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New insights on the regulation of cancer cachexia by N-3 polyunsaturated fatty acids

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ABSTRACT

Cancer cachexia is a multifactorial syndrome that develops during malignant tumor growth. Changes in plasma levels of several hormones and inflammatory factors result in an intense catabolic state, decreased activity of anabolic pathways, anorexia, and marked weight loss, leading to cachexia development and/or accentuation. Inflammatory mediators appear to be related to the control of a highly regulated process of muscle protein degradation that accelerates the process of cachexia. Several mediators have been postulated to participate in this process, including TNF-α, myostatin, and activated protein degradation pathways. Some interventional therapies have been proposed, including nutritional (dietary, omega-3 fatty acid supplementation), hormonal (insulin), pharmacological (clenbuterol), and nonpharmacological (physical exercise) therapies. Omega-3 (n-3) polyunsaturated fatty acids (PUFAs), especially eicosapentaenoic acid (EPA) and docosahexaenoic acid, are recognized for their anti-inflammatory properties and have been used in therapeutic approaches to treat or attenuate cancer cachexia. In this review, we discuss recent findings on cellular and molecular mechanisms involved in inflammation in the cancer cachexia syndrome and the effectiveness of n-3 PUFAs to attenuate or prevent cancer cachexia.

Contents

Abbreviations: 4E-BP1, Eukaryotic initiation factor-4E binding protein-1; AA, Arachidonic acid; ActRIIB, Activin receptor IIB; ALK, Activin-like kinase; AP-1, Activator protein-1; Apc (Min+/+) mice, Adenomatous polyposis coli (multiple intestinal neoplasia) mice; COX, Cyclooxygenase; CRP, C-Reactive protein; DHA, Docosahexaenoic acid; eIF4E, Eukaryotic initiation factor-4E; EPA, Eicosapentaenoic acid; ERK, Extracellular signal-regulated kinase; FIS-1, Mitochondrial fission-1; FOXO-1, Forkhead box protein O-1; GSK-3β, Glycogen synthase kinase-3 beta; IGF-I, Insulin-like growth factor-I; IL, Interleukin; IL-6R, Interleukin-6 receptor; INF-γ, Interferon-gamma; iNOS, Inducible nitric oxide synthase; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; LTB4, 4-Series leukotrienes; LMF, Lipid-mobilizing factor; LOX, Lipoxygenase; LPL, Lipoprotein lipase; LPS, Lipopolysaccharide; MAFbx, Muscle atrophy F-box; MAPK, Mitogen-activated protein kinase; Mfn, Mitofusin; MMP-9, Matrix metalloproteinase-9; mTOR, Mammalian target of rapamycin; MuRF-1, Muscle ring-finger protein-1; MyoD, Myogenic differentiation; NADPH, Reduced nicotinamide adenine dinucleotide phosphate; NF-κB, Nuclear factor-kappa B; NO, Nitric oxide; NPY, Neuropeptide Y; PGC-1α, Peroxisome proliferator-activated receptor-gamma coactivator-1 alpha; PGE2, Prostaglandin E2; PGI2, Prostacyclin I2, PI3-K, phosphoinositide 3-kinase; PIF, Proteolysis inducing-factor; PKC, Protein kinase C; PUFA, Polyunsaturated fatty acids; ROS, Reactive oxygen species; SOCS-3, Suppressor of cytokine signaling-3; STAT, Signal transducer and activator of transcription; TGF-β, Transforming growth factor-beta; TNF-α, Tumor necrosis factor-α; TXA2, Thromboxane A2; UCP, Uncoupling protein; ZAG, Zinc-alpha2-glycoprotein.

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1. Introduction to cancer cachexia

1.1. General view

Cancer cachexia is a multifactorial syndrome that develops during malignant tumor growth. This condition involves changes in plasma levels of several hormones and immune-inflammatory factors, resulting in an intense catabolic state, decreased activity of anabolic pathways, anorexia, and marked weight loss (Argiles, Busquets, Stemmler, & Lopez-Soriano, 2014; Mantovani & Madeddu, 2010). Elevated degradation of carbohydrates, lipids, and proteins is associated with chronic and systemic inflammation, anemia, and reduced energy intake and physical activity, which leads to a negative protein and energy balance. Under this condition, body mass wasting, a progressive decrease in body weight to a debilitated state, impaired tolerance to anticancer therapies, and a reduced quality of life and survival rate of the patients are reported (Argiles et al., 2014; Bruera et al., 2003; C. Deans & Wigmore, 2005; Dewys et al., 1980; Fearon, 2011, 2012; Gordon, Green, & Goggin, 2005; Tan & Fearon, 2008). Despite the clinical relevance, the mechanisms involved in the development of cancer cachexia are not completely understood to date.

Appropriated therapy, including surgery, chemotherapy, or radiotherapy, are hampered by the debilitated condition imposed by cancer cachexia (Argiles et al., 2014; Fearon, 2011, 2012). High morbidity and mortality ratios are reported in cancer cachexic patients. Weight loss, fatigue, and markers of systemic inflammation can exacerbate this process (Muscaritoli, Bossola, Aversa, Bellantone, & Rossi Fanelli, 2006; Wallengren, Lundholm, & Bosaeus, 2013). Approximately half of all patients with cancer develop cachexia (Diffee, Kalfas, Al-Majid, & McCarthy, 2002; Tijerina, 2004), and 22% of these patients do not survive (Skipworth, Stewart, Dejong, Preston, & Fearon, 2007; Warren, 1932). Thus, the great challenge for these patients is to support themselves by receiving adequate interventional therapy, especially therapies that can increase body weight and survival rate. Some interventional therapies have been proposed, including nutritional (dietary, omega-3 fatty acid supplementation), hormonal (insulin), immunological, pharmacological (clenbuterol), and nonpharmacological (physical exercise) therapies (Balakrishnan, 2016; Giacosa & Rondanelli, 2008; Peisch, Van Blarigan, Chan, Stampfer, & Kenfield, 2017; Schoenberg, 2016; Terepka & Waterhouse, 1956). However, a clinically effective therapy (or combined therapy) is still lacking. Omega-3 (n-3 or w-3) polyunsaturated fatty acids (PUFAs), especially eicosapentaenoic acid (EPA) and docosahexaenoic acid, are recognized for their anti-inflammatory properties, reducing proinflammatory cytokines, cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2) and nuclear factor-kappa B (NF-κB) activities. Additionally, PUFAs have been used in therapeutic approaches to prevent or treat cachexia (Abe et al., 2018; Fernandes, Machado, Nogueira, Carpinelli, & Curi, 1990; Giacosa & Rondanelli, 2008; Murphy, Mourtzakis, & Mazurak, 2012; Schiessel et al., 2015). In this review, we discuss recent findings on cellular and molecular mechanisms involved in inflammation in the cancer cachexia syndrome. Additionally, the effectiveness of n-3 PUFAs to attenuate or prevent cancer cachexia will be updated.

1.2. Metabolic mechanisms regulating cachectic disturbances

In the 1930s and 1950s, pioneering reports based on patient necropsy (Terepka & Waterhouse, 1956; Warren, 1932) and animal studies (Fenninger & Mider, 1954), respectively, postulated that tumor tissue would work as an energy and protein trap in the host. The main problem in this theory is that few human tumors exceed 5% of body weight. Therefore, a single nutrient-trapping mechanism is unlikely to fully account for the development of cancer cachexia. Studies performed in the 1970s and 1980s shed light on specific disturbances of intermediary metabolism in cancer patients with weight loss. The metabolic disturbances have the following in common: increased glucose output by the liver in the fasting condition, markedly elevated lipolysis and proteolysis, fat mass reduction, impaired insulin release and action and, in male cancer patients, the presence of hypogonadism. Several factors released from the tumor tissues and immune system associated with an elevated plasma concentration of catabolic hormones and markedly reduced plasma levels of insulin are the main contributors to the high rate of catabolism and low rate of anabolism reported in cancer patients (Fernandes et al., 1990).

Patients with tumors display significant body weight loss (Robbins & Cotran, 2005) even with a tumor mass corresponding to 0.01% of the total body weight (Nathanson & Hall, 1974). Thus, the tumor is proportionally very small to cause all metabolic disturbances only through the simple competition for nutrients between the host and the tumor. Healthy subjects have anabolic and catabolic activities in balance; the insulin effect prevails in the fed state, and the glucagon, catecholamine, growth hormone, thyroid hormone, and cortisol effects prevail in the fasting state. The tumor growth shifts this balance to a more prominent catabolic state due to the high plasma levels of catabolic hormones (Heber & Tchekmedyian, 1992).

Except for prolonged starvation and during the lifetime of the fetus, the brain uses glucose as the main fuel (Bolli & Fanelli, 1999). In stress conditions, the body mobilizes stored metabolites very rapidly to supply energy metabolites for all cells and glucose for the brain and erythrocytes. Under physical injury, severe infection, or neoplasia, this mobilization occurs at high rates. As a matter of fact, metabolic disturbances reported in neoplasia are more similar to the infection-induced condition rather than to starvation (Argiles, Moore-Carrasco, Busquets, & Lopez-Soriano, 2003; Moldawer, Svaninger, Gelin, & Lundholm, 1987).

Demetrakopoulos, Linn, and Amos (1978) described the dependence on glucose of tumor development and growth. They reported that in the absence of glucose, cells are able to maintain levels of ATP within a normal range for at least 24 h, whereas cancer cells can only maintain ATP levels for barely 4 h. Another feature of the increased glucose metabolism by cancer cells is the shunt of the pentose phosphate pathway, where glucose-6-phosphate and fructose-6-phosphate are channeled for the biosynthesis of nucleic acids (Dang, Lewis, Dolde, Dang, & Shim, 1997; Levin & Gevers, 1981; Newsholme, Gaudel, & McClenaghan, 2010). Glucose uptake and anaerobic glycolytic activity are quite high in tumor tissue (Warburg, 1930). Cancer cells have a high level of glycolysis associated with an increase in lactate dehydrogenase activity, the enzyme that converts pyruvate into lactate (Goldman, Rosales, Villavicencio, & Guerra, 1964). This increased activity leads to the release of this metabolite by the tumor tissue into the circulation. Several studies in cancer patients (Hill, 1957; White, 1958) and in tumor-bearing animal models (Argiles & Lopez-Soriano, 1990; Beck-Nielsen & Pedersen, 1978) reported an increase in lactate dehydrogenase activity and lactate levels in serum. Thus, increased glucose utilization by the tumor tissue causes a progressive state of hypoglycemia in the host. Lactate is an important source of glucose through liver gluconeogenesis (Warburg, 1956) and a powerful anorexic agent (Baile, Zinn, & McLaughlin, 1970; Lam, Chari, Wang, & Lam, 2008).

Among several characteristics that differentiate neoplastic cells from normal cells, we can cite the presence of a low number of mitochondria (up to 50%), altered activities of key enzymes of the glycolytic pathway, expression of enzymes with fetal features and type and amount of glucose transporters in neoplastic cells (Argiles & Lopez-Soriano, 1990; Beck-Nielsen & Pedersen, 1978; Medina, Carrascosa, & Nunez de Castro, 1990). To supply the increased energy demands, neoplastic cells highly express glucose transporter-1 (GLUT-1). This transporter is responsible for maintaining elevated glucose uptake and utilization by cancer cells. Recent studies showed that GLUT-1 not only has an important role in glucose metabolism but also regulates signaling pathways involved in the tumor growth of breast cancer, such as the Ras/MAPK pathway (Oh, Kim, Nam, & Shin, 2017). It is noteworthy that high glycolytic activity is not restricted to cancer cells or is even a universal feature of all neoplastic cells.

Some tumors do not rely only on glucose since they can grow in the presence of other substrates (Wice, Reitzer, & Kennell, 1981). Another important fuel for cancer cells is glutamine. Glutamine is most abundant in the organism, and skeletal muscle tissue has been recognized as the main source of this amino acid. Glucose and glutamine are generally accepted as the main metabolites used in tumor cell growth to supply the required respiratory fuel and nitrogen required during proliferation (Medina, Sanchez-Jimenez, Marquez, Rodriguez Quesada, & Nunez de Castro, 1992).

