REVIEW

PATHOPHYSIOLOGY OF CANCER CACHEXIA

Riad N. Younes and Yoshikazu Noguchi

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Cancer cachexia is a frequent complication observed in patients with malignant tumors. Although several decades have passed since the first focus on the metabolic dysfunction's associated with cancer, few effective therapeutic interventions have been successfully introduced into the medical armamentarium.

The present study thoroughly reviews the basic pathophysiology of cancer cachexia and the treatment options already investigated in that field. Experimental and clinical studies were evaluated individually in order to clarify the intricate alterations observed in tumor-bearing patients. The difficulties in introducing sound and effective nutritional support or metabolic manipulation to reverse cancer cachexia are outlined in this review.

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The origin of malnutrition in cancer patients is multi-factorial. Anorexia may be attributed to altered taste and smell[1], or to changes in the hypothalamic food regulation[2]. Food intake is diminished by mechanical obstruction of the alimentary tract. Disturbance of digestion and absorption also accompanies some tumors. Nutritional demand in the tumor-bearing state is increased due to alterations either by the neoplasm itself or by the stressed host. Wasting is accelerated by the proteolysis of skeletal muscle and consumption of body fat. Accelerated mobilization and consumption of host protein stores from peripheral tissues occurs to support gluconeogenesis and acute phase protein synthesis[3,4]. In contrast, simple starvation is associated with a relative sparing of lean tissue with the preferential consumption of fat[5,6]. Substrate consumption by the tumor, whether based on analogy with glucose consumption in the human brain[7], on in vivo studies in transplanted tumors[8], or on in vivo use of the substrate by sarcoma-bearing human limbs[9], can be substantial and may account for small increases in energy expenditure at rest. However, only a very large tumor (above 1.4 kg) would consume 50% of the intake of the patient at rest[10].

Understanding the basic mechanisms of metabolic alterations observed in the tumor-bearing state is the basis for developing optimum treatment for those patients with malignancy.

In this chapter, the basic pathophysiology of metabolic alterations observed in the tumor-bearing state both in animal and humans is presented, followed by a re-focusing on clinical significance and current problems in applying nutritional support to those patients.

From the Department of Surgery, Hospital das Clínicas, Faculty of Medicine, University of São Paulo (LIM 62), Department of Thoracic Surgery, Hospital do Cancer AC Camargo and Universidade Paulista.

I. Metabolic Alterations in Cancer Patients

- Alterations specific to cancer patients-

1. Glucose Metabolism

Altered glucose metabolism in cancer patients is characterized by increased whole-body glucose turnover rate, decreased glucose uptake and utilization due to insulin resistance, and increased hepatic glucose synthesis, or gluconeogenesis, from substrates derived from proteolysis and lipolysis.

Whole-body carbohydrate metabolism

Increased whole-body glucose turnover has been documented in gastrointestinal cancer patients, and this increase was proportional to the extent of the disease[11]. Whole-body glucose production rates were also significantly

increased in patients with lung cancer (n=29, 3.4±0.2 mg/kg/min) compared to levels in controls (n=18, 2.3±0.1 mg/kg/min)[12]. In those patients, the fasting serum alanine level was significantly lower than for controls, suggesting that alanine was being released at a normal or enhanced rate and was utilized more rapidly for the production of glucose in patients than in controls. Increased Cori cycle activity or glucose carbon recycling in patients with malignant disease is well documented by several studies[13,14,15].

Peripheral carbohydrate metabolism

Glucose intolerance is one of the earliest recognized metabolic alterations in patients with cancer. In experimental animal models, hypoglycemia is a characteristic finding. In cancer patients, fasting hypoglycemia is not commonly seen; however, Glicksman and Rawson[16] reported that approximately 37% of all patients with cancer had abnormal glucose tolerance. Details of glucose intolerance or insulin resistance are discussed in the following section. The decreased glucose metabolized or glucose clearance from the circulation resulted in both significantly decreased glucose storage and glucose oxidation in gastrointestinal (GI) and lung cancer patients.

Increased circulating lactate was found in animal models as well as in some cancer patients. Studies in vivo of human tumors demonstrated significant glucose use and lactate production[17]. Lactate thus produced may be used by the liver as a gluconeogenic precursor to synthesize glucose, which may be used by both the host and the tumor. In this process, energy is wasted, because only 2 molecules of ATP are produced by glycolysis while 6 molecules of ATP are utilized to synthesize glucose from lactate.

