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Recent Advances in Metabolomics and Therapeutics for Cancer Cachexia

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Abstract

Cancer Cachexia afflicts 50 - 80 percent of cancer patients with roughly 20 percent of all cancer patients dying of cachexia. Metabolomics is the study of different metabolites, their location in the body, and the timing of their appearance and disappearance. As a result, this science of Metabolomics can be applied to solve the problem of Cancer Cachexia. In this review, I examine recent studies on metabolism that use Metabolomics as their instrument of discovery. Further, this review details potential therapeutic interventions at the cellular, animal, and human level that show promise for attenuating Cancer Cachexia.

Keywords

Drug Discovery, Stable Isotopes, Muscle Wasting, Oncology

1. Introduction

A question arises: how much evidence of efficacy and safety is enough evidence to use a pharmacological agent in humans to attenuate, or stop cancer cachexia? For FDA approved drugs there is Mount Everest to climb before drug approval for human use or in other words 10 - 15 years of Clinical Research. When in-reality one relatively short-term, well conducted study of a precisely chosen sample of specific cancer patients within the population of cancer patients should be enough to prove safety and efficacy and to use in a patient population if efficacy is proven at the probability of 95% ($p < 0.05$). This is the nature of statistics-high-efficacy requires fewer patients to reach statistical significance. However, even if you could prove efficacy with a low patient number, this is not consistent with FDA regulations for Phase III studies which require several hundred to 3000 patients (www.FDA.gov). However, safety is a tougher question but a moderate or

less risk of adverse event should be utilized to prove safety. It is ludicrous the amount of money spent and more important to the cancer patient, the amount of time spent in FDA sanctioned clinical trials to prove efficacy. Ten-fifteen years of Clinical Trials to prove efficacy and safety would appear overkill especially for the cancer patient for whom life-saving medicines are researched to death. Every effort should be made to get a drug to market with widespread applicability to different types of cancers in an expeditious manner. The present system is killing people. Repurposing of already approved drugs *i.e.* "off-label" use should be used in many instances [1]. The benefit-risk ratio is in the favor of the cancer patient to prolong survival and potentially to cure cancer using repurposed drugs. Additionally, nutritional supplements which show efficacy in treating cancer cachexia in small well-done clinical trials should be used expeditiously and with a wide sweeping brush meaning if it attenuates one type of cancer cachexia clinicians should try it in other types of cancer. In this review, I will discuss the organs and system metabolomics and I will also discuss therapeutic strategies for attenuating cancer cachexia. This will include FDA approved drugs-which I will propose a role for repurposing to "off-label" uses and also non-FDA approved nutritional supplements. Please see **Figure 1** (information from the American Cancer Society website; https://www.cancer.org/) for the projected deaths from cancer over 5, 10, 15 year intervals if they remain constant from 2010 statistics. By reducing the number of years to FDA approval of efficacious and safe drugs we can save many lives as can be inferred from **Figure 1**. Assuming these drugs have that potential.