Other substrates can also be metabolized by tumor cells, including palmitate, ketone bodies, arginine, asparagine, serine, and alanine (Argiles & Azcon-Bieto, 1988; Medina et al., 1992). In relation to glutamine utilization by tumor cells, the rate of glutaminolysis is proportional to cell malignancy (Parry-Billings et al., 1991; Theologides, 1976). In fibrosarcoma with a high growth rate, glutamine utilization is approximately 45% higher than that observed in any organ (Souba, 1993). Glutamine influx is mediated by three transporter systems, namely A, ASC, and N (Bhutia & Ganapathy, 2016). ASCT2, an ASC family member, has an important role in glutamine-dependent tumor cell growth. Experimental strategies for ASCT2 inhibition are associated with growth repression and apoptosis in several human cancer types (Dong et al., 2017).

In cachexia, increased lipid catabolism occurs due to elevated expression of hormone-sensitive lipase and lipolytic response to catecholamines, leading to loss of adipose tissue. This metabolic feature is also associated with the presence of lipid-mobilizing factor (LMF) in the urine of cachectic cancer patients. This factor causes lipolysis through a cyclic AMP-mediated process by interaction with a beta3-adrenoreceptor (Tisdale, 2004). Elevated rates of whole body fatty acid oxidation were demonstrated in cancer patients who presented a 10% loss of initial body weight (Dahlman et al., 2010).

Lipolysis is activated in the adipocyte, which reduces its cellular volume and is accompanied by a decrease in the rate of de novo lipogenesis (Inacio Pinto et al., 2015). Studies in healthy rodents and human adipocytes have linked stimulation of lipolysis in white adipose tissue with increased fatty acid oxidation and uncoupling in white adipose depots (Bordicchia et al., 2012; Jaworski et al., 2009). The activation of mitochondrial uncoupling proteins (UCPs) is an alternative mechanism contributing toward hypermetabolism. These proteins have important role in brown adipose tissue which is characterized by abundant mitochondria, lipid droplets, and rich vascularization (Richard & Picard, 2011). Tsoli et al. (2012) showed that the increased UCP1, Pbe, and Cpt-1α expression is accompanied by high brown adipose tissue temperature in cachectic mice during the dark cycle, suggesting a temporal stimulation of thermogenesis in cachexia.

The increased lipolysis also can modify the microenvironment of adipose tissue and induce secretion of inflammatory peptides, resulting in the infiltration of macrophages, lymphocytes and stromal cells (Nieman, Romero, Van Houten, & Lengyel, 2013).

Recently, an adipokine, zinc-alpha2-glycoprotein (ZAG) was identified as a lipolytic factor produced by certain cachexia-inducing tumors, and subsequently adipose tissue. Expression of ZAG is increased in cancer induced cachexia (Bing et al., 2004). ZAG increases lipolysis in adipose tissue through cyclic AMP signaling and also PPARγactivation (Elattar, Dimri, & Satyanarayana, 2018; Russell, Zimmerman, Domin, & Tisdale, 2004). These pathways are involved in the increase of UCP1 expression in brown adipose tissue, which stimulates utilization of the released fatty acids to generate heat (Elattar et al., 2018).

Cachexia and skeletal muscle loss, which are frequently observed in cancer patients, are not caused only by reduced food intake. Increased metabolic demand and gastrointestinal tract dysfunction also play an important role. In fact, cancer patients, despite ingesting an adequate amount of calories, fail to maintain or gain body weight, which supports the proposition that these individuals are in a hypermetabolic state. Studies in animal models reported that even in the beginning of the disease, the tumor-bearing host may appear healthy and have regular food consumption but already exhibit glutamine depletion. Tumor growth causes a marked reduction in skeletal muscle glutamine content. Concomitant with these changes, the specific activity and amount of mRNA of glutamine synthase are increased (Thompson, Koons, Tan, & Grigor, 1981), perhaps as an attempt to keep the glutamine tissue store constant through intracellular glutamine synthesis. This compensation mechanism, however, maintains tissue glutamine content unchanged only for a certain period of time because a high catabolic state prevails.

The depletion of glutamine in cancer patients is caused by the disease itself as well as by the catabolic effects of antineoplastic therapies. Signaling factors released by the tumor and/or by immune cells accelerate glutamine release from skeletal muscles (Matthys & Billiau, 1997; Noguchi et al., 1996). During cancer progression, liver and tumor tissues take up glutamine at a high rate, and in the skeletal muscles, the release of glutamine is also increased as an attempt to maintain plasma glutamine levels in the normal range. Glutamine depletion becomes severe due to the high metabolic demand of the neoplastic tissue and leads to the death of the tumor-bearing host.

Compared to healthy individuals, cancer patients and tumor-bearing animals are more sensitive to the catabolic effects of cytokines released by the tumor and/or immune cells. Using a parabiotic preparation of a rat sarcoma, metabolites produced by cancer cells cause the main metabolic alterations in the host (Norton, Moley, Green, Carson, & Morrison, 1985; Theologides, 1976; Theologides & Lee, 1972). A lipid-mobilizing substance, toxohormone-L, was described in the tumor extracts and body fluids obtained from cancer patients and tumor-bearing rats. The injection of this latter hormone into the lateral ventricle of the rat brain markedly reduced food and water intake (Masuno, Yoshimura, Ogawa, & Okuda, 1984). Tumor necrosis factor-α (TNF-α) isolated from macrophages inhibits lipoprotein lipase (LPL) activity in peripheral tissues (Beutler, Mahoney, Le Trang, Pekala, & Cerami, 1985; McAndrew, 1986; Thompson et al., 1981; Torti, Dieckmann, Beutler, Cerami, & Ringold, 1985; Vlassara, Spiegel, San Doval, & Cerami, 1986). Low activity of LPL increases serum concentrations of triacylglycerol, cholesterol, and free fatty acids. When added to adipocyte culture medium, TNF-α inhibits the transcription of several enzymes involved in lipogenesis, e.g., fatty acid synthetase and acetyl-coenzyme A carboxylase. The association between high plasma levels of TNF-α and human cancer cachexia has been reported by some authors (Balkwill et al., 1987; Saarinen, Koskelo, Teppo, & Siimes, 1990). However, others found only very low levels of TNF-α in plasma (Selby et al., 1987; Socher, Martinez, Craig, Kuhn, & Oliff, 1988) and described a weak correlation between this cytokine and cancer cachexia development in some patients. The obvious conclusion is that other factors act as mediators of cancer cachexia in human subjects. We do not rule out the possibility of episodic appearances of different cytokines at low concentrations but at sufficient amounts to induce the metabolic changes observed in cancer patients.

MAC16 is a colon adenocarcinoma model that induces accentuated weight loss in host animals with relatively small tumor burdens (>0.1% of host body weight) without alteration in food and water intake

(Beck & Tisdale, 1987). This model is advantageous for studying the metabolic effects of the tumor in the absence of anorexia. Catabolic factors produced by the tumor were reported to promote loss of adipose tissue and reduction in skeletal muscle mass in the MAC16 host, namely, LMF and proteolysis-inducing factor (PIF), respectively (Beck & Tisdale, 1987). High plasma concentrations of LMF in tumor-bearing animals are compatible with a systemic effect rather than a local effect and cause breakdown of the host lipid storage for tumor growth. PIF secreted by the tumor tissue accelerates the catabolic rate, leading to an increase in proteolytic activity.

The congenital cancer of the sympathetic nervous system (neuroblastoma) secretes substances related to epinephrine (Voorhess, 1974). Insulin plasma concentration is quite low in cancer patients, which favors catabolic and antianabolic processes. The body weight loss caused by this catabolic condition is observed even when a diet with an adequate content of amino acids and calories is prescribed (Fearon & Carter, 1988). Other contributors to body weight loss are anorexia, lack of taste perception, impaired gastrointestinal function (swallowing issues in head and neck cancer and digestion in pancreatic cancer), surgery itself, and chemotherapy. In summary, due to the presence of cancer, the host presents systemic inflammation and high catabolic rates of carbohydrate, lipid, and protein, leading to negative protein and energy balance. The mechanisms involved in the etiology of this catabolic state are multiple and complex, with the cytokines playing a pivotal role.

Therefore, how do clinicians manage this underestimated condition of tissue hypercatabolism? For many years, the focus was on the palliation of the symptoms, trying to improve the patient's quality of life. Hydrazine sulfate is a noncompetitive inhibitor of phosphoenolpyruvate carboxylase, a key enzyme of the gluconeogenesis pathway (Chlebowski, Heber, Richardson, & Block, 1984; Gershanovich, Danova, Ivin, & Filov, 1981; Gold, 1975; Heber, Chlebowski, Ishibashi, Herrold, & Block, 1982), and has been administered to cancer patients. Only some clinical studies have reported the benefits of metabolic or nutritional indicators, necessitating further clinical trials. To suppress abnormal glucose metabolism in cancer, an insulin therapy has been proposed (Schein, Kisner, Haller, Blecher, & Hamosh, 1979). Administration of this hormone at physiological level (20–70 μU/mL) has been reported to improve cancer cachexia (Heber & Tchekmedyian, 1992; Heslin, Newman, Wolf, Pisters, & Brennan, 1992; Megeney, Kablar, Garrett, Anderson, & Rudnicki, 1996) with a significant effect upon muscle protein wasting and adipose tissue reduction.

Effectively, a therapeutic approach combining pharmacology (insulin, megestrol acetate, β_2-adrenergic agonists, corticosteroids, and nonsteroidal anti-inflammatory drugs, among others), nutritional supplements (fish oil, eicosapentaenoic acid, leucine, β-hydroxy-β-methylbutyrate), and physical exercise has been shown to have better effects than each intervention separately (Ericsson, Liu, Hart, & Sawchenko, 1995; Giacosa & Rondanelli, 2008; Moldawer et al., 1987; Moldawer & Copeland 3rd., 1997; Plata-Salaman, Sonti, Borkoski, Wilson, & French-Mullen, 1996; Tan & Fearon, 2010; Terepka & Waterhouse, 1956).

Megestrol acetate administered at normal doses to women with metastatic breast cancer increased appetite and induced body weight gain (Ruiz Garcia, Lopez-Briz, Carbonell Sanchis, Gonzalvez Perales, & Bort-Marti, 2013; Ruiz-Garcia, Lopez-Briz, Carbonell-Sanchis, Bort-Marti, & Gonzalvez-Perales, 2018). This drug is the most common agent used to treat cachexia and the only drug approved by the Food and Drug Administration (FDA); it increases appetite and muscle mass. The mechanism of action of megestrol acetate involves the elevation of neuropeptide Y in the hypothalamus, suppression of proinflammatory cytokines (such as IL-1, IL-6 and TNF-α), and decrease in muscle protein degradation by the inhibition of the proteolytic system mediated by the ubiquitin-proteasome pathway (Dutt, Gupta, Dabur, Injeti, & Mittal, 2015). However, recent data (Ruiz-Garcia et al., 2018) suggest that the increase in weight gain is very limited in clinical use. In addition, treatment with megestrol acetate has several collateral effects, including thromboembolism, transient adrenal insufficiency, edema, and central nervous system effects (confusion, headaches, dizziness, and sleep disturbances), all of which impair the debilitated state of the patients with cancer cachexia (Ruiz-Garcia et al., 2018).

Some studies in animal models of cancer cachexia suggest the use of β2 adrenoceptor agonist drugs for preventing or reducing muscle loss. The pioneering work of Carbo et al. (1997) showed that the administration of different β2-agonists (salbutamol, salmeterol, and clenbuterol) partially prevents muscle mass wasting induced in tumor-bearing rats (Yoshida AH-30 ascites hepatoma) without altering food intake or tumor growth. Similar results were found using formoterol, another type of β2-agonist (Busquets et al., 2012; Fuster et al., 2007). Toledo et al. (2016) found that the combination of formoterol with soluble activin receptor II (ActRIIB), which results in inhibition of the myostatin/activin pathway, increases food intake and reverts muscle wasting in cachectic mice with Lewis lung carcinoma. However, studies in human patients with cancer cachexia are incipient to date.