Hepatic glucose metabolism

Increased gluconeogenesis in the tumor-bearing state has been claimed to be one of the major causes of cancer cachexia, mobilizing peripheral lean tissue mass as a substrate for gluconeogenesis. Roh et al[18] reported increased gluconeogenesis from alanine and lactate in tumor-influenced hepatocytes in the presence of decreased serum glucose level. It was associated with increased gluconeogenic capacity and accelerated alanine transport.

The increased energy cost of enhanced gluconeogenesis would only be significant if this process persisted throughout a 24-hour period and may not be detected if feeding is a compensating factor[19]. Waterhouse et al.[20] demonstrated normal suppression of increased gluconeogenesis from alanine with a small amount of carbohydrate in overnight-fasted patients with progressive malignant disease. This finding brings into question the significance of the observed increase in gluconeogenesis in the tumor-bearing state and emphasizes the possible regulation of this catabolic pathway by nutritional manipulation[21].

We previously studied the alterations of this pathway by examining a key regulatory enzyme, phosphoenolpyruvate carboxykinase (PEPCK) at both the activity and mRNA levels. PEPCK is a well-studied pacemaker enzyme of gluconeogenesis[22]. A number of hormones are known to regulate the synthesis of this enzyme[23], including glucagon, epinephrine[24], and thyroid hormone[25], which increases, and insulin, which decreases the synthesis. PEPCK activity in liver cytosol, after a 24-hour fast, was significantly higher in tumor-bearing rats than in their pair-fed controls. The increase in enzyme activity was clearly evident at 8% tumor burden and correlated positively with the degree of tumor burden ($r=0.85$, $p<0.01$). Removal of the tumor produced a complete reversal of PEPCK activity 10 days after excision. Regular feeding also abolished this increased enzyme activity. PEPCK mRNA levels were equally elevated in tumor bearers and controls in the 24-hour-fasted state. These results suggest that tumor-bearing stimulates the fasted state associated with hypoglycemia, which in turn triggers induction of the gluconeogenic enzyme, PEPCK. Substrate availability may be a key in induction of gluconeogenesis in this tumor animal model.

We also measured PEPCK activity in the livers of GI cancer patients. Although there were cases in which PEPCK activity was elevated, the mean value in patients with advanced GI cancer without significant weight loss was not different from that of controls (submitted for publication). Increased gluconeogenesis in cancer patients has been documented by isotope infusion techniques, but no data on PEPCK activity in the liver is available except our current study. If this enzyme is a key, therapy targeting this enzyme may modulate cancer cachexia. Hydrazine sulfate inhibits the conversion of oxaloacetate to phosphoenolpyruvate by inhibiting PEPCK irreversibly, and 3-mercaptopicolinic acid is a specific blocker of PEPCK. Although clinical trials had been attempted on both drugs, no significant benefits were demonstrated[26,27,28].

2. Fat Metabolism

Fat loss is frequently observed in advanced malignant disease, but may also occur in patients with early stage cancer when tumor volume is still relatively small[29]. Studies in experimental animals have shown a progressive depletion of carcass fat stores during tumor growth[30,31,32]. Profound alterations in host lipid metabolism occur in both tumor-bearing animals[33,34,35,36] and humans[37,38,35,15,39,40], manifested by hypertriglyceridemia and increased circulating non-esterified fatty acid (NEFA).

Hyperlipidemia and whole-body lipid kinetic study

In our model of Fisher 344 rats with methylcholanthrene-induced (MCA) sarcoma, hyperlipidemia is one of the early changes, progressively aggravated by tumor growth and completely abolished by curative tumor removal. In human cancers, some patients with leukemia and lung cancers have been documented to have elevated levels; however, hyperlipidemia is not universally observed[41]. Patients with solid tumors such as esophageal, gastric, colorectal, and breast cancer very rarely manifest these alterations[42]. Shaw and Wolfe[43] demonstrated increased rates of glycerol and fatty acid turnover in weight-losing gastrointestinal cancer patients, compared with either weight-stable cancer patients or controls.

De novo fatty acid synthesis

We have previously shown that *de novo* fatty acid biosynthesis in the livers of tumor-bearing rats is significantly decreased as a function of degree of tumor burden[33]. Lipogenesis by adipose tissue was also shown to be decreased in the tumor-bearing mouse[44]. Thompson et al.[44] demonstrated a gradual decline of lipogenesis per gram wet weight of liver with tumor growth by measuring the incorporation of ^{3}H from $^{3}H_2O$ into lipids. Their conclusion was that the total amount of lipid synthesis was not significantly altered in tumor-bearing mice, since liver weight increased as the tumor grew. However, the tissue composition analysis of our model[45] has previously shown that liver protein content in tumor-bearing animals is no greater than that of pair-fed controls, although liver wet weight of the former is greater than that of the latter.

