Conflict of interests

The authors declare no conflict of interest.

References

An, H. J., Koh, H. M., & Song, D. H. (2019). Apolipoprotein E is a predictive marker for assessing non-small cell lung cancer patients with lymph node metastasis. *Pathology-Research and Practice, 215*(10), 152607. http://https://doi.org/10.1016/j.prp.2019.152607

Babic, A., Schnure, N., Neupane, N., Zaman, M., Rifai, N., Welch, M., & Yuan, C. (2018). Plasma inflammatory cytokines and survival of pancreatic cancer patients. *Clinical and Translational Gastroenterology, 9*(4), 145. http://10.1038/s41424-018-0008-5

Barton, B. E. (2001). IL-6-like cytokines and cancer cachexia: consequences of chronic inflammation. *Immunologic research, 23*(1), 41-58. http://https://doi.org/10.1385/IR:23:1:41

Bayliss, T. J., Smith, J. T., Schuster, M., Dragnev, K. H., & Rigas, J. R. (2011). A humanized anti-IL-6 antibody (ALD518) in non-small cell lung cancer. *Expert opinion on biological therapy, 11*(12), 1663-1668. http://https://doi.org/10.1517/14712598.2011.627850

Carson, J. A., & Baltgalvis, K. A. (2010). Interleukin 6 as a Key Regulator of Muscle Mass during Cachexia. *Exercise and Sport Sciences Reviews, 38*(4), 168-176. http://10.1097/JES.0b013e3181f44f11

Chen, J. L., Colgan, T. D., Walton, K. L., Gregorevic, P., & Harrison, C. A. (2016). The TGF-β signalling network in muscle development, adaptation and disease. *Growth Factors and Cytokines in Skeletal Muscle Development, Growth, Regeneration and Disease*, *900*, 97-131. http://https://doi.org/10.1007/978-3-319-27511-6_5

Daou, H. N. (2020). Exercise as an anti-inflammatory therapy for cancer cachexia: a focus on interleukin-6 regulation. *American Journal of Physiology-Regulatory Integrative and Comparative Physiology, 318*(2), R296-R310. http://10.1152/ajpregu.00147.2019

Eley, H. L., Russell, S. T., & Tisdale, M. J. (2007). Effect of branched-chain amino acids on muscle atrophy in cancer cachexia. *Biochemical Journal*, *407*(1), 113-120. http://https://doi.org/10.1042/BJ20070651

Eskiler, G. G., Güney Eskiler, G., Bezdegumeli, E., Ozman, Z., Ozkan, D. A., Deveci Özkan, A., Bilir, C., Bilir, C., Kucukakca, B. N., Ince, M. N., Men, A. Y., Aktas, O., Horoz, Y. E., & Akpinar, D. (2019). IL-6 mediated JAK/STAT3 signaling pathway in cancer patients with cachexia. *Bratislava Medical Journal-Bratislavske Lekarske Listy, 120*(11), 819-826. http://10.4149/BLL_2019_136

Evans, W. J., Morley, J. E., Argilés, J., Bales, C., Baracos, V., Guttridge, D., & Mantovani, G. (2008). Cachexia: a new definition. *Clinical Nutrition, 27*(6), 793-799. http://https://doi.org/10.1016/j.clnu.2008.06.013

Fisher, D. T., Chen, Q., Skitzki, J. J., Muhitch, J. B., Zhou, L., Appenheimer, M. M., & Wang, W. C. (2011). IL-6 trans-signaling licenses mouse and human tumor microvascular gateways for trafficking of cytotoxic T cells. *The Journal of Clinical Investigation, 121*(10), 3846-3859. http:// https://doi.org/10.1172/JCI44952

Gyamfi, J., Eom, M., Koo, J. S., & Choi, J. (2018). Multifaceted Roles of Interleukin-6 in AdipocyteBreast Cancer Cell Interaction. *Translational Oncology, 11*(2), 275-285. http://10.1016/j.tranon.2017.12.009