Insulin and insulin sensitivity-modifying drugs (e.g., rosiglitazone, pioglitazone and metformin) have been investigated alone or in association with other therapies for cancer cachexia. Rosiglitazone and pioglitazone have demonstrated a positive effect in animal models of advanced cancer cachexia (Trobec et al., 2014). On the other hand, de Fatima Silva et al. (2018) found that insulin alone or in combination with metformin does not attenuate the muscle and adipose mass loss in Walker 256 tumor-bearing rats. A combination of insulin with naproxen, a nonsteroidal anti-inflammatory drug, and clenbuterol, a B2-agonist, results in synergistic effects, reducing body weight loss and tumor growth and improving nutritional markers in Walker 256 tumor-bearing rats (Piffar et al., 2003). Similar results were found using insulin in combination with indomethacin, a nonsteroidal anti-inflammatory drug, and growth hormone in mice with colon-26 adenocarcinoma (Chen & Qiu, 2011).

Due to the complexity and multifactorial characteristics of the syndrome, the combination of interventions rather than one single treatment appears to be a successful strategy for the treatment of cancer cachexia (Dev, Wong, Hui, & Bruera, 2017; Mattox, 2017; Tuca, Jimenez-Fonseca, & Gascon, 2013). Although numerous studies on cancer cachexia have been conducted to evaluate the effects of several treatments with promising results, only a few drugs are available for treating it, and further work is required to confirm the findings, especially involving clinical trials.

Another important pathway involved in cancer cachexia is the mechanistic target of rapamycin (mTOR). Particularly, mTORC1 is one of the mTOR protein complexes that stimulates anabolic processes, involving lipids, proteins and nucleotide synthesis, and inhibits catabolic pathways such as autophagy (Duval, Jeanneret, Santoro, & Dormond, 2018). Evidence for an involvement of mTORC1 in tumor-induced cachexia was found in Apc (Min/+) mice, a colorectal cancer model that develops cachexia in an IL-6-dependent manner. Analysis of the gastrocnemius muscle of these animals showed a progressive decrease in mTORC1 activity from the beginning of cachexia to extreme weight loss, evidencing the importance of this complex in cachexia (White et al., 2013). In addition, mTOR inhibition promotes proteolysis via the ubiquitin-proteasome systems (UPS), demonstrating that mTOR avoids protein loss via the induction of anabolic processes (Rousseau & Bertolotti, 2016; Zhao, Zhai, Gygi, & Goldberg, 2015). Thus, the mTOR pathway is an important target to treat cancer cachexia.

Recently, Wang et al. (Wang et al., 2018) identified the metal-ion transporters, ZRT- and IRT-like protein 14 (ZIP14), as critical mediators involved in cancer-induced cachexia. ZIP14 is upregulated in mice cachectic muscles and in patients with metastatic cancer. The expression of this protein is stimulated by TNF-α and TGF-β cytokines. Interestingly, the muscle-specific depletion of Zip14 decreases muscle atrophy in metastatic cancer models. The authors observed that ZIP14 represses MyoD expression and blocks muscle cell differentiation. Another

important effect is the zinc accumulation mediated by ZIP14 in muscle cells, resulting in myosin heavy chain loss.

As described above, there are several important pathways involved in cancer cachexia development that can be important targets of new treatments. The development of new pharmacologic-nutrition-exercise approaches toward metabolic disturbances will ultimately lead to better treatment of cancer cachexia by impairing cancer progression and improving the host quality of life. The crosstalk between metabolic and inflammatory pathways is particularly related to muscle protein degradation modulation. Therefore, in the following section, we will elucidate the role of inflammation in cachexia.

1.3. Inflammation in cancer cachexia

Inflammatory mediators appear to be related to the control of a highly regulated process of muscle protein degradation that accelerates the process of cachexia. There is considerable evidence that cytokines play an important role in anorexia and cancer cachexia (Klimek, Olszewska, & Tokar, 2010; Murphy, Yeung, Mazurak, & Mourtzakis, 2011; Zhou et al., 2010). The role of cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-1β, and interferon gamma (IFN-γ) has been reported in cachexia. These cytokines are associated with the activation of protein degradation and/or the inhibition of protein synthesis in muscle tissue. Argiles, Busquets, Toledo, and Lopez-Soriano (2009) classified cytokines as procachectic or anticachectic factors. The balance between these factors plays a key role in the control of cachexia (Fig. 1).

The systemic inflammation caused by tumor cells also plays a critical role in the pathogenesis of white adipose tissue (WAT) browning. Increased serum levels of proinflammatory cytokines and myokines are indeed present in patients with cachexia and test animals (Wankhade, Shen, Yadav, & Thakali, 2016). These circulating markers include tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-1β, and prostaglandin E2 and have been detected in cachectic rat adipose tissue (Wankhade et al., 2016).

Several studies report that there are systems inside the brain that promote the cachectic state in response to proinflammatory cytokines (Grossberg, Scarlett, & Marks, 2010). Cytokines can be transported across the blood-brain barrier where they interact with the luminal surface of the brain causing the release of substances that affect appetite (Banks, 2001). The increased circulating levels of IL-1β, IL-6, and TNF-α in cancer cachexia are implicated in physiological and behavioral responses of inflammation, such as anorexia, in rodents (Plata-Salaman et al., 1996).

Although a conflicting study reports IL-1β does not affect food intake or weight loss (Albrecht & Canada, 1996), this cytokine and TNF-α cause an increase in the plasma concentration of tryptophan. This amino acid in turn increases serotonin production and levels in the hypothalamus that cause early satiety and suppress hunger (Laviano & Meguid, 1996; Picton, 1998; Yeh & Schuster, 1999). Experimental evidence that TNF-α mediates cancer cachexia was first reported by Torelli

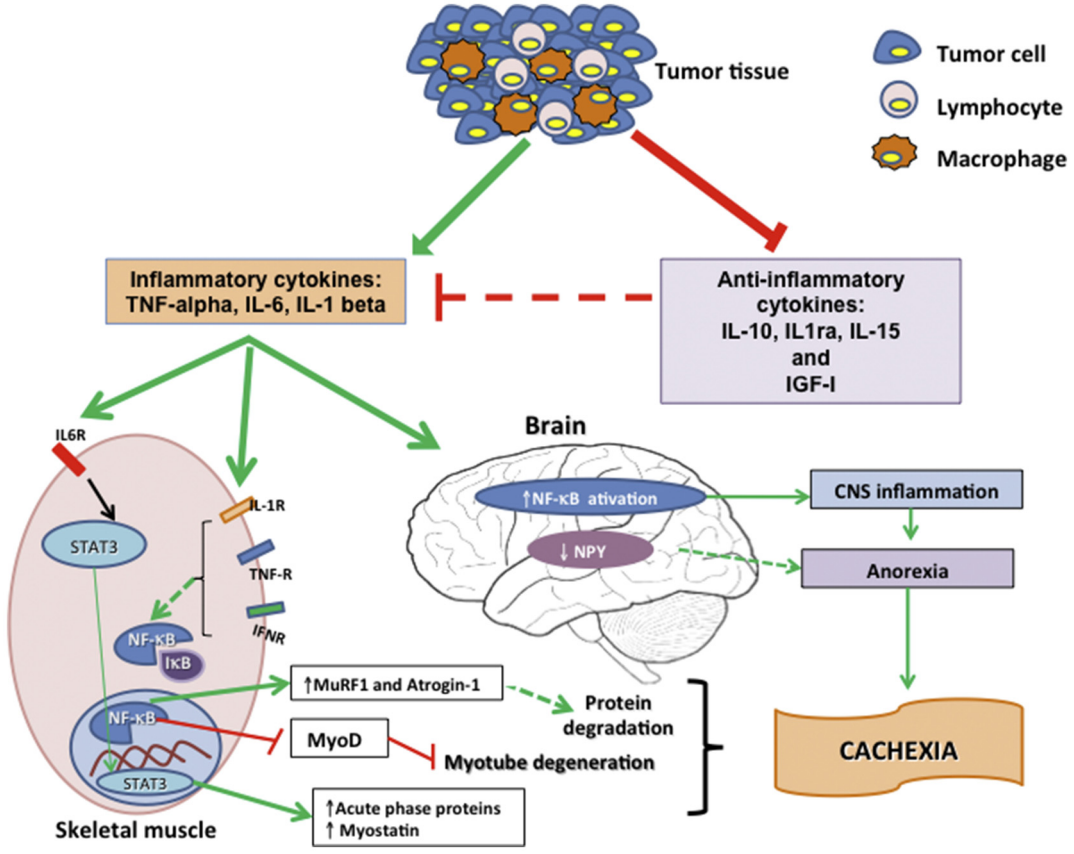

Fig. 1. Role of inflammation in cancer cachexia. Inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin 1 beta (IL-1), IL-6, and interferon gamma (IFN-γ) act on membrane receptors activating signaling pathways that result in NF-κB and STAT3 transcription factor activation in several tissues, especially in muscle. These factors promote other inflammatory mediator transcription and activation of protein degradation factors in skeletal muscle contributing to cachexia progression. TNF-α and IL-1β also prevent muscle repair as indicated by decreased expression of the transcription factor MyoD. MyoD is expressed in undifferentiated myoblasts that are at a highly proliferating stage and is activated in the beginning of skeletal muscle differentiation. Some of the inflammatory cytokines, mainly IL-1β and TNF-α, act on central nervous system activating NF-κB localized exclusively in the hypothalamus and brainstem contributing to reduction of food ingestion leading to cachexia. IL-1β is associated with induction of anorexia because it blocks neuropeptide Y (NPY) that is an inducer of food ingestion. Anti-inflammatory cytokines, such as IL10 and IL1ra, inhibit inflammatory cytokine action, contributing to cachexia progression. IL-10 acts by decreasing TNF-α and IL-6 gene expression and IL-1ra blocks IL-1β receptor. IFN, interferon; IL, interleukin; NPY, neuropeptide Y; R, receptor; MyoD, myogenic differentiation 1; MURF, Muscle Ring- Finger protein.

et al. (1999). The intraperitoneal injection of a soluble recombinant human TNF-receptor antagonist improved food intake and weight gain in tumor-bearing rats. However, its inhibition has not been shown to stop or to reverse cancer cachexia (Tisdale, 1997), indicating that TNF-α is truly involved in the development of cachexia and that this cytokine is not solely responsible for the effects observed in cachectic patients.

Some inflammatory cytokines activate the transcription factor NF-κB localized exclusively in the hypothalamus and brainstem (Friedman & Moe, 2006). The neurons and glia within the hypothalamus act in response to inflammatory stimuli by initiating the local production of cytokines that are involved in the regulation of feeding behavior (Namiki, 2007). The feeding centers in the hypothalamus, the paraventricular and arcuate nuclei, express the receptors for these cytokines (Ericsson et al., 1995). Elevated plasma levels of inflammatory cytokines induce cachexigenic effects through energy balance control in hypothalamic centers (Fig. 1). IL-1β is associated with the induction of anorexia (Plata-Salaman, 2000) because it blocks neuropeptide Y (NPY), which is an inducer of food ingestion. NPY level is inversely correlated with the brain IL-1β level in anorectic rats with cancer (Fig. 1).

