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Review

Beyond anorexia -cachexia. Nutrition and modulation of cancer patients' metabolism: Supplementary, complementary or alternative anti-neoplastic therapy?

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ABSTRACT

Anorexia and muscle wasting are frequently observed in cancer patients and influence their clinical outcome. The better understanding of the mechanisms underlying behavioral changes and altered metabolism yielded to the development of specialized nutritional support, which enhances utilization of provided calories and proteins by counteracting some of the metabolic derangements occurring during tumor growth. Inflammation appears to be a key factor determining the cancer-associated biochemical abnormalities eventually leading to anorexia and cachexia. Interestingly, inflammation is also involved in carcinogenesis, cancer progression and metastasis by impairing immune surveillance, among other mechanisms. Therefore, nutritional interventions aiming at modulating inflammation to restore nutritional status may also result in improved response to pharmacological anti-cancer therapies. Recent clinical data show that supplementation with nutrients targeting inflammation and immune system increases response rate and survival in cancer patients. This suggests that nutrition therapy should be considered as an important adjuvant strategy in the multi-dimensional approach to cancer patients.

Contents

1. Introduction

The progressive deterioration of nutritional status is a common feature of cancer patients (Laviano et al., 2005). Anorexia and reduced food intake coupled with profound metabolic changes (i.e., increased proteolysis and lipolysis, reduced insulin sensitivity) are the main factors contributing to wasting of cancer patients (Laviano et al., 2005). It is important to note that tumor growth *per se* may trigger the onset of neurochemical alterations, inflammation, behavioral changes, muscle loss, adipose tissue depletion, insulin resistance. In the clinical settings, these symptoms and signs are variably observed in cancer patients, and the ample heterogeneity of clinical manifestations is now recognized as a characterizing feature of cancer cachexia (Fearon et al., 2011). However, anti-tumor therapies may also influence food intake, and thus worsen cachexia, by altering detection and recognition thresholds of basic tastes and smell (Sanchez-Lara et al., 2010).

The clinical relevance of cachexia has been extensively demonstrated. Cachectic cancer patients suffer from greater chemo- and radiotherapy associated toxicity (Arrieta et al., 2010), which frequently leads to interruption of the planned therapies, and thus probably contributes to reduced survival (Pressoir et al., 2010). Also, weight loss and anorexia are major contributors to the reduction of quality of life of cancer patients (Ravasco et al., 2004). Strengthening the association between nutritional status and cancer patients' outcomes, many clinical trials demonstrated

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that early nutrition intervention, i.e., when cachexia has not become refractory yet (Fearon et al., 2011), improves tolerance to aggressive anti-tumor therapies (Paccagnella et al., 2010), ameliorates quality of life (Marin Caro et al., 2007), and prolongs survival (Gupta et al., 2010), at least in some clinical settings. This impressive series of evidence recommend that evaluation of nutritional status should be included in the multi-dimensional initial approach to cancer patients. Since the assessment of nutritional status is a complex and time consuming procedure which should be performed by specifically trained professionals, screening for nutritional risk appears more feasible in the daily oncology practice, reserving complete assessment for selected patients. Interestingly, the use of simple and validated nutritional screening tools, like the Mini Nutritional Assessment or the Malnutrition Universal Screening Tool, has been recently demonstrated to be easily integrated into daily routine, to timely identify nutritional risk, and to provide robust anticipation of cancer patients' clinical outcome (Boleo-Tomé et al., 2011; Gioulbasanis et al., 2011).

The pathogenesis of cancer cachexia has been extensively investigated during the last decade. Consistent evidence show that inflammation induced by growing tumor is the key factor responsible for most of the symptoms and signs reported by cancer patients, including anorexia and cachexia (Seruga et al., 2008). The inflammation-induced molecular mechanisms which trigger muscle wasting have been detailed by experimental and clinical studies (Tisdale, 2009), and contributed to the development of pathogenesis-based therapeutic strategies (Argiles et al., 2010). However, cancer cachexia is a systemic syndrome and increased circulating levels of pro-inflammatory cytokines have not been consistently reported. Therefore, the inflammatory signals generated by the interaction between the tumor and the host immune system should use other highways to reach different tissues and organs and then influence metabolism and behavior. The central and peripheral nervous systems are suitable candidates.

2. Neuroinflammation and cachexia

The central role of the nervous system in controlling human behavior and metabolism is increasingly being recognized. As an example, insulin sensitivity and circulating cholesterol levels are centrally controlled (Perez-Tilve et al., 2010; Xu et al., 2010). It is therefore tempting to speculate that the central nervous system may also mediate, at least in part, the behavioral, clinical, and biochemical features of cancer cachexia.