Beta oxidation

Arbeit[46] and Hansell[47] in separate studies documented that patients with diffuse disease or weight loss had significantly higher fat oxidation rates, while Waterhouse et al[48] could not see a significant difference in the rate of NEFA oxidation under basal conditions in cancer patients and control. We examined the role of fatty acid oxidation by carnitine palmitoyltransferase activity in the Fisher344 rat with MCA sarcoma[49]. This enzyme is bound to both the inner and outer surface of the inner mitochondrial membrane and regulates the membrane transport of cytosolic fatty acylCoA into mitochondrial matrix where oxidation takes place[50]. In this model, there was no difference in enzyme activity between tumor-bearing rats and controls, which suggested that the tumor bearers did not utilize an augmented supply of NEFA for oxidation in the fed state. Since fatty acylCoA formed in the cytosol is either oxidized in the mitochondria or converted to TG and phospholipids in the cytosol, enhancement of the latter may contribute to the significant increase in circulating TG levels.

Lipolysis

The rate of free fatty acid (FFA) production in epididymal adipose tissue removed from tumor-bearing rats was shown to be increased, compared to that of controls[51]. We previously documented on increased rate of lipolysis (elevated FFA-Ra), associated with the maintained FFA clearance rate by the hepatocytes, which are major sites of uptake of FFA in Fisher344 rats with MCA sarcoma[52]. A significant increase in the FFA-Ra has been also shown in patients with significant weight loss[53].

Why is liberation of FFA needed in the tumor-bearing state? Some investigators have suggested that tumor growth is associated with an enhanced mobilization of stored triglycerols so that the resulting liberation of FFA can be utilized for tumor growth[54]. However, the delivery rate of FFA to rapidly growing tumors is slow[39]. An augmented supply of NEFA by lipolysis to the liver[44,55] may not be utilized for oxidation[56] preferentially esterified to form TG, which is secreted as very low density lipoprotein.

Lpolytic factor

The concept of a lipolytic factor secreted by the tumor has been proposed[57,58]. Costa and Holland[32] were able to induce a substantial fat loss in non-tumor-bearing mice following the injection of nonviable tumor preparation. Although data from several studies indirectly support the existence of a tumor-related "lipolytic factor", attempts to discover such a factor have been unsatisfactory in animal models[41] and patients[40,51].

Triglyceride clearance

Lipoprotein lipase (LPL), synthesized by parenchymal cells of adipose and muscle tissues and transported to the vascular endothelium, regulates the rate at which hydrolysis of circulating TG occurs, delivering NEFA for metabolic needs of the tissue[59]. This enzyme is unique in that the tissue-specific changes in the catalytic activity closely reflect alterations in the physiological state. Reciprocal changes during starvation in LPL activity in muscle, where LPL provides fatty acids for fuel, and adipose tissue, where the acyl groups are used for TG storage, are well documented[60,61].

We documented decreased enzyme activity with increasing tumor burden, and the reversal of these changes, by tumor removal in Fisher344 rats with MCA sarcoma[62]. One possible mechanism to explain the decreased LPL in the fasted tumor-bearing rats is hypoglycemia, induced by the presence of tumor. The LPL response to dietary carbohydrate appears to depend largely on the insulin secretory response to the ingested carbohydrate[63]. The finding that withdrawal of glucose from the

media decreased LPL activity in 3T3-L1 adipocytes[56] suggests that the substrate itself may play an important role in the regulation of this enzyme. Ong and Kern[64] demonstrated that insulin stimulated LPL by increasing the level of LPL mRNA, whereas glucose stimulates LPL translation and post-translational processing in cultured rat adipocytes.

Our results in adipose tissue agree with those of Thompson et al[44] and Lanza-Jacoby [65]. Vlassam et al[66] documented a reduction in post-heparin plasma LPL activity in overnight fasted patients with malignant-associated weight loss. The level of total peripheral LPL correlated well with the presence of body weight loss in their patients ($r=0.6$, $p<0.01$). Our recent data on post-heparin serum LPL in GI and breast cancer patients revealed that decreased LPL activity in those patients was significantly correlated with degree of weight loss and with advanced stages of disease. However, complete tumor removal did not result in reversal of deceased LPL activity, unlike insulin resistance in glucose metabolism[67]. Decreased LPL activity in the absence of hyperlipidemia, especially in patients with GI or breast cancer, may be induced by malnutrition, not by tumor effects. Therefore, in studying lipid metabolism in cancer patients, classification of subsets of patients into those with and without hyperlipidemia may be the key in further dissecting the mechanisms of these alterations.