Acute-phase response proteins, such as C-reactive protein (CRP), serum amyloid A (SAA) and fibrinogen produced during the inflammatory process (Blum & Strasser, 2011; Deans et al., 2009), are related to muscle wasting and body weight loss observed in cachexia (Pepys et al., 2006; Scott, Zalcberg, & Irving, 1996; van den Brekel et al., 1995). The acute-phase response proteins and cytokines increase gluconeogenesis, lipolysis and proteolysis, and decrease the synthesis of proteins, lipids and glycogen (Read et al., 2007; Tijerina, 2004). CRP is synthesized by hepatocytes in response to proinflammatory cytokines, especially IL-6, and may be used as a prognostic marker in patients with hepatocellular carcinoma (Kinoshita, Onoda, Imai, Nishino, & Tajiri, 2015). SAA is also produced by the liver in response to cytokines secreted by tumor or immune cells. In addition, in some cancers, SAA is produced directly by cancer cells. Bonetto et al. (2011) showed that STAT3 activation by IL-6 induces skeletal muscle to synthesize SAA, which is associated with high IL-6, increased acute-phase response proteins, and muscle wasting (Bonetto et al., 2011).

Glucocorticoids, reactive oxygen species (ROS), myostatin, activin A, PIF and LMF are important modulators of protein and lipid breakdown in cancer (Gordon et al., 2005). As demonstrated in Fig. 1, the anti-inflammatory cytokines IL-4, IL-10, IL-15, IL-1ra, and insulin-like growth factor-I (IGF-I) improve the effects of the procachectic factors in mouse experimental models (Argiles et al., 2009). Proinflammatory cytokine signaling leads to the expression of adhesion molecules, cell proliferation, survival, regeneration and the acute phase response in the inflammatory focus. However, in cancer cachexia, prolonged activation of cell proliferation and survival and acute phase proteins lead to tumorigenesis, hypermetabolism and protein breakdown.

The role of IL-6 in cachexia is not completely understood. This cytokine failed to reproduce cachexia in an animal model (Tijerina, 2004); however, the expression levels of proteins that regulate mitochondrial biogenesis and fusion in the initiation of cachexia are regulated by IL-6, and these events precede the loss of muscle mitochondrial content during cancer progression (White et al., 2011).

TNF-α is considered the major proinflammatory cytokine in tumor tissue. It is associated with chronic inflammation in carcinogenesis and leads to the production of proinflammatory mediators that act as protection from tumor cell apoptosis and the promotion of tumor growth and angiogenesis (Fearon, 2012). Moreover, TNF-α inhibits both adipocyte and skeletal myocyte differentiation (Abdul-Ghani & DeFronzo, 2010; Kontrogianni-Konstantopoulos, Benian, & Granzier, 2010). TNF-α stimulates the expression of uncoupling protein-2 and 3 (UCP-2 and UCP-3) in cachectic skeletal muscle (Giordano et al., 2003). These metabolic changes result in unbalanced protein synthesis and the degradation and loss of adipose tissue mass, which promotes weight loss (Moley, Morrison, & Norton, 1987).TNF-α also promotes the expression of genes that mediate the breakdown of myofibrillar proteins in cultured cells through the ubiquitin-proteasome pathway (Martins et al., 2012; Newsholme, Keane, Welters, & Morgan, 2007) leading to myotube atrophy. In patients with cancer cachexia, Jatoi and colleagues (Jatoi et al., 2004) reported that the treatment with anti-TNF-α antibodies has no beneficial effects. This observation supports the proposition that TNF-α alone is not sufficient to promote tissue atrophy. This cytokine acts as a facilitator, having synergistic activities with other inflammatory factors on tumor development (Fearon, 2012).

The combined action of TNF-α and IL-1β promotes reduction in the muscle protein content (Roden, 2004). These two cytokines activate NF-κB transcription (Li, Schwartz, Waddell, Holloway, & Reid, 1998), increasing muscle mass loss through the activation of protein degradation pathways via muscle ring-finger protein-1 (MuRF1) and atrogin-1 (Roden et al., 1996). TNF-α and IL-1β also prevent muscle repair as indicated by the decreased expression of the transcription factor MyoD (Fig. 1) (Abdul-Ghani & DeFronzo, 2010). Myogenic differentiation (MyoD) is expressed in undifferentiated myoblasts that are at a highly proliferating stage and is activated in the beginning of skeletal muscle differentiation. MyoD-deficient skeletal muscle exhibits impaired regeneration after tissue injury. These findings suggest that MyoD has a specific role in the replacement of lost muscle (Megeney et al., 1996). Guttridge, Mayo, Madrid, Wang, and Baldwin Jr. (2000) reported that treatments with IFN-γ, IL-1β or IL-6 alone have no effect on skeletal muscle-specific gene expression. Differentiated myotubes treated concomitantly with TNF-α and IFN-γ exhibited significant reductions in MyoD protein expression. Thus, TNF-α and IFN-γ together promote myotube degeneration. These effects did not occur in the absence of NF-κB transcription activity (Ladner, Caligiuri, & Guttridge, 2003). Therefore, TNF-α and IFN-γ acting through NF-κB promote a disruption of injured skeletal muscle repair mechanisms (Fig. 1). Thus, several cytokines are associated with cachexia, and a set of cytokines and other cachectic factors act in concert to promote the remarkable body weight decrease induced by cancer cachexia.

IFN-γ, TNF-α and IL-1β are potent activators of the expression of inducible nitric oxide synthase (Kinoshita et al., 2015), which produces toxic levels of nitric oxide (NO) leading to the inhibition of oxidative phosphorylation key enzymes (Lenk, Schuler, & Adams, 2010). NO reduces the contractile performance of skeletal muscle (Murata et al., 2013). IL-6 is also strongly related to muscle wasting in a mouse model of cachexia (Bashan, Kovsan, Kachko, Ovadia, & Rudich, 2009). The *Adenomatous polyposis coli* (multiple intestinal neoplasia) (*Apc* Min) mouse is characterized by a mutation in the *Apc* gene, which is a tumor suppressor gene that leads to the development of intestinal polyps at 4 weeks of age. This mouse develops cachexia in 6 months and exhibits significant loss of muscle and fat tissue. The administration of IL-6 receptor antibody attenuates the progression of cachexia in these mice, which attests to the importance of IL-6 (Baltgalvis et al., 2008). White et al. (2011) described that the expression of proteins involved with mitochondrial biogenesis regulation is altered by IL-6 in cancer cachexia and precedes the loss of muscle mitochondrial content. *Apc* Min mice were examined during the progression of cachexia after systemic IL-6 receptor (IL-6R) antibody treatment or after IL-6 overexpression. IL-6R antibody administration improved mitochondrial content, increasing peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α), mitofusin-1 and -2 (Mfn-1 and Mfn-2), and mitochondrial fission-1 (FIS-1) protein expression. The overexpression of IL-6 in precachectic mice potentiated body weight and muscle loss, with no effect on mitochondrial content. However, PGC-1α and Mfn-1/Mfn-2 protein expression decreased, and FIS-1 protein expression increased under this condition.

IL-6 is associated with its membrane-bound receptor and leads to the activation of the Janus kinase (JAK)/signal transducer and the activator of the transcription (STAT) pathway with translocation of activated STAT proteins into the nucleus (Mendes, Pimentel, Costa, &

Carvalheira, 2015). This signaling pathway is involved in cachexia and signaling muscle atrophy associated with the ubiquitin-proteasome pathway. Upstream activation is carried out through the NF-κB, STAT-3 and p38 mitogen-activated protein kinase (MAPK) pathways (Onesti & Guttridge, 2014; Tisdale, 2003). As mentioned above, IL-6 binds to its receptor (α-chain), leading to the activation of associated JAK. Afterwards, the STAT-3 and the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase cascade pathways are activated. STAT-3 is a transcription factor that modulates gene expression of the acute-phase response and is associated with skeletal muscle wasting. The acute-phase response genes are activated by STAT-3 in response to lipopolysaccharide (LPS), IL-6, or TNF in the liver. The level of STAT-3 phosphorylation increases the severity of the cachexia and serum concentrations of IL-6. STAT-3 deletion decreases the expression of CCAAT/enhancer-binding protein δ (C/EBPδ), which reduces the myostatin expression in cachexia (Fig. 1). Myostatin inhibits muscle growth, leading to cachexia. Another mechanism modulated by STAT-3 is the alteration of transcriptome and proteome in muscle tissue. Studies in the colon-26 (C26)-carcinoma cachexia model reported that muscle might be a better source of certain acute-phase response proteins than the liver (Bonetto et al., 2011). Cachexia was associated with increased muscle STAT-3 localization in myonuclei. The expression levels of the target genes of STAT-3, such as the suppressor of cytokine signaling-3 (SOCS-3) mRNA and acute-phase response proteins (SAA and fibrinogen), were greatly enhanced in cachectic muscle.

Anti-inflammatory cytokines in turn are involved in the inhibition of cachexia progression. IL-10 decreases TNF-α and IL-6 expression (Fig. 1). This cytokine activates a negative feedback control system, prevents the excessive activation of the inflammatory cascade and contributes to cancer cachexia (Calder, 2006). Other factors that can influence the effects of IL-10 on cancer cachexia are the polymorphisms in this cytokine gene. A single-nucleotide polymorphism in TNF-α, IL-1β, and IL-10 genes controls the production of these cytokines and is associated with the prevalence of cachexia in some types of cancer (Tan & Fearon, 2010). The genetic predisposition of patients to inflammation contributes to cancer genesis, progression, and cachexia development. The influence of cytokine gene polymorphisms has been suggested to be a potential tool to evaluate cancer prognostics. Deans et al. (2009) reported in a Chinese population, that the occurrence of IL-10-1082G allele polymorphism (rs1800896) is associated with an increased weight loss and the G/G genotype with an elevated risk for developing cachexia. The ethnicities and cancer types could influence the effect of SNPs in inflammatory genes on the development of cancer cachexia. A meta-analysis (Zhang, Zhou, Xu, & Tang, 2012) of 2090 cases of cancer and 4224 controls suggests an increase of cancer risk both in Caucasian and non Caucasian people with a haplotype in IL-10 promoter. However, a recent meta-analysis with 6101 cases of cancer and 8557 controls demonstrated a significant association between IL-10 -1082 A/G polymorphism and gastric cancer in Asians, but not in Caucasian and Latin populations. Another study also demonstrated a lack of association between IL-10 gene promoter polymorphism and prostate and breast cancer in the overall population and Caucasians (Zou, Wang, & Feng, 2011). Other polymorphisms such as IL-6 -597G/A and IL-18 -137G/C and CXCL8–251 A/T also can be important for cancer risk and cachexia development.

Possible immunologic targets for the treatment of cachexia in pancreatic ductal adenocarcinoma include transforming growth factor-beta (TGF-β). Greco et al. (2015) found that TGF-β inhibition using anti-TGF-β antibody improved weight loss, fat mass, lean body mass, bone mineral density, and skeletal muscle proteolysis in mice with advanced pancreatic cancer. In fact, TGF-β is involved in several cellular functions, including cell differentiation, growth, immunosuppression, and apoptosis (Moustakas, Pardali, Gaal, & Heldin, 2002).

Patients with resectable pancreatic cancer have higher levels of MCP-1, and this cytokine is an important marker of cancer cachexia. In addition, although circulating levels of leptin and granulocyte-macrophage colony-stimulating factor (GM-CSF) were decreased in the same cachectic patients, these factors were related to body mass index (Talbert et al., 2018).

The interaction between different cytokines is frequently reported in inflammatory diseases and cancer, triggering signaling pathways (Moldawer & Copeland 3rd., 1997) that promote muscle protein degradation and weight loss. Specific neutralization of cytokines using anti-TNF-α, anti-IL-6, anti-IL-1β, and anti-IFNγ antibodies can relieve anorexia and cachexia (Matthys & Billiau, 1997; Noguchi et al., 1996; Tisdale, 1997).

