Cancer cachexia and metabolism: a challenge in nutrition oncology

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Abstract

Cancer causes cellular inflammation with constant production of inflammatory signals which can alter metabolism, food consumption and energy utilization of the body. Insulin resistance which increases the lipolysis and the breakdown of fatty acids (lipid oxidation) is also involved. Inflammatory signals can also reduce appetite (anorexia) via the central nervous system, hence affecting body weights in cancer patients. Malnutrition of cancer patients can cause cancer cachexia, a group of syndromes including anorexia, muscle atrophy, immune dysfunction, inflammation and metabolism change. Long term consequences without any treatment could lead to develop cancer anorexia-cachexia syndrome (CACS). Prolonged release of the inflammatory signals prevents the body from utilizing nutrition supplements to revitalize or regain normal cell mass and functions, decreasing the survival rate and life expectancy of the patients in chronic states. Thus, the nutritional care alone may not be effective for cancer patients although it seems to be one of the promoted strategies. It is best to prevent prolonged inflammatory signal release in cancer by endorsing programs which combine regular nutritional assessment and screening for warning signs of cancer cachexia. Thus, CACs in cancer patients using this constant assessment and screening may reduce the risks of other fatal conditions including opportunistic infections.

Introduction

Advanced stage cancer can introduce the production of inflammatory cytokines including interleukin-1 alpha (IL-1α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which can permeate and affect certain cells and biological functions. The inflammatory cytokines can be transported through the blood brain barrier into the brain, reaching the hypothalamus and the luminal surface of brain endothelial cells, and affect appetite control. Some inflammatory cytokines can cause the brain to decrease neuropeptide Y (NPY) production, resulting in an increase in pro-opiomelanocortin (POMC) and an increase in α-MSH from hypothalamic melanocortin. These substances can bind to Mc3r and Mc4r in the hypothalamus area of the brain which results in signaling to inhibit appetite. An injection of Mc3r and Mc4r antagonist directly to the brain that was shown to increase appetite and reduce the incidence of anorexia in rats, however direct injection into the brain may not be appropriate for human use (Pinedo *et al*, 2012).

Ghrelin is a ligand for the growth hormone secretagogue receptor. Ghrelin plays a critical role in a variety of physiological processes, including the stimulation of GH secretion and regulation of energy homeostasis by stimulating food intake and promoting adiposity via a GH-independent mechanism. It was shown to reduce the level of IL-1β, IL-6 and TNF-α (Akamizu and Kangawa, 2010). The state of ghrelin resistance can be found in cancer patients and also found that ghrelin has the effect to increase the level of insulin-like growth factor (IGF-1) which helps the normal persons to build muscle mass (Maggio *et al*, 2013). However, the higher levels of IGF-1 are needed in cancer patients so as to overcome the proliferation of cancer cells which increases tremendously. A clinical trial of ghrelin in cancer cachexia patients demonstrates that intravenous administration of ghrelin increased the amount of food intake (Akamizu *et al*, 2010), but researcher reported that ghrelin did not change the amount of food intake, which may contribute to genetic polymorphism of the related ghrelin receptor or the state of ghrelin resistance (Delporte, 2013), which requires in-depth studies especially the precautions of ghrelin on the proliferation of cancer cells.

Carbohydrate metabolism in cachexia: Cancer cachexia patients have changes in carbohydrate metabolism as a result from the proliferation and spreading cancer cells (Lazaro, 2008), thus creating hypoxia-inducible factor 1 (HIF) on a large scale, resulting in an increase in transcription of glucose transporter 1 (GLUT1). HIF also stimulates the pyruvate dehydrogenase kinase (PDHK) which functions by addition of a phosphate to the pyruvate dehydrogenase, and thus, inactivating the pyruvate dehydrogenase which converts the pyruvate into the acetyl CoA. Therefore, the metabolism pathway is changed to lactate, causing the Cori cycle in cancer patients, resulting in a waste of energy that should be gained from the metabolism of carbohydrate approximately 300 Kcal/day (Tisdale, 2009).

