Chronic Inflammation in Cancer Cachexia

Subjects: Primary Health Care | Cell Biology

Contributor: Rosa Divella , , Antonio Mazzocca

Cachexia, a type of metabolic syndrome linked to the disease, is associated with a dysregulation of metabolic pathways. Cancer Cachexia is a subtle condition that reduces patients' quality of life by impairing their response to therapy and survival. Inflammatory mediators that may play a role in the pathogenesis of neoplastic cachexia, for example, overlap with those that may play a role in the pathogenesis of obesity. Cachexia is a complication of cancer-related malnutrition associated with catabolic/hypermetabolic changes.

chronic inflammation cachexia

1. Malnutrition and Cancer

A change in nutritional status is common during the natural history of a neoplastic disease [1][2]. Even with adequate nutritional support, neoplasia has a limited reversibility, which distinguishes malnutrition from "regular" malnourishment [3]. Because of this characteristic, this condition is referred to as neoplastic cachexia rather than malnutrition associated with neoplasia [4]. Cachexia may be caused by a tumor–host interaction [5]. Tumors may produce pro-inflammatory cytokines (TNF-, IL-6, and so on), lipid mobilization factors (LMF), and catabolic-inducing protides (CIP) [6][7][8]. If a tumor is present, the host's inflammatory and neuroendocrine stress responses will be activated [9][10]. In this case, changes in body composition (and their functional consequences) as well as anomalies in the humoral system would emerge. Neoplastic cachexia is defined by weight loss and metabolic abnormalities across multiple substrates, as follows:

- Improved glucose metabolism (from lactate and amino acids in the muscles), increased lactic acid synthesis, peripheral insulin resistance, and increased lactate excretion [11][12].
- Increased protein metabolism is defined by an increase in blood levels of a factor that stimulates proteolysis (PIF), an increase in muscle tissue protein catabolism, and a decrease in lean mass and liver protein synthesis [13][14].
- LMF (lipid mobilizing factor) is an enzyme that increases lipid metabolism, beta-oxidation, and turnover-free fatty acid synthesis to promote lipolysis [15][16].

2. Dysregulation of Metabolic Pathways during Cachexia

The long-term release of tumor cytokines into the bloodstream may disrupt the neuroendocrine control of metabolism in multiple organs [17][18]. If metabolites were difficult to obtain or were used incorrectly, cachexia would worsen [19][20]. As a result of the activation of the brown adipose tissue (BAT), which causes a fever, patients with anorexia and cachexia are committed to energy-intensive, maladaptive reactions to anorexia. Obesity and cachexia are associated with increased lipolysis, elevated free fatty acid (FFA), ceramides, and insulin resistance [21][22]. Other metabolic pathways also changing in an unusual way [23][24][25]. Insulin resistance is important in the context of pathogenic bacteria because it diverts nutrients away from anabolic and antimetabolic pathways, and toward immune system energy supplies. This lays the groundwork for understanding insulin resistance caused by inflammation [26]. Immune cells that have been stimulated can receive nutrients via an energy recourse reaction using this adaptive technique [27]. Once the infection has been cleared and equilibrium has been restored, anti-inflammatory chemicals are typically used to counteract this response [28]. Chronic inflammatory disorders such as inflammatory arthritis and chronic obstructive pulmonary disease (COPD) share molecular recognition sensors and mediators with cancer and obesity [29].

3. Cancer Cytokines and Inflammation

Proinflammatory cytokines, which play a role in the development and progression of cancer, play a critical role in survival rates, quality of life, and therapy response [30][31]. Many types of cancer patients have elevated levels of cytokines and soluble receptors in their blood. IL-6 and IL-8 concentrations appear to be strongly predictive of prognosis and outcome in a number of studies [32][33][34][35]. When cancer cells interact with other cells in the tumor microenvironment, such as endothelial and immune cells, as well as necrotic tissue, they can process cytokines [36]. The release of cytokines into the bloodstream by tumors has the potential to affect organs located far from the tumor's location. In contrast to their well-known normal biological roles, these tumor cytokines have the potential to subvert physiological systems when produced chronically by tumors in the absence of sufficient negative feedback regulatory signals [37][38]. Some of these cancer cytokines may be difficult to identify because they are produced by a diverse mix of malignant and normal cells in the tumors of different patients. Because tumors produce and express them in high quantities, their function differs from those of cytokines and myokines, which are also produced and expressed in high quantities by tumors [39][40]. Tumors produce IL-6 continuously, in contrast to immune cells' precise circadian regulation of IL-6 and other cytokines, and skeletal muscle's transitory spikes in plasma IL-6 production during exercise. IL-6 concentrations, on the other hand, can increase up to 100-fold during physical activity but quickly return to pre-exercise levels once the activity is completed [41][42][43]. Cachexia has a negative impact on the health and well-being of cancer patients. Individuals with cachexia's clinical and nutritional care will be improved if the metabolic anomalies and treatment options are better understood [43]. A tumor's overproduction of cytokines alters the energy balance in many organ systems and reveals treatment options. Researchers can investigate cancer cytokines' normal and malignant functions, as well as their interactions with inflammatory signals and metabolic abnormalities, to identify cancer cytokines. [44]. Researchers now have new insights into both obesity and neoplastic cachexia, which share many of the same molecular recognition sensors and process mediators [45][46].