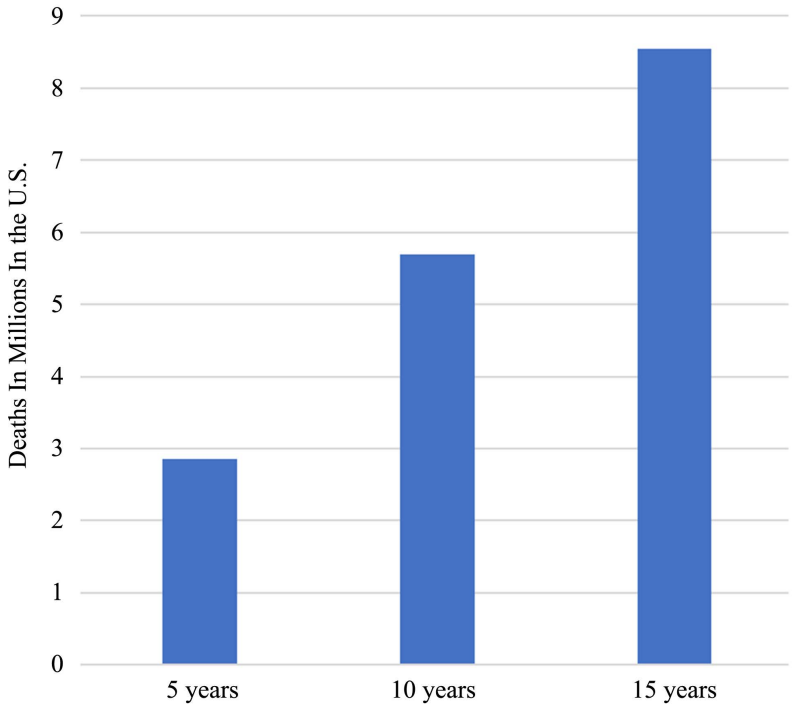

Figure 1. Projected number of cancer deaths in the U.S. in different time periods with 10 - 15 years being the time it takes for FDA approval of a drug. Source: American Cancer Society Website.

2. Metabolomic Findings in Different Tissues and Compartments

2.1. Metabolomic Findings in Blood and Urine

Plasma metabolomic studies in humans and animals reveal greatly elevated ketone bodies in plasma as well as elevated or reduced [2] amino acids and reduced plasma glucose [3] and liver glycogen [3] as a result of cancer muscle wasting. These data indicate that the tumor = and/or skeletal muscle becomes reliant on glucose as metabolic fuel and uses up available glucose and that the patient goes into ketosis (the incomplete breakdown of fat as fat requires carbohydrate; oxaloacetate, in the tricarboxylic acid cycle to be fully oxidized) [4]. The data also indicate that amino acids are liberated into plasma likely from muscle protein breakdown but they are subsequently taken up by likely the tumor. So as a result amino acids are first elevated in plasma and then decline as they are used up. It is impossible to determine the exact rate of appearance and rate of rate of disappearance from a snap-shot in time of the plasma compartment. Either Arterio-venous differences in amino acid uptake or release from muscle tumor or tissue or tracer studies are needed for plasma kinetics are required [5]. These would require both analysis of the tumor turnover of substrates and the skeletal muscle turnover of substrates *i.e.* Rate of appearance and rate of disappearance for both skeletal muscle and tumor. It is unclear whether it is the skeletal muscle that becomes reliant on glucose or the tumor does. Tumors are known to increase their uptake of glucose and convert it to lactate via glycolysis rather than to CO_2, water, and energy via oxidative phosphorylation despite intact mitochondria. The purpose of this Warburg effect is currently obscure [6]. On the one hand, skeletal muscle mass is a large portion of body mass in non-cachectic patients; however, the turnover of glucose could be extremely high in the tumors. What remains to be determined is tumor metabolomics and the rate of glucose turnover and amino acid turnover by the tumor. Although, in a recent study Viana *et al.* [7] reported using Positron Emission Tomography that leucine supplementation reduced tumor glucose uptake; they also used Computed Tomography scanning to examine the effects of leucine supplementation on tumor size. They found no effect of leucine on tumor size.

Another manifestation of cancer cachexia appears to be a large increase in low density lipoproteins [3] in plasma which also could be a turnover problem: increased production and/or decreased removal.

2.2. Findings in Skeletal Muscle

Pin *et al.* [3] reported that murine C26 tumor hosts and that were treated with chemotherapy (Folfori) resulted in the greatest reduction in skeletal muscle mass compared to tumor alone and chemotherapy alone (*i.e.* 38% loss of quadriceps mass relative to vehicle for chemotherapy plus tumor). They also found a decrease in plasma glucose and liver glycogen. The authors suggested the increase in glucose demand was both the result of cancer cachexia and chemotherapy. This

group of researchers suggests that a decrease in mitochondrial function and citric acid cycle flux with cachexia and chemotherapy in skeletal muscle results in muscle wasting due to the reduction mitochondrial ATP production. The authors [3] suggest that high AMP/ATP ratio in this situation in skeletal muscle activates AMP activated protein kinase and this leads to inhibition of mTOR a key regulator of skeletal muscle protein synthesis and likely tumor protein synthesis. Based on the interpretations of Pin *et al.* [3], it would appear imperative to isolate either skeletal muscle and/or the tumor and treat either or both appropriately: inhibit AMP activated protein kinase in skeletal muscle and activate AMP activated protein kinase in the tumor to increase synthesis of skeletal muscle protein and inhibit synthesis of tumor proteins, respectively.

