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Cancer cachexia and immunomodulation

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Summary

Cachexia is derived from the Greek words "kakos" meaning "bad" and "hexis" meaning "condition". Cachexia is a debilitating state of involuntary weight loss complicating malignant, infectious and inflammatory diseases. Several hypotheses for its etiology have been suggested including cytokines, circulating hormones, neuropeptides, neurotransmitters, and tumor-derived factors. Cachexia syndrome is caused predominantly by cytokines either produced by cancer or released by the immune system cells as a response to the presence of cancer, as well as other tumor products that induce profound lipolysis or protein degradation. Several strategies have been applied in the management of cachexia and related immunodeficiency including: 1.hypercaloric feeding; 2.administration of glucocorticoids; 3.progestational drugs; 4.cyproheptadine and other antiserotonergic drugs; 5.branched-chain aminoacids; 6.prokinetic agents; 7.eicosapentanoic acid (EPA); 8.cannabinoids; 9.5'-deoxy-5-fluorouridine; 10.emerging drugs: melatonin, thalidomide, β2-agonists, non-steroidal anti-inflammatory drugs (NSAIDs); 11.others: pentoxifylline, hydrazine sulfate, anabolic steroids.

Better understanding of the mechanisms underlying cancer and cachexia leading to immune dysfunction has guided immunomodulatory strategies to reverse cachexia and immunodeficiency. The concept is that the tumor itself may lead to cachexia and immune dysfunction but also cachexia is related and mediated with immune dysfunction. Thus the purpose is to affect the tumor itself and cachexia immune pathways in order to restore immune efficiency. However, more experimental and clinical studies are needed to evaluate the efficacy of immunomodulatory intervention in cancer cachexia and related immunodeficiency.

Key words: cachexia, cancer, inflammation, immune dysfunction, lipolysis, proteolysis

Introduction

Cachexia is a well known clinical phenomenon, characterized by progressive weight loss and depletion of adipose tissue and skeletal muscle mass [1]. The word means "bad condition" according to the Greek words *"kakos hexis"*, and has been described clinically 2300 years before by Hippocrates: *"...the flesh is consumed and becomes water..., the shoulders, the clavicles, chest and thighs melt away. This illness is fatal..."*. Sometimes, the wrong term *"sarcopenia"* is used, which refers mostly to body composition changes in the elderly and is characterized by subnormal protein content of muscle mass without any actual weight loss.

Most of the chronic and end-stage diseases, such as cancer, severe infections, congestive heart failure, rheumatoid arthritis, tuberculosis and others, demonstrate many clinical characteristics of cachexia. Cachexia should be suspected any time there is involuntary weight loss greater than 5% within a 6-month period. Generally, it represents the clinical consequence of a chronic, systemic inflammatory response, which involves high hepatic synthesis of acute phase proteins and an increase in liver mass resulting in

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depletion of essential aminoacids. Loss of muscle mass affects mainly skeletal proteins rather than visceral. On the other hand, in "starvation", only fat metabolism is increased, lean body mass is preserved and the liver may actually decrease in mass [1,2]. *Anorexia,* defined as the loss of appetite, is present in up to 50% of newly diagnosed cancer patients. Chemotherapy and radiation also produce anorexia and contribute to additional weight loss. However, anorexia alone cannot explain the complex metabolic changes that occur during cachexia, as in many clinical trials nutritional supplements and appetite stimulants failed to increase body weight.

The abnormalities associated with cancer cachexia include anorexia, weight loss, muscle loss, chronic nausea and asthenia, anaemia and progressive changes in the body image accompanied by psychological distress. *Asthenia* is characterized by profound tiredness occurring under usual or negligible effort in addition with an unpleasant sensation of generalized weakness and fatigue. Most patients with advanced cancer have a combination of cachexia and asthenia but each of the two conditions can take place in a different degree.

Cancer cachexia varies according to the exact type of tumor. There is a very high (85%) incidence seen in patients with carcinoma of the pancreas and stomach, while it is much less in patients with breast cancer (40%). Those differences are probably due to variations in the tumor phenotype [3]. Weight loss can arise from a decrease in energy intake, or increased energy expenditure. Resting energy expenditure (REE) was found elevated in patients with both lung and pancreatic cancer, whereas patients with colorectal and gastric cancer had shown no elevation [2,4]. Loss of skeletal muscles leads to immobility and death due to loss of respiratory muscle function. Patients with body weight loss greater than 15% are likely to have impaired physiological function, while patients with 30% loss or more have very high mortality rates. The survival of cancer patients is directly related to the total weight loss and the rate that this occurs. Even small amounts of weight loss can affect the prognosis.