3. Protein Metabolism

Tumors have been known not only as "glucose eaters" but also as "nitrogen sinks", depleting the host of protein mass and resulting in characteristic alterations in protein metabolism. Several investigators have suggested that redistribution or translocation of peripheral proteins to support visceral or tumor protein synthesis is an essential feature of amino acid metabolism in cancer cachexia[68]. Because the rate of protein synthesis in human tumors is approximately the same as that of the tissue of origin[69], and human tumors rarely exceed 1% of body mass[70], the observed alterations in whole-body protein metabolism are unlikely to be secondary to the tumor itself, but rather to tumor-influenced alterations in host protein metabolism[71].

Aminograms

Basal postabsorptive aminograms in several homogeneous groups of patients with different malignancies have been reported with variable results. Only one paper by Clarke et al.[72] showed elevations of alanine, isoleucine, and lysine, but all the others showed either decrease or no alterations. Heber et al.[12] demonstrated decreased alanine levels in patients with advanced lung cancer. Those may support the hypothesis that gluconeogenesis from alanine and other gluconeogenic precursor proteins is increased. In 55 patients with a variety of tumors, proline levels were significantly reduced in lymphoma and sarcoma patients. Patients with esophageal cancer and weight loss demonstrated a marked reduction in all circulating amino acids except BCAA. No cancer-specific amino acid profile has emerged from the studies so far published[73,74]. However, it appears that patients with extraintestinal nonobstructive malignancies have minimal aberrations in their amino acid profiles, and it is possible that with more advanced malignancy with weight loss, more profound changes in amino acid concentrations occur.

Whole-body protein metabolism

With few exceptions, whole-body protein turnover, synthesis, and catabolism have been reported to be elevated in both tumor-bearing animals[75] and cancer patients. Those changes are not tumor-site specific but may be related to the advancement of the tumor. Shaw et al[43] examined rates of whole-body protein synthesis and catabolism by isotopic infusion of alpha-[^{15}N]-lysine and [^{15}N]2-urea in 20 patients with advanced-weight-loss (AWL) upper gastrointestinal cancer, 7 patients with early non-weight-loss (ENWL) lower gastrointestinal cancer, and a group of volunteers. ENWL cancer patients and normal volunteers had similar protein dynamics, and in both groups, glucose infusion resulted in a significant decrease in protein loss. In AWL cancer patients, the rate of net protein catabolism was significantly higher than in either the volunteer or ENWL group ($p<0.05$). Glucose infusion did not result in a decrease in net protein catabolism. TPN significantly decreased net protein catabolism from 2.24 ± 0.30 to 0.17 ± 0.09 gm/kg/day ($p<0.01$). This decrease was due to the combined effect of a significant decrease in whole-body protein catabolism coupled with an increase in whole-body protein synthesis. Increase in whole-body protein catabolism—and whole-body protein synthesis to a lesser extent—in patients with cancer cachexia from a variety of tumors (n=47) was also confirmed in the subsequent study by the same group by intraoperative isotopic infusion of ^{14}C-leucine[83]. They concluded that patients with cancer cachexia were actively losing protein as a result of an increase in whole-body protein catabolism that was only partially compensated for by an increase in whole-body protein synthesis. In a patient group studied by Borzotta et al.[79], patients with advanced malignancy or stage 4 cancer had significantly greater protein turnover, synthesis, and catabolism than patients with localized disease. Similarly, significant correlation between alterations in protein metabolism and stages of disease was documented by Carmichael et al.[68].

Skeletal muscle protein metabolism and regional amino acid kinetic study

A common effect of tumor-bearing on protein metabolism in skeletal

muscle has been shown to be depressed protein synthesis and increased protein breakdown. Clark et al.[90], demonstrated those changes in the skeletal muscle in rats bearing the Wealker 256 carcinoma. Gastrocnemius muscle weight, RNA/DNA ratio, and incorporation of ^{14}C-valine were significantly decreased. Incorporation of ^{3}H-lysine into protein in the gastrocnemius polysome preparation was decreased, and net tyrosine release and $^{14}CO_2$ production from ^{14}C-leucine, representing protein degradation, were increased.