Chiocchetti *et al.* [8] found differences in the amino acid profile of the gastrocnemius muscle in Walker 256 tumor bearing rats depending on the age of the animal. These results suggest that in tumor bearing animals and possibly humans the age of the animal and/or human is an important consideration in cancer cachexia. Age appropriate medications and/or nutritional supplements may be required to attenuate cancer cachexia based on the data of Chiocchetti *et al.* [8].

Kunz *et al.* [9] reported that muscle protein synthesis was depressed in cancer cachexia in animal model. They also found that two methylarginine species were elevated in this model of cancer cachexia. This was also the case in a human model of cancer cachexia. They then injected C2C12 human muscle cells with methylarginines and found a reduction in muscle protein synthesis. The authors concluded the muscle protein synthesis is depressed in cancer cachexia and methylarginines appear to be the causative factor in this reduced muscle protein synthesis.

2.3. Findings in Liver (Animal Studies Only)

Pin *et al.* [3] reported decreased liver glucose and glycogen as well as increased flux through gluconeogenesis and the tricarboxylic acid cycle in the liver of rodents undergoing cancer cachexia and/or(chemotherapy). Once the glucose/liver glycogen stores are depleted the animal and human must rely on non-carbohydrate sources such as amino acids and glycerol to synthesize glucose by way of gluconeogenesis. Glucose to the best of our knowledge cannot be synthesized from fatty acids [4]. It must be noted that a rodent liver is somewhat different than a human liver as the capacity for gluconeogenesis is much greater in a rodent liver [10]. This is evidenced by the fact a rodent can partially replete muscle glycogen without feeding after exercise [10] but this is not the case for human muscle after exercise (J.O. Holloszy personal communication). Clearly, the distinction between rodent hepatic metabolism and human hepatic metabolism suggests that humans should be the primary focus of cancer cachexia research as rodent metabolism in the liver is not reflective of metabolism in the human liver. The liver is not just a static single organ but communicates with tissues all over

the organism and the divergence of rodent and human liver metabolism is an issue.

Miyaguti *et al.* [11] reported higher lipid metabolites and impaired mitochondrial CII and CIV complexes in Walker 256 tumor bearing animals this impairment in liver metabolism was more pronounced in weanling than adult animals. These results suggest that younger animals are at disadvantage if they present with tumors than older animals.

2.4. Findings in the Tumor

Viana *et al.* [12] fed a leucine rich diet to Walker 256 tumor bearing rats and compared to controls. They reported that leucine, which increases muscle protein synthesis [13], had no effect on tumor growth. Thus, study illustrates the importance of measuring both muscle metabolism and tumor mass when administering protein anabolic agents.

3. Therapeutics

3.1. AR-42

Tseng Y-C *et al.* [14] reported the histone deacetylase inhibitor AR-42 reduced cachexia in the Colon-26 tumor bearing mouse. Acetylation of histones binds them to amino acids and continues the process of protein synthesis. Deacytylation would decrease this process of protein synthesis. AR-42 inhibits deacytlation and through reducing IL-6, IL-6Ralpha, Leukemia Inhibitory Factor, FOXO1, atrogin-1, MURF1 among others, acts to stimulate protein synthesis in skeletal muscle. Histone deacetylase inhibitor AR-42, also reduced body weight and muscle mass losses, reduced expression of Murf and Atrogin-1, and reduced tumor cytokine production in two mouse models of cachexia [14] [15].

Collier *et al.* [15] reported AR-42 was well tolerated and had beneficial effects of longer disease free survival and in various types of cancers. This phase I trial can be considered a success. It is the opinion of this author that this drug should be "fast-tracked" by the FDA, in an effort to save lives, in a similar way that this regulatory agency "fast-tracked" Enobosarm (Ostarine-MK-2866) to facilitate FDA approval.

3.2. Putatative Therapeutic Agents (Cell Culture and Rodent Experiments)

3.2.1. Silibinin

Shukla *et al.* [16] reported that Silibinin a natural product reduced c-MYC and glut1 expression and glucose uptake in tumor cells of pancreatic ductal adenocarcinoma cells and reduced muscle wasting. Glut-1 is active under basal conditions of glucose uptake in skeletal muscle cells. It is assumed it serves this function in tumor cells. Murf-1 and atrogin-1mRNA from muscle samples taken from a mouse model of pancreatic adenocarcinoma were down regulated by Silibinin.