4. Chronic Inflammation in Obesity and Cancer Cachexia

Researchers now have a new avenue for studying inflammation and how it affects metabolic pathways after discovering that metabolic illnesses are frequently accompanied by a low-grade inflammatory condition. The primary cause of metabolic homeostasis disruption appears to be intercellular communication between immunological and metabolic cells. When a person overeats, immune sensors such as TLRs or inflammasomes detect high levels of lipid in the diet or their metabolic products, resulting in the production of inflammatory cytokines in various metabolic organs. Furthermore, dietary lipids can alter gut bacteria, resulting in an increase in proinflammatory molecules, which can result in an incorrect immunological response. Saturated fatty acids, inflammatory cytokines, and bacterial lipopolysaccharides, LPS, all influence insulin signaling, altering cellular metabolism. As a result, in addition to the obvious strategy of reducing caloric intake, saturated fats, and a low glycemic index, which has been shown to lower insulin levels and reduce systemic inflammation and relapse, new therapeutic strategies aimed at targeting immune sensors and different protein kinase can also be used to improve obesity-related complications. Despite growing scientific attention, this nutritional problem requires a better understanding and a more precise formal description by the health care industry in order to implement numerous therapies that must be tailored to each patient's needs. The "diet" (in the broadest and most original sense of "lifestyle") retains its extraordinary importance and merits careful consideration, according to the most recent scientific evidence, given the positive effect demonstrated in numerous studies of physical activity on the associated symptomatology of cachexia.

References

1. Caccialanza, R.; Pedrazzoli, P.; Cereda, E.; Gavazzi, C.; Pinto, C.; Paccagnella, A.; Beretta, G.D.; Nardi, M.; Laviano, A.; Zagonel, V. Nutritional Support in Cancer Patients: A Position Paper from the Italian Society of Medical Oncology (AIOM) and the Italian Society of Artificial Nutrition and Metabolism (SINPE). J. Cancer 2016, 7, 131–135.
2. Mayne, S.T.; Playdon, M.C.; Rock, C.L. Diet, nutrition, and cancer: Past, present and future. Nat. Rev. Clin. Oncol. 2016, 13, 504–515.
3. Muscaritoli, M.; Molfino, A.; Gioia, G.; Laviano, A.; Rossi Fanelli, F. The "parallel pathway": A novel nutritional and metabolic approach to cancer patients. Intern. Emerg. Med. 2011, 6, 105–112.
4. Skipworth, R.J.; Stewart, G.D.; Dejong, C.H.; Preston, T.; Fearon, K.C. Pathophysiology of cancer cachexia: Much more than host-tumour interaction? Clin. Nutr. 2007, 26, 667–676.
5. Prado, B.L.; Qian, Y. Anti-cytokines in the treatment of cancer cachexia. Ann. Palliat. Med. 2019, 8, 67–79.
6. Argilés, J.M.; López-Soriano, F.J.; Busquets, S. Mediators of cachexia in cancer patients. Nutrition 2019, 66, 11–15.