Detection of cachexia

Cachexia can be evaluated with a combination of clinical and laboratory tests [5]. The most important clinical tests are:

1. Body weight and body mass index (BMI) measurements.
2. Skin fold thickness, mainly triceps.
3. Mid-arm circumference.

Laboratory tests also assist in the evaluation of nutritional status. The most commonly used are:

1. Serum albumin concentration: it is used in the absence of liver or renal diseases.
2. Measurement of short half-life proteins, such as transferrin and transthyretin.
3. Analysis of urine metabolites, such as creatinine.
4. Bio-electrical impedance: it measures impedance between surface electrodes and estimates total body lean mass.
5. Muscle thickness measurements by ultrasound [6].
6. Skeletal muscle protein turnover using labelled aminoacids.
7. Skeletal muscle size measurements through MRI, CT or body densitometry.

Mechanisms of cachexia

Cancer cachexia is thought to result from a complex and multidimensional interaction between host neuroendocrine and cytokine systems, in addition with tumor-derived proteins (Figure 1). There are two main theories about the mechanisms of development of cachexia:

The first theory refers to the pathological alteration of control cycles. Neuropeptide Y (NPY) is the most potent feeding stimulatory peptide of this cycle and is regulated by hypothalamic hormones. NPY may stimulate feeding on its own and also via stimulation of other orexigenic peptides (galanin, opioid peptides, orexin, melanin-concentrating hormone (MCH) and agouti-related peptide (AGRP) [7]. In cachexia the peptide is downregulated, leading to decreased energy intake. In addition, high levels of leptin, a hormone secreted by lipocytes, block the release of NPY altering the control cycle. Tachyphylaxis develops quickly, such that in advanced cancer leptin levels are lower than normal [8-9].

The second theory is based on tumor-derived factors which maintain the syndrome of cachexia. The proteolysis inducing factor (PIF), which was extracted from the urine of cachectic patients and induces protein degradation, is closely related to weight loss. A second factor which induces lipolysis is the lipid mobilizing factor (LMF), which produces a significant increase in mitochondrial uncoupling proteins (UCPs) in brown adipose tissue in skeletal mass and liver. UCPs are a family of mitochondrial membrane proteins related to energy metabolism by controlling thermogenesis in
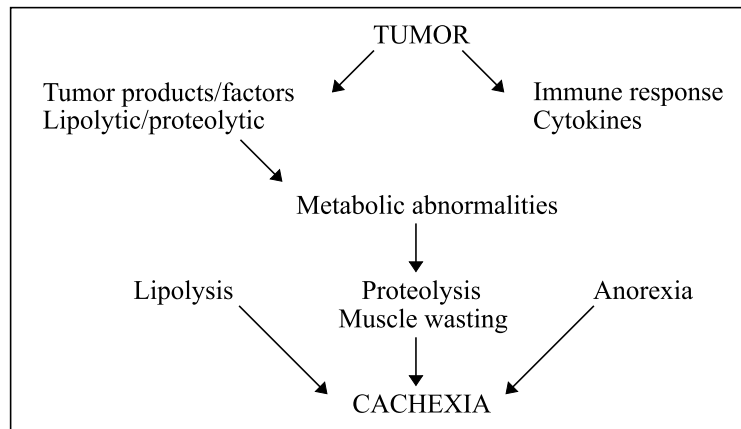
Figure 1. Probable mechanisms of cachexia.

brown adipose tissue and probably in skeletal muscle mass. UCP 1 is only expressed in brown adipose tissue, UCP 2 is widely distributed in many tissues, and UCP 3 is expressed only in brown adipose tissue and skeletal proteins. Increased thermogenesis through UCPs elevates total energy expenditure and contributes to tissue wasting in cachexia (mainly UCP 1). During starvation, there is also a decline in UCP 3 levels in brown adipose tissue, but an increase in skeletal muscle mass, in order to facilitate the oxidation of free fatty acids. Changes in UCPs expression might be induced by tumor products, or by cytokines that are produced during the antitumor process [2].