Moreover, proinflammatory cytokines such as TNF-α and IL_6 also induce muscle atrophy partially through inhibiton of PI3 kinase/Akt inhibition leading to stimulation of the Forkhead Box O (FOXO)-3/ubiquitin-proteasome proteolysis pathway (Fig. 2). TNF-α binding to its receptor activates PTEN that is involved with PIP3 dephosphorylation and inhibition of Akt. Simultaneously, there is an increase of ROS leading to JNK activation which phosphorylates IRS-1 in serine leading to its inhibition. These associated effects are involved with FOXO-3 activation (Crossland, Constantin-Teodosiu, Gardiner, Constantin, & Greenhaff, 2008). As described before, in cachexia, muscle proteolysis is predominately caused by the ubiquitin proteasome system (UPS). The FOXO-3 transcription factor is an important factor that increases expression of muscle-specific ubiquitin conjugating enzymes E3 ligase, MAFbx/atrogin-1 and MuRF-1. MuRF-1 and muscle atrophy F-box (MAFbx) are associated with skeletal muscle atrophy. MuRF1 and MAFbx are recognized by ubiquitin protein ligases (E3) that control regulatory proteins and inhibit activation of the phosphoinositide 3-kinase (PI3-K)/Akt/mammalian target of rapamycin (mTOR) and glycogen synthase kinase-3 beta (GSK-3) pathway that induces hypertrophy (Argiles et al., 2014; Fearon, 2011; Gordon et al., 2005; Tisdale, 2003).

TNF receptor stimulation is also involved with PTP-1B activation that induces insulin receptor (IR) dephosphorylation, contributing to insulin resistance (Fig. 2). This blocking of IR is also related to inhibition of protein synthesis pathways leading to a predominance of protein degradation pathways (Gordon et al., 2005). In the same way, IL6 binding to its receptor leads to caspase 3 activation through p38 pathway activation. Caspase-3 promotes apoptosis of muscle cells. On the other hand, glucocorticoids also are involved through production of myostatin and actin A. Myostatin, a member of the transforming growth factor-beta (TGF-β) superfamily of growth factors, is recognized as one of the most potent negative regulators of muscle mass. It binds to its receptor complex (activin receptor IIB – ActRIIB/activin-like kinase-4 or -5 – Alk-4 or -5) on skeletal muscle resulting in activation of the SMAD-2/3, mitogen-activated protein kinase and inhibition of the PI3-K intracellular signaling pathways resulting in muscle atrophy. Activin A promotes muscle wasting via the myostatin signaling pathway by activating the SMAD-2/3 transcription factors, which increase protein degradation by up-regulation of the expression of muscle-specific ubiquitin ligase atrogin-1 and depression of protein synthesis via inhibition of the Akt/mTOR pathway (Abdul-Ghani & DeFronzo, 2010; Chen & Zhao, 2013). SMAD-2/3 transcription factors, also activate FOXO-3 that is also involved with autophagy (Fig. 2).

TNFα plays a direct role in cachexia by inhibiting lipoprotein lipase activity and enhancing protein degradation (Onesti & Guttridge, 2014). TNF-α promotes atrophy of cultured myotubes through induction of E3 ligase genes that mediate the breakdown of myofibrillar proteins via the ubiquitin-proteasome pathway. TNF-α decreases phosphorylation of eukaryotic initiation factor-4E (eIF4E) binding protein-1 (4E-BP1) leading to increased binding of eIF4E and a reduction in the active eIF4F complex (Tisdale, 2003; Wigmore, Plester, Richardson, & Fearon, 1997). TNF-α and PIF appear to induce muscle cachexia through a similar pathway, by activating NF-κB. PIF activates reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, leading to ROS production and increased expression of MuRF1 in skeletal muscle (Mirza & Tisdale, 2014). PI3K/AKT pathway inhibition also decreases PDE-3B, leading to lipolysis (Fig. 2).

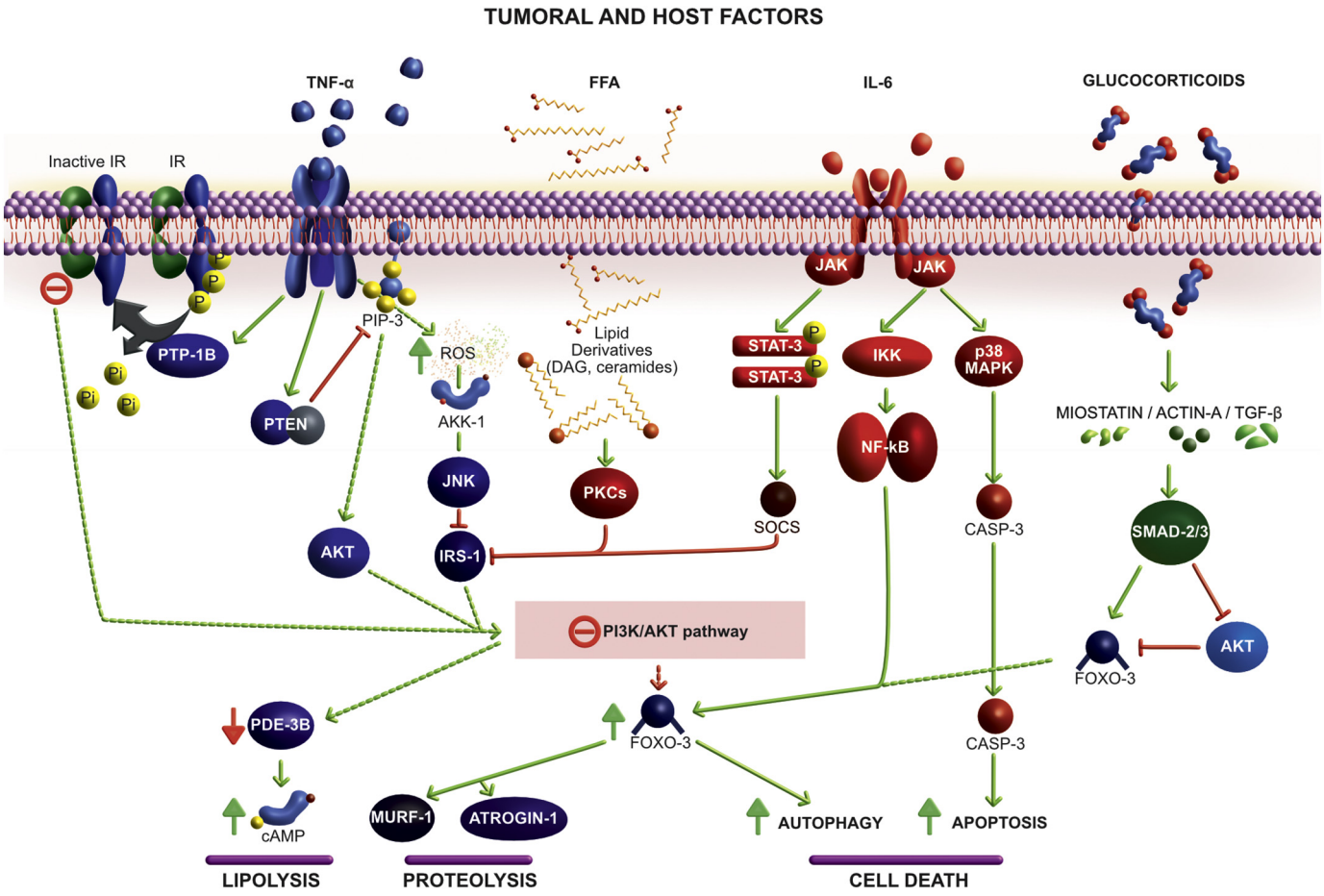

Fig. 2. Molecular mechanisms of inflammatory mediators secreted by tumor microenvironment that contribute to cachexia. TNF-α binding to its receptor activates PTEN that is involved with PIP3 dephosphorylation and inhibition of Akt. Simultaneously, there is an increase of ROS leading to JNK activation which phosphorylates IRS-1 in serine leading to its inhibition. These associated effects are involved in FOXO-3 activation that stimulates MURF-1 and Atrogin-1. MuRF-1 is associated with skeletal muscle atrophy. MuRF1 is recognized by ubiquitin protein ligases (E3) that control regulatory proteins and inhibit activation of the phosphoinositide 3-kinase (PI3-K)/Akt/mammalian target of rapamycin (mTOR). TNF receptor stimulation is also involved in PTP-1B activation that induces insulin receptor (IR) dephosphorylation, contributing to insulin resistance. This blocking of IR is related to inhibition of protein synthesis pathways. In the same way, IL6 binding to its receptor leads to caspase 3 activation through p38 pathway promoting apoptosis of muscle cells. On the other hand, glucocorticoids induce production of myostatin and actin A. Myostatin, a member of TGF-β superfamily of growth factors, is recognized as one of the most potent negative regulators of muscle mass. Actin A promotes muscle wasting via the myostatin signaling pathway by activating the SMAD-2/3 transcription factors, which activates FOXO-3 that is also involved in autophagy. PI3K/AKT pathway inhibition also decreases PDE-3B, leading to lipolysis.

Since cancer cachexia is characterized by a highly inflammatory condition, the use of steroidal (prednisolone) and nonsteroidal (indomethacin, naproxen) anti-inflammatory drugs has been proposed to treat this syndrome. In a randomized study with 135 patients with cancer cachexia bearing different solid advanced tumors, the administration of prednisolone or indomethacin increased the survival (mainly indomethacin) and improved the outcome of patients, as demonstrated by a higher Karnowsky index compared to that of the placebo group (Lundholm et al., 1994).

As described above, inflammatory mediators significantly contribute to the establishment of cancer cachexia through several signaling pathways. Although some interventional therapies have been applied, such as hormonal and pharmacological strategies, omega-3 supplementation may be a coadjuvant treatment, which may offer a decrease in side effects or lack side effects when compared with traditional therapies.

2. OMEGA-3 polyunsaturated fatty acids

2.1. General view

N-3 PUFAs are found mainly in plants and marine sources, primarily from cold-water fish (Friedman & Moe, 2006). In animals, α-linolenic acid (18:3n-3) can be converted to stearidonic acid (18:4n-3) by delta-6 desaturase, and then, stearidonic acid can be elongated to eicosatetraenoic acid (20:4n-3), which can be further desaturated by delta-5 desaturase to yield eicosapentaenoic acid (20:5n-3; known as EPA). The same enzymes are recruited by competitive mechanisms for the conversion of linoleic acid to arachidonic acid (20:4n-6) and conversion of α-linolenic acid to EPA. The delta-6 desaturase reaction is rate limiting in this pathway. Increasing α-linolenic acid intake for a period of weeks to months results in an increase in the proportion of EPA in plasma lipids, erythrocytes, leukocytes, platelets and in breast milk, but there is no increase in the level of docosahexaenoic acid (22:6 n-3; DHA) (Burdge & Calder, 2005).

The pathway for conversion of EPA to DHA involves the addition of two carbons to EPA to form docosapentaenoic acid (22:5 n-3; DPA), the addition of two further carbons to produce 24:5n-3, desaturation at the delta-6 position to form 24:6n-3, and translocation of 24:6n-3 from the endoplasmic reticulum to peroxisomes where two carbons are removed by limited β-oxidation to yield DHA (Calder, 2012). Fish oil and related supplements are usually evaluated in the studies involving the n-3 fatty acids, EPA and DHA. Encapsulated oil preparations that contain n-3 fatty acids in higher amounts than those found in standard fish oils are also available ('fish oil concentrates'). In fish oil capsules, fatty acids are usually present in the form of triacylglycerols (Calder, 2012).

N-3 PUFAs have been associated with various health benefits in animals and humans. These lipids are incorporated into the phospholipids of cell membranes (also in inflammatory cells) in a dose-dependent way (Calder, 2006). The incorporation of EPA and DHA partly competes with the incorporation of arachidonic acid (AA) (Calder, 2006; Wall, Ross, Fitzgerald, & Stanton, 2010). This competition affects the production of the different eicosanoids in cells (Wall et al., 2010). N-3 PUFAs are signaling molecules or they generate several lipid derivatives that regulate inflammation differently than n-6 PUFA-derived eicosanoids. AA is converted by cyclooxygenase (COX) into prostaglandin E_2 (PGE_2), which is an inflammatory mediator, prostacyclin I_2 (PGI_2), which leads to blood vessel dilation, and thromboxane A_2 (TXA_2) that is related to the activation of blood platelet aggregation. Lipoxygenase (LOX) converts EPA into 4-series leukotrienes (LTB4). On the other hand, an increased intake of EPA may decrease the production of LTB_4, PGE_2, and PGI_2. However, this fatty acid promotes the production of the 3-series prostanoids and 5-series leukotrienes with anti-inflammatory (PGE_3, LTA_5, LTB_5, LTC_5, LTD_5), vasodilative (PGI_3) and antiaggregatory (TXA_3) properties (Wall et al., 2010), reducing the inflammatory response revised by (Wiktorowska, Owczarek, & Orszulak-Michalak, 1999) (Fig. 3).