Han, J., Lu, C. C., Meng, Q. Y., Halim, A., Yean, T. J., & Wu, G. H. (2019). Plasma concentration of interleukin-6 was upregulated in cancer cachexia patients and was positively correlated with plasma free fatty acid in female patients. *Nutrition & Metabolism, 16*(1), 3846-3859. http://10.1186/s12986-019-0409-9

Hendifar, A. E., Petzel, M. Q., Zimmers, T. A., Denlinger, C. S., Matrisian, L. M., Picozzi, V. J., & Tuli, R. (2019). Pancreas cancer-associated weight loss. *The Oncologist, 24*(5), 691-701. http://https://doi.org/10.1634/theoncologist.2018-0266

Iwase, S., Murakami, T., Saito, Y., & Nakagawa, K. (2004). Steep elevation of blood interleukin-6 (IL-6) associated only with late stages of cachexia in cancer patients. *European Cytokine Network, 15*(4), 312-316.

Kang, S., Tanaka, T., Narazaki, M., & Kishimoto, T. (2019). Targeting interleukin-6 signaling in clinic. *Immunity, 50*(4), 1007-1023. http://https://doi.org/10.1016/j.immuni.2019.03.026

Kishimoto, T. (2006). Interleukin-6: discovery of a pleiotropic cytokine. *Arthritis Research & Therapy, 8*(2), 1-6. http://https://doi.org/10.1186/ar1916

Kitawaki, J., Kiyomizu, M., Obayashi, H., Ohta, M., Ishihara, H., Hasegawa, G., & Honjo, H. (2006). Synergistic effect of interleukin-6 promoter (IL6− 634C/G) and intercellular adhesion molecule-1 (ICAM-1 469K/E) gene polymorphisms on the risk of endometriosis in Japanese women. *American Journal of Reproductive Immunology, 56*(4), 267-274. http://https://doi.org/10.1111/j.1600-0897.2006.00426.x

Kotler, D. P. (2000). Cachexia. *Ann Intern Med, 133*(8), 622-634. http://10.7326/0003-4819-133-8-200010170-00015

Kuroda, K., Nakashima, J., Kanao, K., Kikuchi, E., Miyajima, A., Horiguchi, Y., & Murai, M. (2007). Interleukin 6 is associated with cachexia in patients with prostate cancer. *Urology, 69*(1), 113-117. http://10.1016/j.urology.2006.09.039

Liu, Q., Yu, S., Li, A., Xu, H., Han, X., & Wu, K. (2017a). Targeting interlukin-6 to relieve immunosuppression in tumor microenvironment. *Tumor Biology, 39*(6), 1010428317712445. http://10.1177/1010428317712445

Liu, X., Zheng, W., Wang, W., Shen, H., Liu, L., Lou, W., & Yang, P. (2017b). A new panel of pancreatic cancer biomarkers discovered using a mass spectrometry-based pipeline. *British Journal of Cancer, 117*(12), 1846-1854. http://https://doi.org/10.1038/bjc.2017.365

Martignoni, M. E., Kunze, P., Hildebrandt, W., Kunzli, B., Berberat, P., Giese, T., & Friess, H. (2005). Role of mononuclear cells and inflammatory cytokines in pancreatic cancer-related cachexia. *Clinical Cancer Research, 11*(16), 5802-5808. http://10.1158/1078-0432.CCR-05-0185

Miura, T., Mitsunaga, S., Ikeda, M., Shimizu, S., Ohno, I., Takahashi, H., & Ochiai, A. (2015). Characterization of Patients With Advanced Pancreatic Cancer and High Serum Interleukin-6 Levels. *Pancreas, 44*(5), 756-763. http://10.1097/MPA.0000000000000335

Nariţa, D., Seclaman, E., Ursoniu, S., Ilina, R., Cireap, N., & Anghel, A. (2011). Expression of CCL18 and interleukin-6 in the plasma of breast cancer patients as compared with benign tumor patients and healthy controls. *Rom J Morphol Embryol,* 52(4), 1261-1267.