Under physiological conditions, food intake is controlled by the hypothalamus. In the arcuate nucleus of the hypothalamus, orexigenic and anorexigenic neurons are colocalized (Laviano et al., 2008). A subset of arcuate neurons expresses a potent prophagic neuropeptide, i.e., neuropeptide Y. The other subset of arcuate neurons expresses an inert polypeptide, i.e., pro-opiomelanocortin, which is then cleaved into active hormones, the melanocortins (Laviano et al., 2008). Among them, the α-melanocyte stimulating hormone mediates anorexigenic responses via melanocortin MC_4 receptors, which are expressed by second order neurons (Laviano et al., 2008). The functional integration of neuropeptide Y and pro-opiomelanocortin neurons in tightly controlling food intake is highlighted by the evidence that neuropeptide Y neurons also express agouti-related protein, the natural antagonist of melanocortin MC_4 receptors (Laviano et al., 2008).

The arcuate nucleus of hypothalamus is informed on the metabolic status of peripheral tissues by an extensive network of neural afferents and hormonal input, and then triggers the appropriate response: feeding in presence of failing energy stores and catabolic metabolism, or satiety when energy stores are repleted and metabolism switches to anabolic pathways (Laviano et al., 2008). In the presence of a growing tumor, the physiological equilibrium between neuropeptide Y and pro-opiomelanocortin neurons is altered, and the arcuate nucleus is set on an anorexigenic mode, which is insensitive to the peripheral orexigenic signals and is expressed by persistently activated pro-opiomelanocortin neurons and inhibition of neuropeptide Y neurons (Laviano et al., 2008). Consistent evidence and the identification of receptors for proinflammatory cytokines on arcuate neurons suggest that neuroinflammation, which results from increased expression of proinflammatory cytokines in brain areas, is key in determining the functional switch of the arcuate nucleus and the resistance to peripheral signals.

Of biological and clinical relevance is the investigation on the mechanisms by which the hypothalamus is informed of the presence of a peripherally growing tumor, which could be a few millimeters in size. Based on experimental evidence, it has been postulated that the inflammatory microenvironment of growing tumors is sensed by vagal afferents and this information is transferred to the hypothalamus (Laviano et al., 2008), which triggers the response to stress by activating pro-opiomelanocortin neurons and inhibiting neuropeptide Y neurons. The acute phase response is characterized by sickness behavior. This includes anorexia and reduced food intake, but also the activation of the nicotine anti-inflammatory pathway which is mediated by the vagus nerve (Guijarro et al., 2006). Indeed, inflammation suppresses immune surveillance, thus favoring tumor growth, and modulation of inflammatory microenvironment could be key to restore anti-tumor immune responses (Laviano et al., 2009). If the biochemical and behavioral responses fail to regulate inflammation and suppress tumor growth, persistent activation of pro-opiomelanocortin neurons induces the expression of proinflammatory cytokines within the hypothalamus (Laviano et al., 2008), and the resulting neuroinflammation maintains the arcuate nucleus in the catabolic mode and thus perpetuates the anorexigenic behavior.

During the last few years, the dual role of the hypothalamus in controlling energy homeostasis has been increasingly recognized. Beyond its well established role in mediating sickness behavior during acute and chronic diseases, the hypothalamus also controls the metabolism of peripheral tissues (Balthasar et al., 2005). Interestingly, a number of clinical and experimental data allow to translate this concept into the pathophysiology of cancer cachexia, by showing a role for the hypothalamus in cancer-induced changes in metabolism of peripheral tissues. Intrahypothalamic partitioning between fatty acid oxidation and fatty acid synthesis is an additional, leptin-independent, potent regulator of food intake (Laviano et al., 2008). Carnitine palmitoyltransferase-1c is the main regulatory enzyme involved in brain fatty acid oxidation. Inflammation-mediated inhibition of this enzyme may switch intrahypothalamic metabolism from fatty acid oxidation to fatty acid synthesis, and thus suppress food intake (Laviano et al., 2008). Interestingly, knockout animals for carnitine palmitoyltransferase-1c display decreased rates of fatty acid oxidations and depressed food intake (Wolfgang et al., 2006), whereas inhibition of hypothalamic fatty acid synthase reduces food intake and increases energy expenditure in muscles (Cha et al., 2005). Moreover, in cachectic tumor-bearing rats, carnitine supplementation restores deranged hepatic lipid metabolism (Silverio et al., in press). Strengthening the link between the hypothalamus and global energy homeostasis under physiological and disease conditions, body mass index has been demonstrated to be related to autonomic nervous system activity (Molfino et al., 2009). In cancer patients, autonomic dysfunction as measured by heart rate variability correlates with anorexia and energy expenditure (personal observations) and predicts survival (Chiang et al., 2010; Fadul et al., 2010; Kim do et al., 2010). Pharmacologic activation of the nicotine anti-inflammatory pathway inhibits circulating levels of pro-inflammatory cytokines, improves appetite and ameliorates body composition of tumor bearing rats (Molfino et al., 2011). Finally, preliminary observations show that CPT-1c expression is reduced in the hypothalamus of tumor-bearing rats (Seelaender M., unpublished observations).

It is therefore likely that during early tumor growth, the central nervous system is activated by sensing the inflammatory microenvironment surrounding cancer cells and reacts by mediating the onset of sickness behavior and the deployment of the physiological, vagally-