7. Poulia, K.A.; Sarantis, P.; Antoniadou, D.; Koustas, E.; Papadimitropoulou, A.; Papavassiliou, A.G.; Karamouzis, M.V. Pancreatic Cancer and Cachexia-Metabolic Mechanisms and Novel Insights. Nutrients 2020, 12, 1543.
8. Roxburgh, C.S.; McMillan, D.C. Cancer and systemic inflammation: Treat the tumour and treat the host. Br. J. Cancer 2014, 110, 1409–1412.
9. Dolan, R.D.; McLees, N.G.; Irfan, A.; McSorley, S.T.; Horgan, P.G.; Colville, D.; McMillan, D.C. The Relationship Between Tumor Glucose Metabolism and Host Systemic Inflammatory Responses in Patients with Cancer: A Systematic Review. J. Nucl. Med. 2019, 60, 467–471.
10. Baracos, V.E.; Martin, L.; Korc, M.; Guttridge, D.C.; Fearon, K.C.H. Cancer-associated cachexia. Nat. Rev. Dis. Primers 2018, 4, 17105.
11. Dev, R.; Bruera, E.; Dalal, S. Insulin resistance and body composition in cancer patients. Ann. Oncol. 2018, 29 (Suppl. 2), ii18–ii26.
12. Argilés, J.M.; Busquets, S.; Stemmler, B.; López-Soriano, F.J. Cachexia and sarcopenia: Mechanisms and potential targets for intervention. Curr. Opin. Pharmacol. 2015, 22, 100–106.
13. Tisdale, M.J. Catabolic mediators of cancer cachexia. Curr. Opin. Support. Palliat. Care 2008, 2, 256–261.
14. Dalal, S. Lipid metabolism in cancer cachexia. Ann. Palliat. Med. 2019, 8, 13–23.
15. Arner, P.; Langin, D. Lipolysis in lipid turnover, cancer cachexia, and obesity-induced insulin resistance. Trends Endocrinol. Metab. 2014, 25, 255–262.
16. Dalamaga, M. Interplay of adipokines and myokines in cancer pathophysiology: Emerging therapeutic implications. World J. Exp. Med. 2013, 3, 26–33.
17. Manole, E.; Ceafalan, L.C.; Popescu, B.O.; Dumitru, C.; Bastian, A.E. Myokines as Possible Therapeutic Targets in Cancer Cachexia. J. Immunol. Res. 2018, 2018, 8260742.
18. Dev, R.; Wong, A.; Hui, D.; Bruera, E. The Evolving Approach to Management of Cancer Cachexia. Oncology 2017, 31, 23–32.
19. Rohm, M.; Zeigerer, A.; Machado, J.; Herzig, S. Energy metabolism in cachexia. EMBO Rep. 2019, 20, e47258.
20. Beijer, E.; Schoenmakers, J.; Vijgen, G.; Kessels, F.; Dingemans, A.M.; Schrauwen, P.; Wouters, M.; van Marken Lichtenbelt, W.; Teule, J.; Brans, B. A role of active brown adipose tissue in cancer cachexia? Oncol. Rev. 2012, 6, e11.
21. Uomo, G.; Gallucci, F.; Rabitti, P.G. Anorexia-cachexia syndrome in pancreatic cancer: Recent development in research and management. JOP 2006, 7, 157–162.