Narsale, A. A., & Carson J. A. (2014). Role of interleukin-6 in cachexia: therapeutic implications. *Current Opinion in Supportive and Palliative Care, 8*(4), 321-327. http://10.1097/SPC.0000000000000091

Naugler, W. E., & Karin, M. (2008). The wolf in sheep's clothing: the role of interleukin-6 in immunity, inflammation and cancer. *Trends in Molecular Medicine*, *14*(3), 109-119. https://doi.org/10.1016/j.molmed.2007.12.007

Okada, S., Okusaka, T., Ishii, H., Kyogoku, A., Yoshimori, M., Kajimura, N., & Kakizoe, T. (1998). Elevated serum interleukin-6 levels in patients with pancreatic cancer. *Japanese Journal of Clinical Oncology, 28*(1), 12-15. http://10.1093/jjco/28.1.12

Opal, S. M., & DePalo, V. A. (2000). Anti-inflammatory cytokines. *Chest*, *117*(4), 1162-1172. http://https://doi.org/10.1378/chest.117.4.1162

Pal, M., Febbraio, M. A., & Whitham, M. (2014). From cytokine to myokine: the emerging role of interleukin-6 in metabolic regulation. *Immunology and Cell Biology, 92*(4), 331-339. http:// https://doi.org/10.1038/icb.2014.16

Petruzzelli, M., Schweiger, M., Schreiber, R., Campos-Olivas, R., Tsoli, M., Allen, J., Swarbrick, M., Rose-John, S., Rincon, M., Robertson, G., Zechner, R., & Wagner, E. F. (2014). A switch from white to brown fat increases energy expenditure in cancer-associated cachexia. *Cell Metabolism*, *20*(3), 433-447. https://doi.org/10.1016/j.cmet.2014.06.011

Pfitzenmaier, J., Vessella, R., Higano, C. S., Noteboom, J. L., Wallace, D., & Corey, E. (2003). Elevation of cytokine levels in cachectic patients with prostate carcinoma. *Cancer, 97*(5), 1211-1216. http://10.1002/cncr.11178

Ramsey, M. L., Talbert, E., Ahn, D., Bekaii-Saab, T., Badi, N., Bloomston, P. M., Conwell, D. L., Cruz-Monserrate, Z., Dillhoff, M., Farren, M. R., Hinton, A., Krishna, S. G., Lesinski, G. B., Mace, T., Manilchuk, A., Noonan, A., Pawlik, T. M., Rajasekera, P. V., Schmidt, C., Guttridge, D., & Hart, P. A. (2019). Circulating interleukin-6 is associated with disease progression, but not cachexia in pancreatic cancer. *Pancreatology*, *19*(1), 80-87. https://doi.org/10.1016/j.pan. 2018.11.002

Rose-John, S. (2012). IL-6 trans-signaling via the soluble IL-6 receptor: importance for the pro-inflammatory activities of IL-6. *International Journal of Biological Sciences, 8*(9), 1237-1247. http://10.7150/ijbs.4989

Rupert, J. E., Narasimhan, A., Jengelley, D. H. A., Jiang, Y. L., Liu, J. G., Au, E. N., & Zimmers, T. A. (2021). Tumor-derived IL-6 and trans-signaling among tumor, fat, and muscle mediate pancreatic cancer cachexia. *Journal of Experimental Medicine, 218*(6). http://10.1084/jem.20190450

Salgado, R., Junius, S., Benoy, I., Van Dam, P., Vermeulen, P., Van Marck, E., Huget, P., & Dirix, L. Y. (2003). Circulating interleukin-6 predicts survival in patients with metastatic breast cancer. *International Journal of Cancer*, *103*(5), 642-646. https://doi.org/10.1002/ijc.10833

Schreiber, R. D., Old, L. J., & Smyth, M. J. (2011). Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science, 331*(6024), 1565-1570. http://10.1126/science.1203486