Warburg effect: The above process can be further explained by an increase in glycolysis of cancer cells from that of the normal cells despite a state of sufficient oxygen supply, so called the Warburg effect (Lazaro, 2008). Based on the knowledge that cancer cells utilize glucose from glycolysis rather than normal cells, a cancer diagnostic tool was introduced by implementing the imaging technique of positron-emission tomography employed the glucose analogue tracer fluorodeoxyglucose (FdG PET) (Lazaro, 2008).

Glycolysis is an intracellular process which acquires cellular energy associated with the mitochondria through the oxygen-dependent pathway of oxidative phosphorylation (OXPHOS). In addition, p53 protein, involving the control of protein in OXPHOS, especially hexokinase and phosphoglycerate mutase (PGM), also plays a vital role in glycolysis of cancer cells. p53 of cancer cells was found to be lower than that of normal cells due to abnormal glycolysis pathway in line with the Warburg hypothesis (Lazaro, 2008).

Cancer cells also alter aerobic meta-bolism, which includes dysoxia or dysoxic metabolism. Although oxygen supply is sufficient, cancer cells use the metabolites from the glycolysis rather than normal OXPHOS (Lazaro, 2008). A change of carbohydrate metabolism is believed to be due to induce reactive oxygen species (ROS) and O_2*, causing cellular alkalinization (increased pH), resulting in the activation of phospho-fructokinase (PFK) induced by an alkaline condition (Pinedo *et al*, 2012). The activated PFK will increase GLUT expression including hexokinase. Also, pyruvate kinase will propel the glycolysis. Furthermore, the dysoxia process can also increase the amount of hydrogen peroxide (H_2O_2) which enhances production of HIF and thus, resulting in additional glycolysis propelling. The HIF can also stimulate the oncogene which includes ras, src and myc as well (Lazaro, 2008).

Autophagic tumor stroma model of cancer: A biomarker of stroma model is caveolin 1. A loss of caveolin-1 (Cav-1) is a biomarker found in the state of chronic hypoxia, oxidative stress and autography in tumor microenvironment. There have been researches adopting the Cav-1 as a biomarker for cancer prognosis and treatment strategy (Outs-choorn *et al*, 2010). Generally, caveolins are members of a family of membrane-bound scaffolding proteins which involve

in an endocytosis mechanism. The cancer cells that show high expression of caveolins will have low tumor progression due to the inhibition of tumor growth factor signaling pathways. Besides, there was a proposal of new model "Reverse Warburg Effect" from the discovery of a decrease in Cav-1 that affects an increased expression of aerobic glycolysis in cancer-associated fibroblast to produce the high energy metabolites such as lactate and pyruvate that are transferred to the adjoining cancer cells, where they then enter the Krebs' cycle and Electron transport chain reaction, promote an oxidative phosphorylation and result in an increase of ATP production.

From the autographic tumor stroma model of cancer metabolism, oxidative stress is found to be the recycle of nutrients and the occurrence of random mutagenesis. It was found that breast cancer cells induced oxidative stress due to excess ROS production of cancer-associated fibroblasts (CAFs) which leads to the drive of autography via HIF 1 induction and nuclear factor kappa-light-chain-enhancer of activated B cell (NFkB) activation, resulting in mito-graphy which is an autophagic destruct-tion of mitochondria (Saita et al, 2013) and caveolin-1 (Cav-1) (Outschoorn et al, 2010).

An autophagic and mitophagy will induce the occurrence of catabolism and aerobic glycolysis leading to the recycle of nutrients into pyruvate and lactate which will be sent to the adjacent cancer cells. These produced substances will serve as an energy source for the mitochondria metabolism in cancer cells and result in the apoptosis resistance, and a great amount of ROS will destroy the genetic material of the cancer cells, leading to an aneuploidy and genomic instability. If such process repeats itself, a change in genetic matters will lead to the occurrence of tumor stroma co-evolution process.

Co-evolution of cancer cells can be achieved by preventing cancer cells from resistance to treatment. One of the strategies used is to prevent the occurrence of cellular hypoxia and oxidative stress which can reduce Cav-1 and causing Reverse Warburg Effect. The effect of n-acetyl cysteine, quercetin and metformin in prevention of Cav-1 loss was also reported (Outschoorn *et al,* 2010). Thus, nutrition therapy for cancer suggests carbohydrate control by consumption of complex carbohydrates, fruits and vegetables with orange to red colours for sources of quercetin.