3.2.2. Compound A

Compound A which inhibits NF-KB and therefore reduces inflammation only partially restores the non-cancer muscle metabolic phenotype. A weakness of this study is that does not address the anorexia associated with cancer cachexia and reduced macronutrient and total energy intake evident with this disease process [17]. Thus, mostly these authors are examining the degradative side of the muscle protein balance equation and neglecting the muscle protein synthesis side of the equation which clearly is dependent on nutrient intake. Otherwise, this is an excellent study. Der-torossian *et al.* [18] reported that the administration of Compound A which targeted NFKappaB only partially reversed the cachectic outward appearance in gastrocnemius muscle.

3.2.3. Elamipretide: (SS-31)

Interestingly, Ballaro *et al.* [19] reported that Szeto-Schiller Peptide (SS-31), which systemically interacts with cardiolipin and cristae in the mitochondria acts to reduce muscle wasting induced by cancer and chemotherapy.

3.2.4. Activin 2B Receptor Blockade

Lautaoja *et al.* [20] reported that blockade of the activin 2B receptor with a ligand reduced cachexia but muscle and serum metabolites were still dysregulated in the Colon-26 tumor bearing mice. Lautaoja *et al.* reported [20] free phenylalanine is a good biomarker for muscle atrophy or cachexia. In retrospect, free phenylalanine is a good biomarker of muscle protein breakdown. However, it will only stay in plasma as long as it is not taken up by liver, skeletal muscle, or tumor. Advin 2 B blockade was not effective in stopping cachexia in Lautoja *et al.* [20] study.

3.3. "Repurposing" of FDA Approved Drugs for "Off-Label" Uses

3.3.1. Amitriptyline

Toll-Like Receptor-4 agonism leads to production of proinflammatory cytokine production via NF-KB. These Toll-Like receptors are on monocytes/macrophages that infiltrate the tumor microenvironment [21]. Recent evidence suggests that blocking TLR-4 by using amitriptyline will reduce proinflammatory cytokine production in osteoarthritis [22]. The repurposing of this antidepressant drug could be used in cancer to block TLR-4 and reduce proinflammatory cytokine production which leads to angiogenesis, tumor cell proliferation, and metastases [23].

Proinflammatory Leukocyte secretion of cytokines is inhibited by TLR-4 antagonism. This would appear to be important as it appears that leukocytes and not the tumor are the source of proinflammatory cytokines which cause increases in vascularity, metastases, and tumor growth [23]. This is the case in Pancreatic Adenocarcinoma which is a cancer with a high-death rate from cancer cachexia [23]. It is likely that the proinflammatory cytokines secreted from leukocytes are causing atrophy in skeletal muscle *i.e.* degrading muscle protein and liberating the amino acids into blood. Clearly, IL-6 and TNF-alpha are activators

of muscle protein degradation and are inhibitors of muscle protein synthesis [24] [25] [26] [27] [28]. From the preceding discussion it appears proinflammatory cytokines are involved in cancer progression (new blood vessel formation, tumor growth and metastases) as well as muscle wasting. Thus, activation of TLR-4 can lead to a reduction in muscle protein by way of inhibiting synthesis and activating degradation via the release of proinflammatory cytokines and lead to proliferation of cancer in the cancer microenvironment.

3.3.2. Amiloride

Zhou *et al.* [29] reported that amiloride, a diuretic, that acts on membrane transporters is effective in curtailing cancer cachexia by inhibiting the exocytosis of the contents of the tumor cell (reduces release of tumor contents from an exosome). This study was carried in a mouse model of cancer cachexia of colon and lung cancer induced by injecting cancerous cells into (CT26 and LLC, respectively). This is repurposing of a previously approved diuretic in pre-clinical studies. Future studies should evaluate the efficacy of this anti-cachectic in human studies.

3.3.3. FDA Approved Monoclonal Antibodies to IL-6 and TNF-α

In a recent book chapter (open access), Lambert [30] suggested that inhibiting cancer induced IL-6 and TNF-α through the "off-label" use of already FDA approved monoclonal antibodies to IL-6 and TNF-α would a prudent way to inhibit cancer cachexia. This could be administered immediately to cancer patients in which IL-6 and TNF-α are believed to be the culprits in muscle wasting. For FDA approved drugs that can be prescribed "off-label" or in other words repurposed for cancer cachexia.