Lundholm et al.[85,77] examined the regional amino acid kinetics in rectus abdominus muscle obtained at surgery from 43 cancer patients with a variety of tumors and 55 controls. They demonstrated a significant decrease in the in vitro incorporation of ^{14}C-leucine into skeletal muscle protein and an increase in the fractional degradation rate of proteins in cancer group compared with control. Emery et al.[77] confirmed the significantly decreased protein synthesis in 5 cancer patients with weight loss by ^{13}C-leucine enrichment in quadriceps protein obtained by percutaneous biopsy. Protein synthesis in muscle was 0.030%/hour in cancer patients and 0.198 in controls ($p<0.01$). Although most claimed decreased protein synthesis rates in the muscle, only one group found the fractional synthetic rate of protein in rectus abdominus muscle to be increased in cancer patients with cancer cachexia[83].

Contrary results were also reported. Newman et al.[91], evaluated forearm phenylalanine exchange kinetics by infusion of L-phenylalanine under baseline and postabsorptive conditions in 16 cancer patients and 12 healthy controls and found no significant difference in phenylalanine kinetics in the basal state. Indirect evaluation of skeletal muscle protein catabolism by 3-methylhistidine documented no increase in cancer patients[92]. Whether those differences derive from differences in methodology or different types of tumor or stages is not clear.

Hepatic protein metabolism

Generally, protein synthesis in the liver has been reported to be increased in the tumor-bearing state. In the MCA 101 tumor-bearing mouse, increased incorporation of leucine in liver tissue was documented by Lundholm et al.[93]. They suggested that the tumor-bearing state was associated with an increased translational capacity.. Several systems have been defined as mechanisms of amino acid transport in liver. In the Fisher344 rat with MCA sarcoma, both System N (glutamine) and System y^+ (arginine) were increased in the presence of the tumor, while System A (MeAIB) was unaltered. The observation that hepatic glutamine transport activity remained augmented after tumor resection longer than any other transport systems studied suggested a key role for this amino acid in overall hepatic nitrogen metabolism and might partially explain the persistent glutamine depletion that was characteristic of the tumor-bearing host[94]. The arginine pathway, which plays a pivotal role in regulating ureagenesis, polyamine biosynthesis, and nitric oxide production, was significantly stimulated in liver of the tumor-bearing Fisher 344 rats. This response was mediated by an increase in activity of System y+[95].

In human studies, an increased in vitro incorporation of ^{14}C-leucine into homogenized hepatic proteins of cancer patients compared with normal controls was demonstrated[85]. Increased fractional synthesis rates (FSR) of protein in liver ($p<0.05$) and of albumin ($p<0.01$) have been confirmed in vivo in cancer cachexia patients compared with either non-weight losing cancer patient or normal control[83]. Patients with NWLC had a mean FSR of protein in liver of 18.3%±2.2% per day. In contrast, the corresponding value in the patients with cancer cachexia was 29.7%±5.0% per day.

4. Energy Metabolism

Studies on energy metabolism during prolonged fasting are a sharp contrast to the condition of cancer—decreased energy expenditure with increasing starvation. In the cancer, the propensity for elevated energy expenditure in the face of reduced intake has been attributed to a maladaptation of the host to the starvation state[4]. Although there is general agreement that cancer patients experience elevated energy expenditures, several studies have been reported with varied results.

Some investigators have attempted to overcome the problems of the Harris-Benedict formula by normalizing the REE to the metabolically active tissue (body cell mass)[46]. In noncachectic sarcoma patients (n=7), there was a significantly lower percentage of BCM than in controls. Reflecting this, the REE corrected for BSA was 25% greater in male sarcoma patients than in male controls ($p<0.05$), and this difference was doubled when REE was corrected for BCM ($p<0.01$). They concluded that both REE and vital, functional BCM could be significantly altered in sarcoma patients before any overt signs of cachexia develop[99].

Hansell et al.[47] assessed the hypothesis that different tumor types exert different effects on REE. REE in 84 cancer patients correlated significantly with body weight and lean tissue mass. The slope of the regression line for the bronchial cancer patients was significantly different from the colorectal and gastric cancer patients when REE was related to LBM. When REE in the same organ was compared, and results differed. In gastric cancer patients, Frederic et al[96] could not demonstrate any elevation, while Dempsey et al.[98] found significant elevation.

There is no widespread agreement concerning alterations in energy me-

tabolism in cancer patients. The use of a heterogeneous cancer group may be inappropriate in studies of REE as in other parameters in cancer. When REE is significantly elevated there is more likelihood for the disease to be widely spread.