N-3 PUFAs are also precursors to resolvins E1 and D1, protectins D1 and R1, and maresins through the action of cyclooxygenase and lipoxygenase enzymes (Serhan, Chiang, & Dalli, 2017; Serhan, Chiang, Dalli, & Levy, 2014). These mediators facilitate the resolving phase of acute inflammation. In addition, resolvins inhibit human leukocyte migration and infiltration in vivo (Kasuga et al., 2008). Resolvin D1 inhibits IL-1β production, and protectin D1 inhibits TNF-α and IL-1β production. These mediators have an important role in the inflammatory process, limiting damage to tissue and response spread (Calder, 2010). These lipid mediators can possibly prevent and/or provide treatment tools for inflammation-related diseases (Moro, Nagahashi, Ramanathan, Takabe, & Wakai, 2016) (Fig. 3). In fact, n-3 PUFA intake has been associated with reduced inflammation in colorectal cancer and improved treatment in breast cancer.

Resolvins have beneficial effects on the resolution of acute kidney injury and acute lung injury, vascular response to injury, and inflammation in neurodegenerative disorders. In addition, these molecules have some advantages in comparison to other anti-inflammatory drugs due to their effects on the resolution of inflammation without modulating the production of other eicosanoid molecules that have important physiological effects (Moro et al., 2016).

The effects of n-3 PUFAs are closely associated with their metabolism in various cancers (Simopoulos, 2002; Wang et al., 2000; Wang, Pan, Lu, Li, & Li, 2012) and in other clinical disorders, including rheumatoid arthritis (Galarraga et al., 2008; Rennie, Hughes, Lang, & Jebb, 2003),

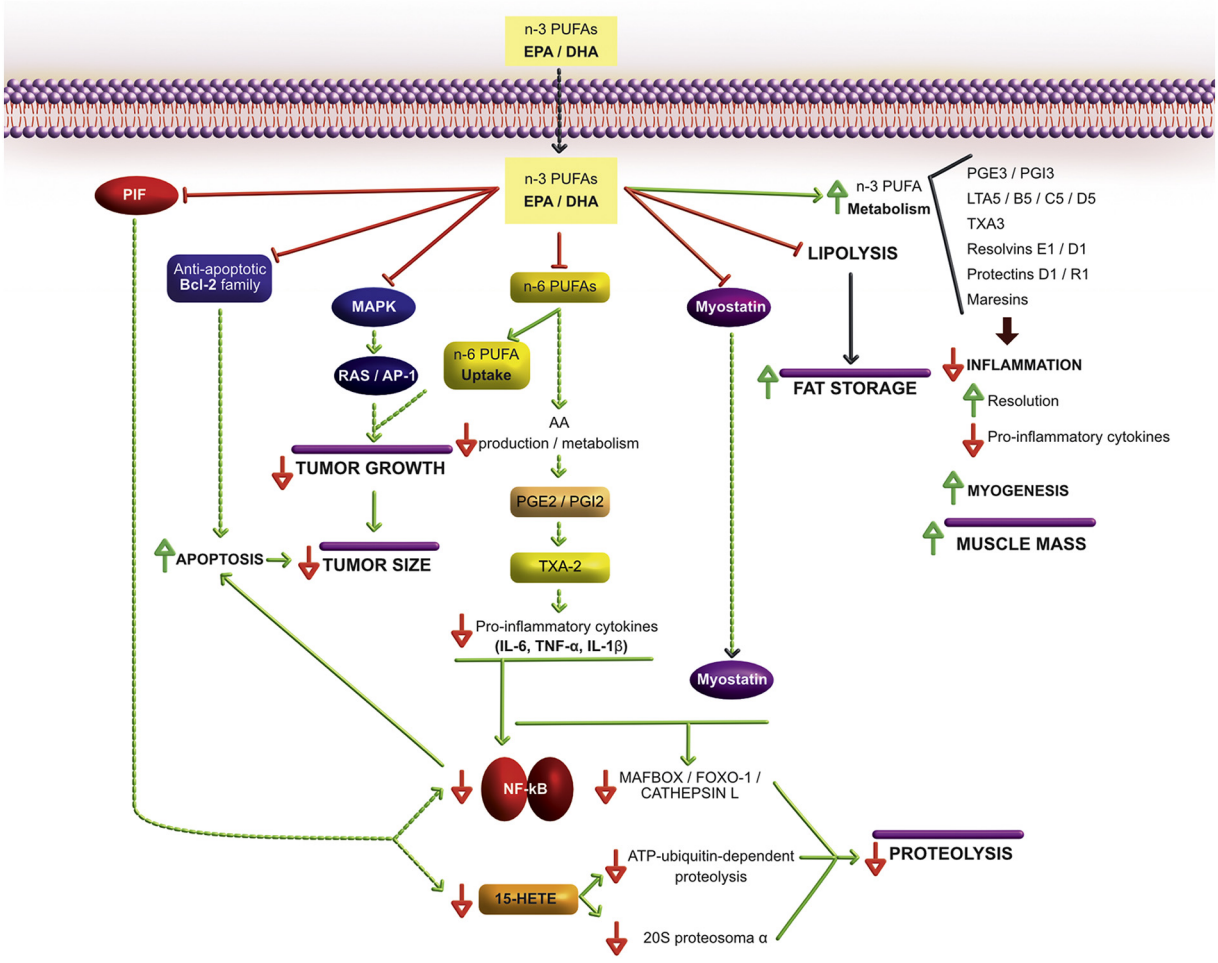

Fig. 3. Potential targets of the n-3 polyunsaturated fatty acids in cancer cachexia. EPA inhibits MAP kinase signaling, particularly Ras/ERK1/2, decreasing AP-1 transcription factor leading to antiproliferative effects that are responsible for tumor growth blockage. EPA can also restore functional apoptosis by downregulating Bcl-2 family genes. The transcription activity of NF-κB is inhibited by EPA and production of the proinflammatory cytokines, mainly IL-1, TNF-α, and IL-6, is decreased. EPA and DHA inhibit myostatin in cachectic mice, thus down-regulating the proteolytic signaling pathways, MAFbx, FOXO-1, and cathepsin L. EPA also downregulates expression and activity of the ubiquitin-proteasome proteolytic pathway through a direct effect on PIF signaling, by attenuating the production of 15-HETE. EPA inhibits protein catabolism by ATP-ubiquitin-dependent proteolytic pathway and down-regulation of 20S proteasome alpha-subunits in cachexia-inducing tumor and caused by PIF. n-3 PUFAs act on release in inguinal fat pads preserving host fat stores. Another important pathway of EPA and DHA action is through resolvin, protectin and maresin production. These lipidic compounds are involved in decrease of inflammatory mediators leading to inhibition of protein degradation pathways contributing to muscle mass preservation.

psoriasis (Mayser, Grimm, & Grimminger, 2002), *diabetes mellitus* (Woodman et al., 2003), renal disease (Moro et al., 2016), cardiovascular diseases (Coronel, 2017; Schunck, Konkel, Fischer, & Weylandt, 2018), nonalcoholic fatty liver disease (Jump, Lytle, Depner, & Tripathy, 2018), and endometriosis (Tomio et al., 2013).

2.2. Effects of n-3 PUFAs on cancer cachexia

N-3 PUFAs have been reported to reduce cancer cachexia (Tisdale, 1993) as well as tumor growth (Anti et al., 1992; Rose & Connolly, 1993). EPA (95% pure) administered as a free fatty acid starting at 1 g/day and increased to 6 g/day over four weeks and maintained for 12 weeks promoted the stabilization of weight in pancreatic cancer patients. After four weeks of EPA supplementation, a median weight gain of 0.5 kg was observed in patients, and this stabilization of weight persisted over the 12-week study period (Wigmore, Barber, Ross, Tisdale, & Fearon, 2000).

The main mechanisms responsible for the effects of these fatty acids are related to their metabolism. DHA inhibits the synthesis of biologically active leukotrienes of the 4-series and prostanoids of the 2-series by reducing the amount of AA (Obata, Nagakura, Masaki, Maekawa, & Yamashita, 1999; Ringbom et al., 2001; Rose & Connolly, 1998). EPA competes more successfully than AA for LOX and COX enzymes (Needleman, Wyche, & Raz, 1979; Obata et al., 1999; Ringbom et al., 2001; Yang, Felix, Madden, Fischer, & Newman, 2002), both the constitutive COX-1 and the inducible COX-2 isoforms, which are upregulated by proinflammatory signals (Obata et al., 1999; Ringbom et al., 2001). EPA is also a substrate that is converted into leukotrienes of the 5-series and prostanoids of the 3-series with the production of active PGI_3, tipping the balance toward the anti-aggregation of platelets and vasodilatation (Fig. 3) (Dyerberg & Bang, 1979; Fischer & Weber, 1985; Nordoy, Hatcher, Goodnight, Fitzgerald, & Conner, 1994).

Nutritional intervention, including a high-protein diet (mainly enriched with leucine), fish oil, and oligosaccharides, promotes an improvement in body weight accompanied by increased n-3 PUFAs and reduced n-6 PUFAs in precachectic gastrointestinal cancer patients (> 5% weight loss) (Faber et al., 2013). In 27 patients who were evaluated, the skeletal muscle mass was significantly increased at 4 and 8 weeks after enteral supplementation with n-3 PUFA (2 to 4 packs of enteral supplementation containing 200 kcal/300 mg of n-3 fatty acids per pack) (Abe et al., 2018).

Fish oil and selenium supplementation inhibits the expression of IL-6, TNF-α and myostatin in cachectic mice, thus downregulating the proteolytic signaling pathways, MAFbx, FOXO-1, and cathepsin L, as demonstrated in the Fig. 3 (Wang et al., 2012). Likewise, EPA (6 g/day) acts to reduce C-reactive protein (CRP) levels and to suppress IL-6 production by mononuclear cells in patients with pancreatic cancer cachexia (Wigmore et al., 1997). Oro Inca oil, rich in alpha linoleic acid (31.6% of total oil), also promotes an improvement in cachexia parameters (in rats supplemented with 1 g/kg body weight/day), such as glycemia, triacylglycerolemia, and decreased IL-6 and TNF-β levels (Schiessel et al., 2015) (Fig. 3).

The effect of n-3 PUFAs on cancer cachexia is also influenced by n-3 PUFA sources. Werner et al. (2017) observed that intervention with low-dose n-3-FAs (0.3 g per day), either as fish oil or marine phospholipid supplementation, promoted weight and appetite maintenance in pancreatic cancer patients. However, marine phospholipids were better tolerated and caused fewer side effects in relation to FO supplementation.

Inflammation orchestrates the integrated response in cancer cachexia (Straub, Cutolo, Buttgereit, & Pongratz, 2010) through the increase in proinflammatory cytokine activity during cancer progression (Argiles et al., 2009; Macdonald, Kahn, Miller, & Obrand, 2003). EPA alters some signal transduction pathways that explain its potent anti-inflammatory and antiproliferative effects (Calder, 2013). The transcription of NF-κB is inhibited by EPA (Fig. 3) and the production of the proinflammatory cytokines, mainly IL-1, TNF-α, and IL-6, is decreased (Babcock et al., 2003; Babcock, Helton, Hong, & Espat, 2002; Novak, Babcock, Jho, Helton, & Espat, 2003). Since the role of inflammation in cachexia was discussed above, it is well evidenced that proinflammatory cytokine modulation by EPA is important to anti cachectic effects.