Cancer cachexia is a high catabolic state causing a change in metabolism of carbohydrate which induces the occurrence of hypoxia state, thus the glycolysis process then produces the lactate into the Cori cycle instead of aerobic glycolysis. It is also associated with the breaking down of fat resulting in an increase in lactate and ketone as well as the occurrence of oxidative stress that decreases the Cav-1. Cancer cells change their consumption from normal sugar into lactate and ketone as a result of the co-evolution of cancer cells. As a result, the cancer cells then rapidly grow and spread with a developing tendency to resist to treatment (Tisdale, 2009).

Cancer patients at this stage with anti-oxidant consumption were shown to prevent the reduction of Cav-1 and delay the emergence of drug resistance and the dissemination. Thus, it should not be considered as merely energy intake. If cancer cachexia is rectified by the increase of energy intake from food especially the carbohydrate, it demonstrates that the cancer cells develop themselves into more aggressive manner. In such cases, sources of natural food components of anti-oxidants which help promoting the production of glutathione should be considered as an effective retardation of oxidative stress and Cav-1 reduction.

Fat metabolism in Cachexia: By the time the breakdown of triglycerides (TG) for use is needed, then the lipolysis process is required which must be activated by the hormone sensitive lipase (HSL), including the epinephrine, glucagon, adrenocorticotrophic hormone (ACTH) via the signal transduction process of G-couple protein. However, the good function of HSL needs to be phosphorylated first, especially the emergence of phosphorylation at the position of Ser659 and Ser660 which can significantly increase the activities. The final results of the lipolysis process will yield non-esterified fatty acid (NFEA) and glycerol.

Not only the enzymes in HSL group, but also an adipose triglyceride lipase (ATGL), functions as a hydrolyzed long-chain fatty acid. ATGL is the enzyme that controls the triacylglycerol catabolism, with a role in the control of the breaking down of fat in human but not distinct as HSL. In addition, the adipocyte differentiation also relies on the transcription factors to involve in the transformation of those cells. These include CCAAT-enhancer-binding proteins alpha, beta, delta (C/ EBP α, β, δ), sterol regulatory element-binding protein (SREBP), peroxisome pro-liferation activated receptor gramma (PPARγ) etc., which can be found to be affected in the cancer cachexia patients.

The breakdown of adipose tissue is found within the cancer cachexia state which results in an increase in turn-over of glycerol and free fatty acid when compared to cancer patients who are not in the state of cachexia. Also, when the fasting glycerol test is performed in a group of cancer cachexia patients, the majority of the patients do not lose their weight. Moreover, adipocyte differen-tiation into the brown adipose tissue and expression of zinc alpha-2 glycoprotein (ZAG) were higher than usual in the cancer cachexia patients (Pinedo *et al* 2012; Tisdale, 2009).

The levels of TNF-α, IL-1 and IL-6 in cancer cachexia patients were found to be higher than normal in the cancerous lump, as a result of the inflammatory process that occurs in the body which affects the system of lipid metabolism in the body. TNF-α can inhibit cAMP from being changed by phosphodiesterase 3B and also inhibit the lipoprotein lipase, resulting in a greater amount of cAMP. Due to the presence of ZAG and Lipid mobilizing factor (LMF) in high doses in the cancer cachexia state, the ATP is then changed into the cAMP through the activation of adenylyl cyclase. The high amount of cAMP will stimulate the phosphokinase A (PKA) and also stimulate the HSL to have a hydrolyzed TG turned to the NEFA. But the cancer cachexia patients are found with high amount of uncoupling protein 1 (UCP-1) which will function to seize the electron from various complex in the electron transport chain, leading to the release of energy in the form of heat and CO_2, but not in the form of ATP at all (Tisdale, 2009).

Therefore, the determination of fat in cancer cachexia patients is needed to focus on the receipt of fat in the group of omega-3 and omega-9 primarily as well as the decrease in the amount of omega-6 and saturated fatty acid. Eicosapentaenoic acid (EPA) was shown to reduce inflammation in cancer patients (Betiati et al, 2013).