Both theories contribute to a greater understanding of the development of cancer cachexia, but it is still unclear how they interact. Today it is quite clear that proinflammatory cytokines are linked to all pathways that induce the syndrome. High levels of IL-1, IL-6 and INF-γ are present in many cancer patients and they correlate with tumor progression. Monocytes, macrophages, as well as T-lymphocytes are activated by the presence of a tumor, and they produce many of these cytokines, leading to decreased food intake, loss of body weight, asthenia and several major metabolic abnormalities. All mediators of the cachectic process can be divided into two groups.

The first group includes substances produced by host and/or tumor cells, such as IL-1, IL-6, TNF, INF-γ and cilliary neurotrophic factor (CNTF). Especially TNF is identical to "cachectin", a cytokine which was found to suppress lipoprotein lipase in preadipocyte cells. TNF can cause hyperlipidaemia, lipolysis and an increased rate of fatty acid turnover. IL 1 stimulates serotonin release, inhibits NPY transmission, and also influences the corticotrophin-releasing hormone at the hypothalamus. Some tumor lines can produce cytokines

in culture, but it is quite rare to detect circulating concentrations of cytokines.

The second group includes substances produced by tumor cells, such as LMF which acts specifically on adipose tissue, and PIF which induces protein degradation in skeletal muscle through the ubiquitin proteasome pathway. In addition, nuclear factor kappa B (NF-κB) is involved in multiple cellular processes, such as cytokine expression, apoptosis and oncogenesis. High levels of NF-κB have been described in many types of tumors and seem to affect cancer cell survival. The precise mechanism that leads to the secretion of all these mediators is still under investigation, because there seem to be additional systems contributing to pathogenesis of cachexia, such as catecholamines, steroid hormones and leptin.

Inflammation and tissue injury induce a specific reaction, known as the "acute phase response". Maintaining this response requires an excess of essential aminoacids. During the early phase of muscle cachexia, the release of aminoacids can be beneficial to the organism, because it provides the essential substrates for acute phase protein synthesis as well as an energy source for all cells of the immune system. When cachexia becomes prolonged, breakdown of the myofibrillar proteins actin and myosin has significant deleterious consequences. Intracellular protein degradation is regulated by multiple proteolytic pathways, especially the ubiquitin proteasome pathway. Ubiquitin-dependent proteolysis is considered to be the most important pathway in catabolic conditions, such as starvation, sepsis, metabolic acidosis, severe trauma, denervation atrophy and cancer cachexia. The other two proteolytic systems (lysosomal for extracellular proteins and calcium-regulated calpains) are not capable of degrading myofibrillar proteins. Ubiquitin serves as a co-factor

which is linked to the proteins to be degraded in the 26S proteasome complex. This protease specially degrades ubiquitin conjugates and is the main mediator in muscle wasting, studied in conditions such as AIDS, cancer, sepsis and renal failure [10,11]. Cytokines, especially PIF and TNF-α seem to stimulate the ubiquitin proteasome pathway and this suggests that these two factors might provide an appropriate target for future therapies [3].

The current knowledge concerning the pathogenesis of cancer cachexia is shown in Figure 2.

## Management of cachexia and related immunodeficiency

There have been many studies determining the activity of many agents in the treatment of cachexia (Table 1). Researchers have different opinions about the main target of treatment, and the spectrum varies between therapies against the primary disease and maintaining patients' nutritional status. The ideal therapy probably lies between those two extremes, because starvation and cachexia overlap in different degrees in each patient. According to the latest evidence, nutritional support alone is not sufficient enough to reverse the syndrome of cachexia and probably it has to be combined with a pharmacological strategy in order to balance metabolic changes.

1. Hypercaloric feeding

The effects of increased caloric intake are still under debate and consideration, because most of the studies that evaluated total parenteral nutrition combined with radiotherapy or chemotherapy have been disappointing. Parenteral nutrition may have some benefits in patients with decreased food intake because of mechanical obstruction of the gastrointestinal tract. Enteral nutrition has the advantage of maintaining the immunological function of gut-mucosal barrier and also has the benefit of low side effects. Provision of adequate protein content (1.5 g/kg lean body mass/day) in nutrition can reduce protein loss, but further increases failed to reduce proteolysis or increase muscle protein synthesis [12]. A new approach is the supplement of omega-3-fatty acids, in order to reduce IL-1 and TNF-α production, improving the efficacy of nutritional support [7].