5. Mediators—cytokines

Recently, there has been much interest in a variety of monokines, because they can elicit a metabolic response very similar to that seen in the cachectic syndrome induced by tumors: loss of appetite, loss of body weight (body fat and protein), and induction of acute phase protein synthesis[100]. These similarities alone do not prove a cause-and-effect relationship. Possible transfer of endogenous mediators via the circulation was demonstrated by the development of cachexia in non-tumor-bearing rats after parabiotic anastomosis to sarcoma-bearing cachectic rats [101]. However, the results reported by different investigators are not always the same.

TNF-alpha

TNF-alpha/cachectin, a 17kDa protein consisting of 157 amino acids, is produced by stimulated reticuloendothelial cells, principally macrophages and monocytes[102]. The receptors for TNF have been identified in nearly all tissues[103]. The half-life is 14-18 min in humans and 10 min in mice[104]. TNF is a well-documented growth factor for many normal cells, stimulating cellular growth and differentiation[105], and inducing production of a variety of compounds, including PGE2, collagenase, platelet activating factor, IL-1 and IL-6[106]. TNF also enhances angiogenesis[107].

A single injection of TNF alpha can cause a characteristic weight loss due to a reduction in food and water intake and a decreased carcass water content[108]. However, when rats received chronic (5-day) infusions of rH-TNF, profound anorexia and fluid retention, but not accelerated nitrogen losses, were observed[109]. Darling and Norton[110] reported that a continuous i.v. infusion of TNF, rather than an intermittent bolus i.v. resulted in a decreased food intake and a decreased nitrogen balance. After 4 days of treatment, rats treated with intermittent bolus doses of TNF developed tolerance. The TNF decreases LPL activity and increases hepatic lipogenesis[111,112]. Cells transfected with the TNF gene inserted near an active promotor were injected into nude mice, which produced a sustained release of TNF and resulted in a severe wasting of host body fat and lean tissue mass, progressive cachexia and eventual death[113,114,115]. Active TNF genes were demonstrated in the tumor and lymphoid tissue of MCA sarcoma-bearing mice[116] and in human colorectal tumors[117]. However, only a few papers have documented increased serum TNF in tumor-bearing patients[118,119]. No correlation between severity of cachexia and TNF concentrations was found[120,121].

IL-6

IL-6, a 26kDa protein, is perhaps the most extreme example of a pleiotropic cytokine. It has a broad range of activities on different cells and was originally found as a growth factor for transformed B-cells[122]. Some of its functions include stimulation and differentiation of B-cells (BSF-2)[123], supporting hybridoma and plasmacytoma cell growth (HGF/PGF), and stimulating synthesis of host response proteins by liver following exposure to toxic materials or injury (HSF) [124]. IL-6 is secreted by monocytes, fibroblasts, keratinocytes, endothelial cells,and B-cells. A specific, high affinity receptor for IL-6 is distributed on many different cells throughout the organism.

Is IL-6 the circulating message that induces anorexia[125] and the hepatic acute phase reactants? Elevated serum levels of IL-6 were demonstrated in Balb/c x DBA/2(CD) mice with colon 26 carcinoma[126]. The effects of IL-6 in vivo were assessed by inoculating nude mice with Chinese hamster ovarian cells that had been transfected with the murine IL-6. Only those inoculated with the transfected IL-6 gene demonstrated a number of paraneoplastic syndromes including hypercalcemia, cachexia, leukocytosis, and thrombocytosis[127]. Both the injection of IL-6 in mice and the culture of 3T3-L1 adipocytes in the presence of IL-6 reduced tissue and heparin-releasable LPL activity in a dose-dependent manner[128]. IL-6 was also demonstrated immunohistochemically in human tumor specimens[129]. Furthermore, some of the alterations were reversed by neutralizing antibodies to IL-6 (eg. the hypercalcemia associated with a human squamous cell carcinoma[130], the depletion of carcass weight and epididymal fat, hypoglycemia, and the increase in serum amyloid P[126]).

Why are cytokines not found in the circulation ?

To determine a cause and effect relationship between a molecule and any putative effects it may have in vivo, the molecule must first be demonstrated to be in the circulation at the time when host response is initiated[125].

Although Stovroff et al. demonstrated that TNF in the circulation of cachectic sarcoma-bearing rats was correlated with tumor burden and disappeared following tumor resection[114], and Balkwill et al detected labile TNF activity by means of an enzyme-linked immunosorbent assay in 50% of 226 freshly obtained serum samples from cancer patients with active disease [118], increased circulating TNF concentrations are not a regular finding in human or experimental cancer disease[116,132,121]. The magnitude of weight loss and the appearance of TNF in the circulation seem to be poorly correlated[133]. Analytical results at a molecular level are also controversial. Northern blot analy-

sis of human colorectal cancer specimens showed the presence of mRNA for TNF in 15 of 28 tumor samples and 6 of 26 matched normal tissue samples. TNF localized by in situ hybridization was demonstrated to correlate to activated macrophages that infiltrated the tissue. No one had detectable IL-1 or IL-6 mRNA in tumor or normal tissues, although all tissues tested expressed TGF-1[134]. Up-regulation of TNF gene transcription was also found in the liver and spleen despite an inability to detect circulating cachectin[116].