However, cancer cachexia cannot be attributed only to high inflammation and starvation. The most important factor for skeletal muscle atrophy in cancer cachexia is PIF produced by the cachexia-inducing tumor. EPA attenuates the activity of catabolic pathways such as protein degradation, lipid mobilization and reduced glucose consumption in skeletal muscle induced by PIF (Fig. 3) (Hussey & Tisdale, 1999; Lorite, Cariuk, & Tisdale, 1997; Tisdale & Beck, 1991). EPA inhibits protein catabolism by the ATP-ubiquitin-dependent proteolytic pathway and by downregulation of 20S proteasome alpha subunits in the cachexia-inducing tumor caused by PIF (Fig. 3) (Lorite, Thompson, Drake, Carling, & Tisdale, 1998; Whitehouse, Smith, Drake, & Tisdale, 2001). The ubiquitin proteasome pathway is upregulated by transcription factor NF-κB, and EPA reduces the nuclear migration of NF-κB, avoiding the protein breakdown induced by PIF in murine myotubes (Whitehouse & Tisdale, 2003).

Magee et al. (Magee, Pearson, & Allen, 2008) also reported that EPA inhibits necrosis and apoptosis of differentiating myotubes in vitro by reducing the levels of TNF-α, a cytokine involved with the extrinsic pathway of apoptosis death. This effect contributes to reduced muscle mass loss. Other studies have shown that this antiapoptotic effect of EPA in skeletal muscle also involves the downregulation of the ubiquitin proteasome pathway, decreasing muscle wasting (Wigmore et al., 1997; Wigmore et al., 2000). Di Girolamo (Di Girolamo et al., 2014) suggested an association of n-3 PUFAs and anabolic *stimuli* in the prevention of sarcopenia in precachectic patients. However, the effect of EPA on protein degradation pathways in the cachexia-inducing tumor is controversial (Smith, Lorite, & Tisdale, 1999). Vaughan et al. (Vaughan, Sullivan-Gunn, Hinch, Martin, & Lewandowski, 2012) reported an increase in MURF-1 and MAFbx gene expression in a mouse model of cancer cachexia supplemented with EPA (0.4 g/kg/day) when compared to a cancer cachexia control. However, a combination treatment with EPA and oxypurinol promoted a decrease in MURF-1 and MAFbx gene expression. It is important to note that EPA was used in a pure form and in a high dose in this study. The different doses used in studies involving cancer cachexia and n-3 supplementation may explain the divergent results.

Supplementation with n-3 PUFAs, mainly EPA, can contribute to improve body composition, particularly muscle mass and function (Barber, Ross, Voss, Tisdale, & Fearon, 1999; Read et al., 2007), and suppress cancer growth by multiple mechanisms. EPA downregulates the acute-phase response present in the inflammatory process by reducing the serum concentration of CRP, TNF-α, and IL-6 (Dewey, Baughan, Dean, Higgins, & Johnson, 2007; Mocellin, Camargo, Nunes, Fiates, & Trindade, 2016; Mocellin, Fernandes, Chagas, & Trindade, 2017). EPA reduces muscle apoptosis by reducing TNF-α levels, which is associated with the downregulation of the ubiquitin proteasome pathway and the decrease in muscle wasting (Wigmore et al., 1997; Wigmore et al., 2000). Accordingly, skeletal muscle mass has been negatively associated with plasma n-3 PUFA levels in cancer patients (Fearon, 2011; Murphy et al., 2011; Wang et al., 2012). As a consequence of n-3 PUFA supplementation, an enhanced tumor response to antineoplastic treatments was observed, attenuating chemotherapy side effects (Barber & Fearon, 2001; Read et al., 2007).

EPA and alpha-linoleic acid also inhibit saturated, monounsaturated and n-6 PUFA uptake by the tumor and inguinal fat tissue via the Gi protein-coupled signal transduction pathway and suggest that the role of n-3 PUFAs in the release of inguinal fat pads could be a mechanism for their anticachectic actions to preserve host fat stores (Sauer, Dauchy, & Blask, 2000). The n-6 linoleic acid uptake reduction is especially associated with tumor growth inhibition (Sauer et al., 2000). EPA also reduced the membrane Gαs expression associated with

increased expression of Gαi, reverting the effects induced by tumor-derived lipid mobilizing factors in adipose tissue, maintaining the lipid store (Islam-Ali, Khan, Price, & Tisdale, 2001). Reduction in membrane Gαi expression associated with increased expression of Gαs favour mobilization of lipid stores from adipocytes leading to tissue catabolism.

EPA reduces the activation of oncogenic transcription factors Ras and activator protein-1 (AP-1) (Collett, Davidson, Fan, Lupton, & Chapkin, 2001; Liu et al., 2001) by inhibiting the MAPK pathway (Babcock et al., 2003), a direct action to slow the growth of cancer cells. The n-3 PUFAs induce cancer cell differentiation and inhibition of angiogenesis, which suppress the supply of nutrients to the cells and inhibit or limit tumor growth (Rose & Connolly, 1998; Wang et al., 2000).

EPA can also restore functional apoptosis by downregulating NF-κB (Schwartz, Hernandez, & Mark Evers, 1999) and Bcl-2 family genes (Chiu & Wan, 1999; Narayanan, Narayanan, & Reddy, 2001). These effects are important because NF-κB is often upregulated in cancer cells, blocking apoptosis (Schwartz et al., 1999) and genetic damage promoted by chemotherapy drugs or radiation to eliminate cancer cells.

Lai, Ross, Fearon, Anderson, and Carter (1996) and Jordan and Stein (2001) described how EPA inhibits the in vitro growth of pancreatic cell lines through cell cycle arrest and apoptosis and decreases the capacity of proliferation induced by epidermal growth factor. EPA supplementation promoted inhibitory effects on growth and metastases of breast and prostate tumors in nude mouse models (Gabor & Abraham, 1986; Gonzalez, Ramos, & Hernandez, 1995; Gonzalez, Schemmel, Dugan Jr., Gray, & Welsch, 1993; Karmali, 1987; Rose, 1988). In a fibrosarcoma rat model, treatment with n-3 PUFAs reduced tumor volume, improved cachexia and decreased the expression of growth factors (Jho, Babcock, Tevar, Helton, & Espat, 2002; Tevar, Jho, Babcock, Helton, & Espat, 2002). The results of animal studies were confirmed by clinical studies suggesting the importance of n-3 PUFAs or EPA supplementation in human cancer cachexia (Table 1). On the other hand, Mazzotta and Jeney (2009) reviewed several databases through 2006 to identify the clinical efficacy of EPA and DHA in cancer cachectic patients, but the studies reported no clear advantage of n-3 PUFA supplementation. In fact, as observed in Table 1, studies involving the effects of n-3 supplementation on cancer cachexia used different doses of fish oil with different compositions. Most studies supplemented the patients with doses between 2.0 and 3.0 g per day, and the most used n-3 PUFA was EPA. However, there are studies that reported EPA supplementation with doses up 6 g/day and one study provided a dose up to 16 g/day. These different doses can be responsible for the divergent results.

In addition, it is important to note that the combination of EPA with other important anticachectic compounds is an important strategy to improve weight gain and to decrease side effects. Therefore, EPA supplementation also regulates the production of IL-1, IL-6 and TNF-α, reducing protein degradation by suppressing the proteolytic system (Dutt et al., 2015). Kanat et al. (2013) compared the efficacy of MA + meloxicam with a MA + meloxicam + oral EPA-enriched nutritional supplement (2.2 g/day of EPA) and a meloxicam + oral EPA-enriched nutritional supplement. All treatments resulted in increased weight gain and quality of life. However, there was no difference among the groups. Further studies are necessary, since combined therapy of meloxicam + EPA is promising in the treatment of cachexia, as it does not present the side effects observed in MA treatment (Kanat et al., 2013). A long-term supplementation with fish oil, rich in EPA and DHA, resulted in improvement in the effects of naproxen, clenbuterol and insulin on tumor growth, body weight loss, and the metabolic condition of Walker 256 tumor-bearing rats (Pinto et al., 2004).

Coelho et al. (2012) reported that fish oil treatment has renoprotective effects as indicated by less proteinemia, higher renal plasma flow and glomerular flow rate, resulting in attenuated cachexia in tumor-bearing rats. The mechanism for the appetite loss in cachexia may involve proinflammatory cytokines, insulin sensitivity, serotoninergic activity in the hypothalamus and adipokines such as leptin. The role of n-3 PUFAs in the mechanisms associated with food intake requires further investigation.

Cancer cachexia is managed within a multimodal approach, including a decrease in inflammatory profile, adequate nutritional intake and exercise to increase muscle mass and function. Recent studies suggest that n-3 PUFA ameliorate mitochondrial content and function by increasing the expression of genes related to mitochondrial function and biogenesis (Cavaliere et al., 2016; Martins et al., 2018). Hypogonadism, insulin resistance, adrenergic activation, and systemic inflammation coupled with semistarvation lead to muscle atrophy signaling. N-3 PUFAs address a range of targets relevant to the specific treatment of cancer cachexia. Interventions could focus on antagonizing key mediators of systemic inflammation, blocking muscle catabolic pathways and/or stimulating anabolic muscle pathways.

Inhibition of the proinflammatory signaling cascade attenuates muscle atrophy, which has stimulatory effects on muscle mass gain, improving the survival time and quality of life in cachectic patients. Large-scale clinical trials are necessary to rule out any side effects of this treatment. An interesting mechanism of n-3 PUFAs in this context is PIF signaling. EPA effectively increases lean body mass and attenuates the PIF effect on protein degradation in cachectic patients. EPA downregulates the expression and activity of the ubiquitin-proteasome proteolytic pathway through a direct effect on PIF signaling by attenuating the production of 15-HETE (Smith et al., 1999) and inhibiting the activity of NF-κB (Whitehouse et al., 2001; Whitehouse & Tisdale, 2003).

Another promising tool to revert cachexia is related to eicosanoid and pro-resolving lipid mediators (SPM). The association of EPA with COX-2 inhibition is a promising strategy to revert cachexia status. Patients receiving fish oil associated with celecoxib (COX-2 inhibitor) had higher body weight gain, increased muscle strength and decreased plasma CRP levels in comparison to groups that received fish oil plus placebo (Cerchietti, Navigante, & Castro, 2007). In addition, EPA and DHA-derived lipid mediators such as resolvins and protectins are interesting tools due to their pro-resolving effects on the inflammatory process (Fig. 3). The inhibitory effects of resolvin D1 and protectin D1 on TNF-α and IL-1β may block the signaling effects of these cytokines on insulin pathways, improving insulin action (Markworth et al., 2016). Another important fact is that the resolvins D1, D2, and E1 inhibit debris-stimulated cancer progression by increasing the clearance of debris via macrophage phagocytosis. Resolvins diminished the release of cytokines, such as TNF-α, IL-6, IL-8, CCL4, and CCL5, by human macrophages. The decrease in the levels of inflammatory mediators may be related to improvement in cachexia (Sulciner et al., 2018).

The decrease in inflammatory leukocyte function directly by resolvin D1 led to the attenuation of cachexia in a model of rheumatoid arthritis. Skeletal muscle cells express the resolvin E1 receptor, and it plays an important role in myogenesis (Zabel et al., 2014). There are no studies evaluating the effects of these lipid mediators directly on muscle protein synthesis or growth pathways. These receptors are a potential tool to revert cachexia. In fact, administration of the protectin D1 isomer (10S,17S-dihydroxy-DHA) (also known as protectin DX) promoted the stimulation of myokine interleukin-6 (IL-6) release from skeletal muscle and a decrease in glucose intolerance.