22. Han, X.; Raun, S.H.; Carlsson, M.; Sjøberg, K.A.; Henriquez-Olguín, C.; Ali, M.; Lundsgaard, A.M.; Fritzen, A.M.; Møller, L.L.V.; Li, Z.; et al. Cancer causes metabolic perturbations associated with reduced insulin-stimulated glucose uptake in peripheral tissues and impaired muscle microvascular perfusion. Metabolism 2020, 105, 154169.
23. Karpe, F.; Dickmann, J.R.; Frayn, K.N. Fatty acids, obesity, and insulin resistance: Time for a reevaluation. Diabetes 2011, 60, 2441–2449.
24. Johnson, A.R.; Milner, J.J.; Makowski, L. The inflammation highway: Metabolism accelerates inflammatory traffic in obesity. Immunol. Rev. 2012, 249, 218–238.
25. Kominsky, D.J.; Campbell, E.L.; Colgan, S.P. Metabolic shifts in immunity and inflammation. J. Immunol. 2010, 184, 4062–4068.
26. Kulkarni, O.P.; Lichtnekert, J.; Anders, H.J.; Mulay, S.R. The Immune System in Tissue Environments Regaining Homeostasis after Injury: Is "Inflammation" Always Inflammation? Mediat. Inflamm. 2016, 2016, 2856213.
27. Chen, L.; Deng, H.; Cui, H.; Fang, J.; Zuo, Z.; Deng, J.; Li, Y.; Wang, X.; Zhao, L. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget 2017, 9, 7204–7218.
28. Petruzzelli, M.; Wagner, E.F. Mechanisms of metabolic dysfunction in cancer-associated cachexia. Genes Dev. 2016, 30, 489–501.
29. Suzuki, H.; Asakawa, A.; Amitani, H.; Nakamura, N.; Inui, A. Cancer cachexia--pathophysiology and management. J. Gastroenterol. 2013, 48, 574–594.
30. Lippitz, B.E. Cytokine patterns in patients with cancer: A systematic review. Lancet Oncol. 2013, 14, e218–e228.
31. Gunawardene, A.; Dennett, E.; Larsen, P. Prognostic value of multiple cytokine analysis in colorectal cancer: A systematic review. J. Gastrointest. Oncol. 2019, 10, 134–143.
32. Singh, J.; Sohal, S.S.; Lim, A.; Duncan, H.; Thachil, T.; De Ieso, P. Cytokines expression levels from tissue, plasma or serum as promising clinical biomarkers in adenocarcinoma of the prostate: A systematic review of recent findings. Ann. Transl. Med. 2019, 7, 245.
33. Capone, F.; Guerriero, E.; Sorice, A.; Colonna, G.; Ciliberto, G.; Costantini, S. Serum Cytokinome Profile Evaluation: A Tool to Define New Diagnostic and Prognostic Markers of Cancer Using Multiplexed Bead-Based Immunoassays. Mediat. Inflamm. 2016, 2016, 3064643.
34. Wei, C.; Yang, C.; Wang, S.; Shi, D.; Zhang, C.; Lin, X.; Liu, Q.; Dou, R.; Xiong, B. Crosstalk between cancer cells and tumor associated macrophages is required for mesenchymal circulating tumor cell-mediated colorectal cancer metastasis. Mol. Cancer 2019, 18, 64.
35. Turner, M.D.; Nedjai, B.; Hurst, T.; Pennington, D.J. Cytokines and chemokines: At the crossroads of cell signalling and inflammatory disease. Biochim. Biophys. Acta 2014, 1843, 2563–2582.

36. Rider, P.; Carmi, Y.; Cohen, I. Biologics for Targeting Inflammatory Cytokines, Clinical Uses, and Limitations. Int. J. Cell Biol. 2016, 2016, 9259646.
37. Yasukawa, H.; Sasaki, A.; Yoshimura, A. Negative regulation of cytokine signaling pathways. Annu. Rev. Immunol. 2000, 18, 143–164.
38. Hainaut, P.; Plymoth, A. Targeting the hallmarks of cancer: Towards a rational approach to next-generation cancer therapy. Curr. Opin. Oncol. 2013, 25, 50–51.
39. Huuskonen, A.; Tanskanen, M.; Lappalainen, J.; Oksala, N.; Kyröläinen, H.; Atalay, M. A common variation in the promoter region of interleukin-6 gene shows association with exercise performance. J. Sports Sci. Med. 2009, 8, 271–277.
40. Ridker, P.M.; Rifai, N.; Stampfer, M.J.; Hennekens, C.H. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation 2000, 101, 1767–1772.
41. Marceca, G.P.; Londhe, P.; Calore, F. Management of Cancer Cachexia: Attempting to Develop New Pharmacological Agents for New Effective Therapeutic Options. Front. Oncol. 2020, 10, 298.
42. Carnie, L.; Abraham, M.; McNamara, M.G.; Hubner, R.A.; Valle, J.W.; Lamarca, A. Impact on prognosis of early weight loss during palliative chemotherapy in patients diagnosed with advanced pancreatic cancer. Pancreatology 2020, 20, 1682–1688.
43. Siddiqui, J.A.; Pothuraju, R.; Jain, M.; Batra, S.K.; Nasser, M.W. Advances in cancer cachexia: Intersection between affected organs, mediators, and pharmacological interventions. Biochim. Biophys. Acta Rev. Cancer 2020, 1873, 188359.
44. Advani, S.M.; Advani, P.G.; VonVille, H.M.; Jafri, S.H. Pharmacological management of cachexia in adult cancer patients: A systematic review of clinical trials. BMC Cancer 2018, 18, 1174.
45. Sun, X.; Feng, X.; Wu, X.; Lu, Y.; Chen, K.; Ye, Y. Fat Wasting Is Damaging: Role of Adipose Tissue in Cancer-Associated Cachexia. Front. Cell Dev. Biol. 2020, 8, 33.
46. Vaitkus, J.A.; Celi, F.S. The role of adipose tissue in cancer-associated cachexia. Exp. Biol. Med. 2017, 242, 473–481.