3.4. Nutritional Supplements

3.4.1. Leucine

Nutritional supplements are not required to have FDA approval for use as a drug in humans. Fortunately, a few nutritional supplements have been shown to have efficacy and safety over the years and *in vitro* and animal models. I have detailed prominent nutritional supplements with little risk and likely high success rates in humans below. Clinical trials in Cancer Cachexia patients should be conducted using these low-risk supplements in the future. A recent book chapter by Lambert [30] highlights older nutritional supplements and their potential for use in Cancer Cachexia patients and recent review article highlights the use of resistance exercise which is a natural non-pharmacological intervention to reduce Cancer Cachexia [31] for Nutritional Supplements that have potential to effectively treat cancer.

3.4.2. Leucine

Viana *et al.* [32] found that the addition of 3% leucine to a diet that was 18% protein in Walker 256 tumor bearing rats that exhibited cachexia improved muscle strength, maintained body weight, muscle, and fat mass. In a second paper by

Viana *et al.* [7] they examined the effects of leucine on the tumor. Again they used a 3% leucine addition to 18% protein in the diet in the Walker 256 bearing rats. They found no change in tumor size, lower tumor glucose consumption, and decreased metastatic rates. Additionally, there was a conversion from glycolytic metabolism to oxidative phosphorylation as far as metabolic changes.

3.4.3. Curcumin

Zhang *et al.* [33] induced breast cancer in mice and reported that curcumin administration reduced NF-KB levels as well reduced activation of the ubiquitin proteasome system leading to less cachexia in these mice. However, the reduced circulating cytokine levels scene with curcumin administration could also have increased the muscle protein synthesis side of the muscle protein balance equation. Penedo-Vazquez *et al.* [34] found that the areas of the Type I and Type II muscle fibers were significantly greater in the soleus and gastrocnemius muscles of cachectic mice treated with curcumin or reservatrol compared to untreated cachectic mice. Additionally, inflammatory cells were lower in the gastrocnemius and soleus of mice treated with curcumin or resveratrol compared to non-treated controls. With regard to studies in humans a recent study [35] reported a 0.46 kg muscle mass gain compared to as 1.05 kg muscle mass loss in cancer cachectic individuals receiving 34.25 mg/kg of curcumin. This difference was statistically significant ($p = 0.03$). Muscle mass was determined by bioelectrical impedance and there was no difference between groups in hand grip strength.

3.4.4. Taurine

Reactive oxygen species increase in cancer as a result of chemotherapy [36]. Please see Yang *et al.* for a review of this literature [36]. Zhou *et al.* [37] reported that in C2C12 myoblasts, that chemotherapy which leads to oxidative stress and muscle protein degradation reduced the ability of myoblasts to differentiate into mature muscle cells. The administration of the antioxidant Taurine resulted in a reduction in reactive oxygen species and improved conversion of C2C12 myoblasts into mature muscle cells under conditions of chemotherapy.

3.4.5. Anamorelin

Anamorelin is a failed FDA drug turned nutritional supplement in the United States. It is an approved drug for the treatment of cancer cachexia in Japan. It is a non-peptide growth hormone secretagogue. It added muscle mass significantly but did not improve function in Cancer Cachexia [38]. It also significantly stimulates appetite. It does have a beneficial impact on the Cancer Cachexia patient by adding muscle and stimulating appetite.

4. Conclusion

Cancer Cachexia is multifactorial problem. Cachexia afflicts 50 - 80 percent of all cancer patients and kills up to 20% of all cancer patients [39]. As such, it requires a multifactorial approach. The key areas are: 1) reduced muscle protein synthesis, 2) increased protein degradation, 3) tumor proliferation, 4) anorexia,

and 5) chemotherapy induced muscle wasting [37]. Thus, likely multiple agents that address these five enemies of the cancer cachexia patient should be administered to these patients. First, therapies which stimulate muscle protein synthesis (leucine for example), inhibit muscle protein degradation (curcumin appears relevant here), antagonizes TLR-4 induced cytokine production (such as amitriptyline), and stimulates appetite (anamorelin discussed in this review and megestrol acetate reviewed in a recent review of the literature [31]) should be administered. Taurine appears efficacious against reactive oxygen species liberation from chemotherapy [38]. Utilizing agents to affect these five areas and fine tuning their dosage and length of treatment (possibly using them intermittently to attenuate acclimation to these agents) will prolong and potentially save lives and improve quality of life. Some of these therapies for example taurine administration should negate some of the serious side effects of chemotherapy (reactive oxygen species liberation) [39].

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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