Nutritional intervention for cancer sarcopenia

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Abstract
Most patients with advanced cancer develop skeletal muscle atrophy called sarcopenia, which reduces treatment tolerance and social activity and worsens the prognosis. Glucose suppresses skeletal muscle atrophy in cancer-bearing mice, while promoting cancer growth. In contrast, medium-chain fatty acids reduce skeletal muscle atrophy and suppress cancer growth. Simultaneous administration of glucose and medium-chain fatty acids suppresses skeletal muscle atrophy and eliminates the tumor growth seen in glucose. Based on these findings, dietary intervention using a combination of glucose and medium-chain fatty acids is expected to be effective in suppressing sarcopenia in cancer patients.

Introduction
Cachexia affects 80% of advanced-stage cancer patients and is a direct cause of death in 30% [1,2]. As defined by the 2008 cachexia consensus conference “cachexia, is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass”[3], skeletal muscle atrophy is considered a major pathology of cancer cachexia [4,5]. In addition, decreased skeletal muscle mass in cancer patients is not only associated with decreased quality of life for patients, but is also closely associated with survival prognosis [3]. On the other hand, suppressing skeletal muscle atrophy significantly prolongs life prognosis regardless of tumor burden [6]. From these findings, improvement of skeletal muscle atrophy in cancer cachexia is an important issue. In recent years, exercise for improving malnutrition, anticancer treatment, and activity enhancement has been recommended in patients with cachexia [7]. In this review, we focus on nutritional interventions and show the possibility of nutritional interventions aimed at preventing skeletal muscle atrophy using an animal model of cancer cachexia.

Cancer cachexia and nutritional intervention
Cancer cachexia causes anorexia and weight loss in cancer patients, eventually leading to irreversible malnutrition [8]. Along with this, the skeletal muscles are atrophied, and the tolerance for treatment with anticancer agents. Treatment of cancer cachexia requires measures to manage reduced food intake and address catabolism as a result of inflammation [9]. Therefore, nutritional intervention has recently been proposed as a treatment for cancer patients with malnutrition [10,11]. However, nutrients such as carbohydrates and linoleic acid may promote tumor growth [12–14]. Therefore, nutrition interventions in cancerous sarcopenia require careful consideration of their effects on tumors as well as skeletal muscle. However, while there are many reports on the effects of nutritional interventions in cancerous sarcopenia, there are few reports on nutritional interventions that focus on both skeletal muscle and tumors.

Effects of carbohydrates on tumors and skeletal muscle
Glucose is an essential nutrient for skeletal muscle cells, leading to muscle contraction, homeostasis, and muscle cell growth [15]. Glucose uptake in skeletal muscle cells is insulin
After fatty acid undergoes the antitumor effect of medium-chain fatty acids and ketones improve metabolic syndrome [22] and induction of apoptosis in functional maturity of skeletal muscle, showed a significant negative correlation was confirmed between the tumor diameter and blood glucose level. Muscle weight was significantly low in the tumor group; however, SDS-soluble myosin light chain 1 (SDS-MLC1), which indicates the functional maturity of skeletal muscle, showed a significantly high value in a glucose concentration-dependent manner. At 50% sugar concentration, improvement was observed to a level equivalent to that of the control group (non-cancer-bearing mice) [22]. From the above, it was clarified that the glucose load in the tumor-bearing body promotes the increase in tumors, while increasing the functional maturity of skeletal muscle and improving skeletal muscle atrophy. Therefore, it is necessary to carefully consider the administration of carbohydrates to cancer-bearing bodies.

Effects of medium-chain fatty acids on tumors and skeletal muscle

Intake of medium-chain fatty acids has been shown to improve metabolic syndrome [22] and induction of apoptosis in cancer cells has also been reported [23]. We have also reported the antitumor effect of medium-chain fatty acids and ketones [24]. After fatty acid undergoes β-oxidation in mitochondria, the acetyl CoA produced is metabolized in the TCA cycle, and ATP is produced by oxidative phosphorylation. Since long-chain fatty acids are used for energy production, intracellular uptake by transporters such as CD36 and fatty acid binding proteins and translocation into the mitochondria by carnitine shuttle are required [25,26]. In contrast, Medium-chain fatty acids are taken into mitochondria without carnitine shuttle, undergo β-oxidation, and are used for oxidative phosphorylation in the TCA cycle [27]. Thus medium-chain fatty acids are rapidly utilized in mitochondria in equilibrium with changes in blood concentration [28]. Intake of medium-chain fatty acids is expected to forcefully promote mitochondrial metabolism in cells. Mitochondria have been reported to have dysfunction and poor quality control in tumor cells [29,30], and we have found that forced metabolism induces excessive oxidative stress production and apoptosis [24]. On the other hand, medium chain fatty acids in skeletal muscle have been reported to lead to improvement of mitochondrial energy metabolism in skeletal muscle via GPR84 [31]. In addition, normal mitochondria can produce ATP much more efficiently than glycolysis, and thus may promote skeletal muscle growth.