3. Concluding remarks

The effects of n-3 PUFAs in cancer cachexia have been extensively investigated, but the precise mechanisms involved in their effects are not completely known to date. Several signaling pathways of n-3 PUFA action have been speculated on, including altered lipid uptake and metabolism, elevated resolution of inflammation and production of anti-inflammatory mediators, decreased generation of proinflammatory factors, increased tumor cell susceptibility to apoptosis, diminished angiogenesis and metastasis, improved insulin signaling and sensitivity, synergistic effects with antitumoral agents, reduced activation of proteolytic pathways, and increased appetite. Further investigation is

Table 1
Studies of n-3 polyunsaturated fatty acids in cancer cachexia.

Reference	N	Malignancy	Experimental design	Interventional protocol	Findings
Wigmore et al. (1996)	18	Advanced pancreatic cancer	Open-label, single arm Phase II study	Fish oil capsules (EPA 18%; DHA 12%), 2 g/d fish oil, increased at weekly intervals by 2 g, to maximum dose of 16 g/d	Increase in weight at 0.3 kg/month. No significant change in MAMC and TSF values.
Barber et al. (1999)	20	Pancreatic cancer	Single-arm study	Fish oil-enriched oral nutrition supplement, 2 cans/d (2.2 g EPA + 0.96 g), follow-up at 3 and 7 wk. from baseline	Increase in weight at 3 and 7 wk. of median 1 kg and 2 kg, respectively. Increase in LBM at 3 and 7 wk. of median 1.0 and 1.9 kg, respectively.
Barber et al. (2000)	32	Pancreatic cancer	Prospective study	Oral supplement containing 2 g/d EPA for 3 wk.	EPA improved nutritional parameters and LBM
Burns et al. (1999)	21	Advanced cancer - leukemia	Phase I clinical study	Soft gelatina capsules of fish oil 2 capsules/day (378 mg/g EPA: 249 mg/g DHA) 0.3 g/Kg/d for 7 wk	Modification of the lipids of leukemic cells, serum, and blood
Wigmore et al. (2000)	26	Pancreatic cancer	Single-arm study	Gelatin capsules high-purity EPA (500 mg) 1 g/d EPA in first week, 2 g/d in the second week; 4 g/d in the third week and 6 g/d thereafter Follow-up at 4, 8 and 12 wk	Decrease in median weight loss after 4 wk. of EPA vs. pre study values; reduction remained at 8 and 12 wk. No significant change in MUAMC or TSF at 4, 8 or 12 wk. of EPA vs. pre study values.
Zuijdgeest-Van Leeuwen et al. (2000)	33	Various cancers	Prospective double blind RCT	EPA 6 g/d versus oleic acid placebo for 1 wk	EPA failed to inhibit lipolysis in cancer patients but lowered serum triglycerides in healthy subjects
Barber and Fearon (2001)	20	Pancreatic cancer with weight loss	Open-label, single arm study	Fish oil-enriched nutritional supplement (2 g of EPA), during 3 wk	Decreased plasma IL-6, cortisol, and PIF levels Increased plasma insulin level Weight gain
Braga et al. (2002)	196	Various cancers	Prospective RCT	Liquid enteral diet containing omega-3 FAs 1 L/d versus control enteral formula for 1 wk	Perioperative omega-3 FAs reduced the length of hospital stay and postoperative complication rates
Fearon et al. (2003)	95	Unresectable pancreatic cancer	Multicentre, randomized, double blind trial	Oral supplement containing 2.2 g/d EPA for 8 wk.	Increased EPA plasma levels Weight gain Improved quality of life
Barber et al. (2004)	8	Pancreatic cancer	Prospective study	Fish oil oral supplement containing 2 g/d EPA 3 wk	Fish oil promoted bodyweight gain and hepatic production of constitutive proteins
Burns et al. (2004)	36	Advanced cancer with weight loss	Open-label, single arm study	N-3 oral supplementation (7.5 g/70 kg/day), during ~1.2 mo	24 patients presented weight stabilization, 6 weight gain and 6 weight loss Correlation between weight gain and quality of life
Jatoi et al. (2004)	421	Incurable brain, breast, ovarian, prostate or endometrial cancer	Randomized, double blind	Oral supplement containing 2.18 g/d EPA and 0.9 g/d of DHA for 4 wk	No result in notable improvement of weight, survival and quality of life
Moses et al. (2004)	24	Unresectable pancreatic cancer	Multicentre, randomized, double blind trial	Oral supplement containing 2.2 g/d EPA for 8 wk.	High EPA plasma levels Increase in physical activity and quality of life
Bauer and Capra (2005)	7	Pancreatic and lung cancer	Open-label, single arm study	EPA enriched oral nutritional supplement At least 1 can/d (1.1 g EPA/d) Follow-up at 8 wk	Increase in weight and LBM (NS). Increase in LBM associated with better nutritional status
Persson et al. (2005)	24	Advanced gastrointestinal cancer	Double-label, randomized, controlled trial	Fish oil (30 mL/d) and/or melatonin (18 mg/d) supplementation during 4 wk	Fish oil: 38% of the patients presented body weight stabilization or gain Melatonin: 27% Fish oil plus melatonin: 63%
Fearon et al. (2006)	518	Advanced gastrointestinal or lung cancer	Multicentre, double blind, placebo controlled trial	Capsules containing 2 or 4 g/d EPA for 4 and 8 wk	Modest improvement of physical activity No differences in nutritional and quality of life
Cerchietti et al. (2007)	12	Advanced lung cancer	Double-label, randomized, controlled trial	Fish oil (2 g/d) or fish oil plus celecoxib (COX-2 inhibitor, 200 mg/d) during 6 wk	Fish oil and fish oil plus celecoxib: increased appetite and reduced fatigue and plasma CRP level Fish oil plux celocoxib: improved body weight and muscle strength
Read et al. (2007)	23	Advanced colorectal cancer	Open-label, single arm study	EPA enriched oral nutrition supplement 2 cans/d (1.18 g EPA + 0.92 g DHA/day) Follow-up at 3 and 9 wk. 4 cycles of chemotherapy regimen with FOLFIRI, commenced at end of week 3 and repeated every 2 wk	Increase in weight at end of week 3 (mean increase of 2.5 kg from baseline) and maintenance during chemotherapy No significant change in LBM before and during chemotherapy
Bayram et al. (2009)	52	Various cancers - pediatric	Prospective, randomized, single-center, open-label design	Oral supplement containing 300 kcal, 16 g protein, and 1.09 g EPA – 2/day for 3 months	EPA treated patients showed losses in body weight, BMI and a negative deviation in weight percentile
Ryan et al. (2009)	53	Esophageal cancer	Double-label, randomized, controlled trial	EPA enriched enteral feeding (2.2 g EPA/d) during 5 d preoperatively, 2–10 d postoperatively and 11–21 d concomitantly with oral diet. Controls: Feeding regimen with an isocaloric, iso-nitrogenous enteral feed.	EPA enriched feeding regimen group: No significant difference in weight and FFM from preoperatively to day 21 postoperatively. Control group: Weight loss of 1.8 kg and LBM loss of 1.9 kg.
Mantovani and Madeddu	332	Advanced stage tumor at any site	Phase III randomized trial	Nutritional supplement containing 2.2 g/d EPA for 4 months	No benefit in cancer-related anorexia/cachexia syndrome

Table 1 (*continued*)

Reference	N	Malignancy	Experimental design	Interventional protocol	Findings
(2010)					
Taylor et al. (2010)	31	Cancer patients suffering weight loss	Open-label, single arm study	Marine phospholipid capsules (1.5 g/d) Follow-up at 6 wk	Increased plasma EPA and DHA levels Reduced n-6:n-3 ratio Stabilization of body weight Improved appetite and quality of life
van der Meij et al. (2010)	40	Lung cancer	Double-bind, randomized, controlled trial	Fish-oil enriched oral nutritional supplement (energy, protein-dense) 2 cans/d (2 g EPA.0.92 g DHA) Control group: Isocaloric oral nutritional supplement without EPA, DHA. Follow-up at 3 and 5 wk	EPA group: weight maintenance (weight difference between intervention group and control group: 1.3 kg at 3 wk. and 1.7 kg at 5 wk), less decrease in FFM, increase in MUAMC but decrease of MUAMC in the control group
Aronson et al. (2011)	48	Prostate cancer	Double-label, randomized, controlled trial	Subjects were submitted for 4–6 weeks to a low-fat diet containing 5 g of fish oil daily (2:1, n6:n3 ratio) or a control Western diet (15:1).	Low-fat diet: decreased prostate cancer proliferation and n6:n3 ratio.
Murphy et al. (2011)	31	Lung cancer	Open-label, single arm study	Two types of supplementation: 4 × 1 g gelatin capsules fish oil/d (2.2 g EPA) or 7.5 mL of liquid fish oil/d (2.2 g EPA). Control group: No intervention Follow-up after 2 cycles of chemotherapy (at least 6 wk)	Fish oil group: 69% patients maintained or gained weight and muscle. Control group: 29% patients maintained or gained weight and muscle
Weed et al. (2011)	31	Head-neck cancer	Open-label, single arm study	Fish-oil enriched oral nutritional supplement 2 cans/d (2.2 g EPA.0.92 g) Supplement consumed from no later than 2 wk. before surgery until discharge	Increase/maintenance in weight in 57% patients until hospital discharge Increase in LBM increase from trial entry to hospital discharge
Cockbain et al. (2014)	88	Metastatic colorectal cancer	Phase II, double-blind, randomized, placebo-controlled trial	Oral nutritional supplement containing 2 g/d EPA for 30 d	Overall survival and disease free survival benefit
Sorensen et al. (2014)	148	Colorectal cancer	Double-blind, randomized, placebo-controlled trial	Oral nutritional supplement containing 2 g/d EPA + 1 g/d DHA for 14 d	High levels of EPA and DHA and low level of AA in granulocytes No association with improved postoperative outcomes
Lovegrove et al. (2015)	495,321	Prostate cancer	Sistematic review	Relationship between dietary-fish and fish-oil intake and risk, aggressiveness, and mortality of prostate-cancer	Decreased risk of incidence, aggressiveness, and mortality
Mocellin et al. (2016)	475	Colorectal cancer	Systematic review and meta-analysis	Correlation between n-3 polyunsaturated fatty acid supplementation and inflammatory markers	Reduced concentration of inflammatory markers, IL-6 and CRP/albumin ratio
Tasaki et al. (2016)	112	Renal cell carcinoma	Correlational study	Relationship between plasma DHA level and post-surgery survival	Decreased risk for metastasis, increased post-surgery survival
Mocellin et al. (2017)	698	Gastric cancer	Meta-analysis	Correlation between n-3 polyunsaturated fatty acid supplementation and circulating CRP and cytokines	Reduced concentration of pro-inflammatory cytokines (IL-6 and TNF-α); no changes in CRP concentration
Werner et al. (2017)	70	Pancreatic cancer	Double-blind, randomized, controlled trial	Soft gel capsules (500 mg) containing 6.9 g/100 g EPA + 13.6 g/100 g DHA (FO) or 8,5 g/100 g EPA + 12.3 g/100 g DHA (MPL), 3 cap/d for 6 wk	Increased n-3 FFA in plasma Weight stabilization
Abe et al. (2018)	27	Bile duct and pancreatic cancers	Open-label, single arm study	Enteral nutrition with n-3 polyunsaturated fatty acids up to 8 wk	Increased skeletal muscle mass after 4 and 8 wk. of intervention

BIA, bioelectric impedance analysis; CRP, C-reactive protein; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FM, fat mass; FFM, free fat mass; IL-6, interleukin-6; LBM, lean body mass; MM, muscle mass; MUAMC, midupper arm muscle circumference; MUAC, midupper arm circumference; NS, not significant; TNF-α, tumor necrosis factor-α; TSF, triceps skinfold thickness.

required not only for identifying the precise mechanisms of n-3 PUFA action on the cachectic patient but also for discovering new approaches involving these molecules in combination with antitumor drugs, chemotherapy or radiotherapy and alternative interventions.

Conflict of interest

The authors declare that they have no conflicts of interest.

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