Muscle and protein metabolism in cachexia: Cancer cachexia patients will have the muscle atrophy as a significant symptom which is caused by both the depression of protein synthesis and the increase in protein degradation. A release of 3-methylhistidin from the muscle in the leg area of the patients was detected. The report also found the degradation of muscle that linked to a dysfunctional dystrophin glycoprotein complex (DGC). Generally, the degradation of muscle mass, so-called proteolytic pathways which are responsible for the degradation of proteins in skeletal muscles, occurred in a sequence, as follows; 1) The main degradation of extracellular proteins and receptors involves lysosomal system including the cysteine protease cathepsins B, H and L as well as the aspartate protease cathepsin D. 2) Breaking down processes during tissue injury, necrosis and autolysis are the calcium-activated system including the calpains I and II, as the calpains and caspase-3 will degrade the myofilament into the myofibril, myosin and actin. 3) Ubiquitin-proteasome pathway requires an ATP in conjuction to calpain system to degrade of myofilaments in which the myosin is assembled with the ubiquitin. Then the myosin-ubiquitin will be degraded into amino acids by using the enzyme in the ubiquitin-proteasome pathway. 4) If weight loss of greater than 10% occurs in cancer patients, a breakdown of myofibrillar proteins via the ubiquitin-proteasome pathway should be involved (Acharyya *et al*, 2007).

TNF, IL-1, IL-6 and proteolysis-inducing factor (PIF) are increasingly secreted in cancer cachexia patients. These can affect NF-kB and increase the transcription of MuRF1 and MAFBx causing muscle atrophy (Akamizu et al, 2010). Besides, the PIF can also cause the degradation of myosin heavy chain via the induction of proteasome relying on the co-interaction of DGC (Tisdale, 2009).

Conclusion

Cancer cachexia is a group of syndromes that causes severe weight loss and life threatening consequences. It alters carbohydrate metabolism of the entire body in a series of Warburg effect, Cori cycle and the reverse Warburg effect. The cancer cells will finally rely on an emergent ROS in the development of the metabolism of the cell itself to the adaptation to cell survival and escape from the apoptosis

process. This could be a self-developed resistance of chemotherapy or radiation therapies as of the tumor cells themselves survive the ROS and utilize energies from the lactate pyruvate not the normal glucose. Fat is drawn into the beta-oxidation greater, causing an excessive amount of acetyl Co A until it becomes the ketone bodies, and the cancer cells will use those ketone bodies as an energy source for themselves. Similarly, it is seen that when cancer cells develop themselves into the state cancer cachexia, they will try to pull the nutrients and cause the normal metabolism to change. Cancer cells can transform themselves to survive in the state of changing metabolism

Dietetic practice in the past mainly focuses on the concept of the energy issue based on "high protein high energy" in order to preserve the lean body mass and fulfill the body with adequate nutrition. However, when considering metabolism of cancer cachexia, it is essential to refocus on determining high protein nutrition in body weight gain which cannot be possible in cancer cachexia state. The metabolism of cancer cachexia leads to reconsider that extra details must be specified not just the energy issue. Nutrients which provide own glutathione or quercetin-containing fruits and vegetables with carbohydrate consumption to minimize Cav-1 reduction may lead to the development of cancer cells that cause the worse prognosis of the disease.

It is recommended to consider the types of fat, particularly avoiding taking saturated fatty acids. Omega-3 and/or omega-9 should be encouraged in patients. The degradation of muscle mass cannot be compensated by consumption of proteins as it is unable to stimulate the muscle mass in this abnormal proteolytic pathway. Thus, the supplementation of food should focus on the effect of reducing the level of TNF, IL-1, IL-6, as it is the key to alter the way of muscle degradation in the body of cancer cachexia patients.

Thus, food for cancer patients must be well-balanced with an understanding of disease pathology, the biochemical change and the metabolic change, and the food consideration, both macro-nutrients and micronutrients. The patient and the states of their health should be carefully concerned to improve their quality of life and survival rate.

Acknowledgement

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