Many factors have been used to explain the low circulating levels of some of the cytokines. However, the difficulty in detecting TNF in the plasma of cancer patients and the ease of detecting it in cases of sepsis and severe infection does not lead us to conclude that the same molecule works differently in different disease state (i.e. as an autocrine or paracrine factor in cancer and as an endocrine factor in infection). No other hormones function through different mechanisms, depending on the pathologic conditions, unless other factors can recognize the different pathologies. There are increasing data that suggest a role for cytokines in mediating cancer cachexia. However, other reports argue against it. Whether cytokines and a cytokine network are responsible for inducing cancer-specific metabolic alterations or not has to be clarified in further study.

6. Insulin Resistance in Cancer

Insulin resistance in the tumor-bearing state was found as early as 1919 by Rohdenberg et al.[135]. Lundholm et al.[136] showed that a decrease in glucose after insulin infusion is quantitatively smaller in cancer patients compared with controls. Insulin resistance is generally defined as quantitative decrease in response to insulin infusion[137]. It is not rare to find an abnormal glucose tolerance in cancer patients. Glicksman et al.[138], examining 600 cancer patients by glucose tolerance tests, found that 37% of those examined demonstrated a diabetic pattern. In contrast with other alterations, more data on insulin resistance has come from human studies. Initially, it was considered that insulin resistance was the result of malnutrition; however, insulin resistance was found even in those with early sarcoma, esophageal cancer[139], and non-oat cell carcinoma.

Insulin resistance in glucose metabolism

Lundholm et al.[144] documented that in malnourished cancer patients, both insulin sensitivity and responsiveness were decreased in 50%, 70-80% of infused glucose during glucose clamp was taken up by the peripheral tissue, and insulin sensitivity in the peripheral tissue was lower than that in the whole body sensitivity. The decreased insulin sensitivity in the peripheral tissue was difficult to reverse with a large amount of insulin.

Copeland et al.[143], examining 12 patients with colorectal cancer, documented that responsiveness (maximal glucose disposal) was decreased compared to controls, but sensitivity (insulin concentration of half maximal glucose disposal) was not different. These findings suggest that insulin resistance occurs as a post-receptor defect. Most data so far reported agree that glucose disposal is decreased in many cancer patients. The only contradictory paper came from Byerley on patients with head and neck tumors[140]. In their study, glucose disposal rate was increased in cancer patients, suggesting an increased drainage of glucose into the tumor. However, insulin clearance rate was increased in their patients, which might result in increased glucose disposal.

We examined insulin sensitivity in both weight-losing and weight-stable patients with cancer and compared their results with those of a normal volunteer. There was significant decrease in glucose metabolized and metabolic clearance of glucose in both the weight-stable and weight-losing patients compared with controls. This decrease was reversed by complete tumor removal, suggesting that insulin resistance in patients with cancer is not a result of cancer-associated malnutrition but is related to the tumor itself[67].

Insulin resistance in lipid metabolism

There have not been many papers on this issue. The presence of insulin resistance in LPL activity was documented in studies in vivo and in vitro with MCA sarcoma-bearing rats[146]. McRussel et al.[145] found that hyperlipidemia (FFA, 80$\pm$62uM) observed in patients with small cell lung cancer under chemotherapy with hyperalimentation did not respond to the high insulin level of 5.07$\pm$1.66 ng/ml and suggested the presence of insulin resistance in those patients. In our study during glucose clamp, changes in TG, FFA, very low density lipoprotein (VLDL), and LDL levels were not related with M values calculated from the insulin clamp technique. In septic cancer patients, insulin resistance in FFA turnover was more apparent than resistance in suppressing endogenous insulin production. The antilipolytic effect of insulin is induced by 1/4 of the amount necessary for glucose utilization and ½ of that required for suppressing endogenous glucose production. Therefore, insulin resistance in lipid metabolism may be more difficult to be demonstrated[147].