Based on these findings, we investigated the effect of oral intake of medium-chain fatty acids on skeletal muscle hypertrophy in a mouse model [21]. A LAA diet containing lauric acid (LAA, C12: 0, 0%, 2%, 5% w/w) added to a control diet was orally ingested for 2 weeks. As a result, skeletal muscle wet weight was significantly increased in the 2% LAA diet, but significantly decreased in the 5% LAA diet. From these results, it was confirmed that medium-chain fatty acids act to promote skeletal muscle growth at an appropriate concentration. On the other hand, it was shown that at high concentration, excessive mitochondrial activation also causes oxidative stress in skeletal muscle and induces muscle atrophy. Muscle atrophy due to excessive oxidative stress production by LAA is also observed in myocardium [32].

Based on these results, we used a 2% LAA diet, which is considered to be an appropriate concentration for the murine cachexia model, and orally ingested it for 2 weeks [21]. In our cachexia model, male BALB/c mice are inoculated intraperitoneally with syngeneic CT26 colon cancer cells, and cachexia phenotypes such as ascites retention, weight loss, and skeletal muscle atrophy are induced in about 10 days [21]. When a 2% LAA diet was orally administered to the cachexia group, an increase in skeletal muscle mass and an increase in skeletal muscle SDS-MLC1 were confirmed. On the other hand, in tumors, a 2% LAA diet resulted in a decrease in tumor weight and a decrease in ascites retention [21]. Thus, oral ingestion of medium-chain fatty acids is suggested to improve skeletal muscle atrophy and suppress tumors in cancer cachexia model, and medium-chain fatty acids are important in nutritional intervention for cancer sarcopenia. Was considered to be a nutrient.

Effect of combined intake of medium-chain fatty acid and carbohydrate on tumor and skeletal muscle

As described above, glucose and medium-chain fatty acids are the same energy source, but are metabolized by different pathways in intracellular metabolism. Therefore, simultaneous ingestion of both may improve skeletal muscle atrophy without promoting tumor growth. Therefore, in two types of mouse cachexia models of CT26 mouse colon cancer cells and HT29 human colon cancer cells, 10% glucose drinking water, 2% lauric acid diet alone, or the effect of the combined use, after oral ingestion for 2 weeks, The tumor and skeletal muscle were removed and examined [21]. As shown in Table 1, the weight of skeletal muscle decreased in the cachexia group, but significantly increased with the combined intake, and improved to the same level as the non-tumor bearing mice. In addition, there was no significant difference in tumor weight between the combination group and the control diet group.

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**Table 1:** Effect of dietary intervention using glucose and/or lauric acid on cancer sarcopenia.

<table>
<thead>
<tr>
<th>Tumor cell line</th>
<th>Diet</th>
<th>Tumor weight (g)¹</th>
<th>Muscle weight (g)²</th>
<th>SDS-MLC (pg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT26</td>
<td>No tumor/control</td>
<td>-</td>
<td>0.15 ± 0.002</td>
<td>23 ± 1.3</td>
</tr>
<tr>
<td>Control</td>
<td>LAA</td>
<td>1.35 ± 0.15</td>
<td>0.11 ± 0.002</td>
<td>13 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>LAA+glucose</td>
<td>0.63 ± 0.06</td>
<td>0.13 ± 0.01</td>
<td>22 ± 3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.58 ± 0.16</td>
<td>0.14 ± 0.01</td>
<td>27 ± 3.1</td>
</tr>
<tr>
<td>HT29</td>
<td>No tumor/control</td>
<td>-</td>
<td>0.15 ± 0.01</td>
<td>21 ± 2.2</td>
</tr>
<tr>
<td>Control</td>
<td>LAA</td>
<td>1.2 ± 0.11</td>
<td>0.09 ± 0.002</td>
<td>11 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>LAA+glucose</td>
<td>0.3 ± 0.04</td>
<td>0.14 ± 0.01</td>
<td>21 ± 2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.25 ± 0.13</td>
<td>0.15 ± 0.01</td>
<td>23 ± 2.5</td>
</tr>
</tbody>
</table>

1) To measure tumor weight, the peritoneal tumors were dissected from the intestine, mesentery, diaphragm, and abdominal wall, grossly removing non-tumoral tissues.

2) The quadriceps femoris muscle was cut at the muscle end on the upper edge of the patella, peeled off from the femur, and separated at the muscle origin on the frontal surface of the anterior lower iliac spine. The excised quadriceps femoris muscle was weighed immediately, avoiding drying.

3) Whole cell lysate solubilized with 0.1% SDS-RIPA buffer from sonicated muscle were weighed immediately, avoiding drying.

Glucose is an important nutrient for the prevention of skeletal muscle atrophy; however, administration alone promoted tumor growth. In contrast, the simultaneous ingestion of lauric acid into glucose offsets the tumor-growing effect of carbohydrates in tumors by the antitumor effect of ActRIBB antagonism leads to prolonged survival. Cell 142: 531-543. Link: http://bit.ly/390iktC

**Conclusion**

Nutritional interventions in cancer sarcomens require simultaneous consideration of their effects on tumor growth and skeletal muscle atrophy. Co-administration of medium-chain fatty acids and glucose suppressed cancerous sarcopenia without increasing tumors. It is considered that the combined use of glucose and medium-chain fatty acids is effective for the prevention of cancerous sarcopenia. Future clinical applications are strongly expected.

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