Serra, C., Palacios, D., Mozzetta, C., Forcales, S. V., Morantte, I., Ripani, M., & Simone, C. (2007). Functional interdependence at the chromatin level between the MKK6/p38 and IGF1/PI3K/AKT pathways during muscle differentiation. *Molecular Cell, 28*(2), 200-213. http://https://doi.org/10.1016/j.molcel.2007.08.021

Serrano, A. L., Baeza-Raja, B., Perdiguero, E., Jardí, M., & Muñoz-Cánoves, P. (2008). Interleukin-6 is an essential regulator of satellite cell-mediated skeletal muscle hypertrophy. *Cell Metabolism, 7*(1), 33-44. http://https://doi.org/10.1016/j.cmet.2007.11.011

Siegel, R. L., Miller, K. D., & Jemal, A. (2019). Cancer statistics, 2019. *CA: a Cancer Journal for Clinicians, 69*(1), 7-34. http:// https://doi.org/10.3322/caac.21551

Swartz, M. A., Iida, N., Roberts, E. W., Sangaletti, S., Wong, M. H., Yull, F. E., & DeClerck, Y. A. (2012). Tumor Microenvironment Complexity: Emerging Roles in Cancer Therapy Tumor Microenvironment. *Cancer Research, 72*(10), 2473-2480. http://https://doi.org/10.1158/0008-5472.CAN-12-0122

Tao, Q. Q., Chen, Y., Liu, Z. J., Sun, Y. M., Yang, P., Lu, S. J., & Wu, Z. Y. (2014). Associations between apolipoprotein E genotypes and serum levels of glucose, cholesterol, and triglycerides in a cognitively normal aging Han Chinese population. *Clinical Interventions in Aging, 9*, 1063-1067.

Tisdale, M. J. (2000). Protein loss in cancer cachexia. *Science, 289*(5488), 2293-2294. http://doi.org/10.1126/science.289.5488.2293

Tisdale, M. J. (2001). Cancer anorexia and cachexia. *Nutrition, 17*(5), 438-442. http://https://doi.org/10.1016/S0899-9007(01)00506-8

Tsoli, M., Swarbrick, M. M., & Robertson, G. R. (2016, June). Lipolytic and thermogenic depletion of adipose tissue in cancer cachexia. In *Seminars in cell & developmental biology* (Vol. 54, pp. 68-81). Academic Press. https://doi.org/10.1016/j.semcdb.2015.10.039

Wang, Y. Y., Attané, C., Milhas, D., Dirat, B., Dauvillier, S., Guerard, A., Gilhodes, J., Lazar, I., Alet, N., Laurent, V., Le Gonidec, S., Biard, D., Hervé, C., Bost, F., Ren, G. S., Bono, F., Escourrou, G., Prentki, M., Nieto, L., Valet, P., & Muller, C. (2017). Mammary adipocytes stimulate breast cancer invasion through metabolic remodeling of tumor cells. *JCI Insight*, *2*(4). doi: 10.1172/jci.insight.87489

Wang, K., Wang, C., Xiao, F., Wang, H., & Wu, Z. (2008). JAK2/STAT2/STAT3 are required for myogenic differentiation. *Journal of Biological Chemistry*, *283*(49), 34029-34036. http://https://doi.org/10.1074/jbc.M803012200

White, J. P. (2017). IL-6, cancer and cachexia: metabolic dysfunction creates the perfect storm. *Translational Cancer Research, 6*(Suppl 2), S280-S285. http://10.21037/tcr.2017.03.52

Zhang, D., Zhou, Y., Wu, L., Wang, S., Zheng, H., Yu, B., & Li, J. (2008). Association of IL-6 gene polymorphisms with cachexia susceptibility and survival time of patients with pancreatic cancer. *Ann Clin Lab Sci, 38*(2), 113-119.

Zoico, E., & Roubenoff, R. (2002). The role of cytokines in regulating protein metabolism and muscle function. *Nutrition Reviews, 60*(2), 39-51. https://doi.org/10.1301/00296640260085949