Insulin resistance in protein metabolism

The influence of insulin on protein synthesis from phenylalanine in the C57BL/6J mouse skeletal muscle and from leucine in the rectal muscle of cancer patients revealed no difference between cancer patients and controls[148]. Amino acid alterations during hyperinsulinemic glucose clamp were not related with glucose metabolized or

M values (unpublished data). Insulin action on arterial BCAA concentrations and forearm BCAA flux was investigated in 6 weight-losing patients with localized gastrointestinal cancer by euglycemic hyperinsulinemic clamp. Progressive euglycemic insulin infusion induced a marked, comparable insulin-dependent decrease in arterial plasma BCAA concentrations in both patients and controls. There was no difference in post-absorptive forearm BCAA flux with progressive hyperinsulinemia. Insulin-induced branched-chain hypoamino acidemia was unimpaired in this group of patients. Those provide evidences of differential resistance to insulin action in glucose and protein metabolism [74].

Mechanisms of insulin resistance in cancer

Mechanisms of insulin resistance in cancer patients have not yet been clarified. Therefore, mechanisms in diabetes mellitus referred to here and theoretical mechanisms are summarized in table 1. The increase in catabolic hormones in cancer patients such as glucagon, cortisol, and catecholamine is one possibility[147]. Ojamaa et al.[149] suggested a decrease in insulin receptor mRNA and synthesis rate of insulin receptors, a defect at the post-translational levels, or decreased translocation of the transport proteins to the plasma membrane in diabetic patients. Haring et al.[150], studying the Claudman S91 melanoma cell, documented decreased affinity of receptors to insulin and decreased autophosphorylation of beta-subunit tyrosine kinase. Significant correlation between decreased activation of tyrosine specific protein kinase (beta-subunit) and insulin resistance has been suggested. From the fact that the number of insulin receptors necessary for insulin to induce its effect is less than 5% of total insulin receptors, Krett et al.[151] suggested the greater importance of post-receptor events as compared to number of insulin-binding sites.

The mechanisms of defects in kinase is complex, including 1) defects in autophosphorylation of receptor kinase, 2) an alteration in ATP-binding sites for insulin receptor tyrosine kinase, resulting in decreased activity of insulin receptor tyrosine kinase, 3) presence of insulin insensitivity. Other possible mechanisms may include a defect in internalization of insulin receptors, decreased intracellular uptake of insulin-receptor complex, and a defect in signal transduction between receptor kinase and glucose transporter. Dissection of the mechanisms of insulin resistance may give us another key to solve the complex mechanisms of cancer cachexia.

Table 1 - Mechanisms of insulin resistance.

1.	Abnormal insulin molecule
2.	A defect in conversion from proinsulin to insulin
3.	Increased counter regulatory hormones
4.	Anti-insulin antibody
5.	Abnormalities at the level of receptor a) ecreased number of receptor or affinity b) anti-insulin receptor antibody c) a defect in translocation of the receptor d) decreased activity of tyrosine specific protein kinase e) a defect in internalization of insulin receptor
6.	A defect at the post-receptor level a) glucose transporter

CONCLUSIONS

Tumor-bearing hosts suffer from tumor-induced metabolic alterations, some of which are secondary to malnutrition and others that are tumor-specific changes. In evaluating those alterations, the type of the tumor and the stages of the cancer may have to be taken into account.

As in other data, animal results may not necessarily be applicable to tumor-bearing humans. Nutritional support can reverse most but not all alterations. Indications of nutritional support have to be determined from patient-benefit considerations as well as tumor growth. The selection of patients for intensive nutritional support should be recognized as a science not an art. To this end, further dissection of basic mechanisms of tumor-induced metabolic alterations is necessary.

RESUMO RHCFAP/3022

YOUNES RN e col. - Fisiopatolgia da caquexia em câncer. **Rev. Hosp. Clín. Fac. Med. S. Paulo 55**(5): 181-193, 2000.

A caquexia é uma complicação freqüentemente observada em pacientes portadores de tumores malignos. Apesar de várias décadas transcorrerem desde a descrição inicial das disfunções metabólicas associadas ao câncer, poucas medidas terapêuticas foram induzidas com sucesso na prática médica.

O presente estudo apresenta uma revisão detalhada da fisiopatologia básica da caquexia em câncer, e as opções terapêuticas desenvolvidas nesta área. Estudos experimentais, assim como clínicos, são avaliados individualmente para esclarecer as alterações complexas observadas em pacientes portadores de tumores. As dificuldades encontradas para introduzir manipulações metabólicas e terapias de suporte nutricional eficientes são discutidas nesta revisão.

DESCRITORES: **Câncer. Caquexia. Metabolismo. Citoquina. Insulina.**

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