2. Glucocorticoids

They are widely used and seem to have a proven effect for up to 4 weeks on symptoms such as appetite, food intake, nausea and performance status. The mechanism of action includes inhibition of proinflammatory cytokines such as TNF-α, NF-κB and IL-1, increase in NPY expression in the hypothalamus, and also indirect action on other regulatory mediators, such as leptin,
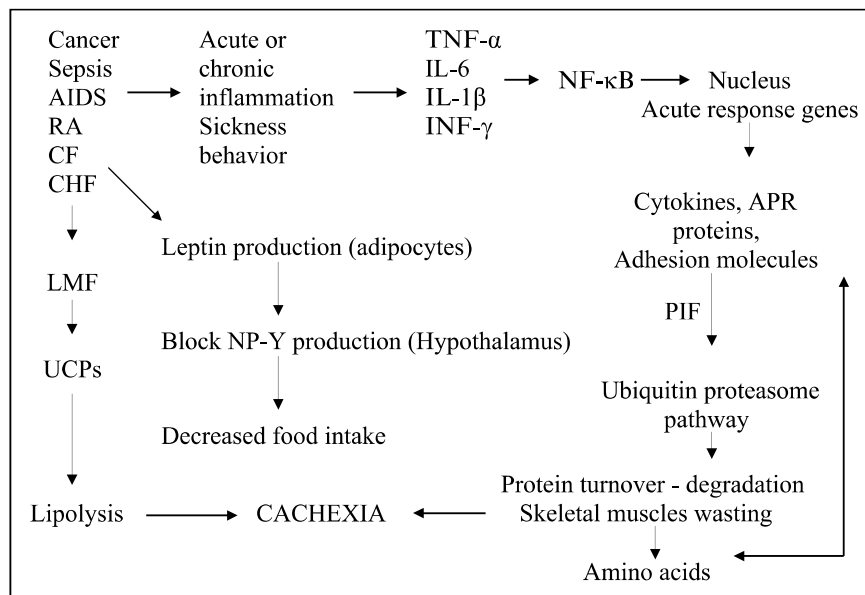
Figure 2. Pathogenetic mechanisms of cachexia.
UCP=Uncoupling proteins; LMF=Lipid mobilizing factor; PIF=Proteolysis inducing factor; APR=Acute phase response; NP-Y=Neuropeptide-Y; CF=Cystic fibrosis; CHF=Congestive heart failure; RA=Rheumatoid arthritis; AIDS=Acquired immunodeficiency syndrome; TNF-α=Tumor necrosis factor-α; IL-6=Interleukin-6; IL-1β=Interleukin-1β; INF-γ=Interferon-γ; NF-κB=Nuclear factor-κB

Table 1. Therapeutic interventions and potential therapies for cachexia

Therapies for cachexia	Comments
1. Hypercaloric feeding	Limited usefulness when used alone
2. Glucocorticoids prednisolone dexamethasone methylprednisolone	Proven benefit (for short-term use)
3. Progestational drugs megestrol acetate medroxyprogesterone	Proven benefit (for long-term use)
4. Antiserotonergic drugs 5HT3 antagonists cyproheptadine	Proven benefit in nausea Limited usefulness in cancer asthenia
5. Branched-chain aminoacids leucine isoleucine valine	More studies needed
6. Anabolic agents rec. growth hormone oxandrolone	More studies needed
7. Gastroprokinetic drugs metoclopramide	Proven benefit in chronic nausea
8. Eicosapentanoic acid	More studies needed of different preparations of the drug
9. Aminoacids glutamine	More studies needed
10. Cannabinoids dronabinol	Proven benefit in appetite, mood and nausea
11. 5'- deoxy-5-fluorouridine	More studies needed
12. Emerging drugs melatonin thalidomide	Proven benefit Proven symptomatic effects
13. Adrenergic agents β-2 agonists	More studies needed
14. Antiinflammatory agents ibuprofen indomethacin COX2 inhibitors	Without proven efficacy-more studies needed
15. Erythropoietin	Without proven efficacy-more studies needed
16. Anticytokine therapies TNF synthesis inhibitors pentoxiffyline rolipram thalidomide Anticytokine antibodies anti IL-6 (suramine) anti INF-γ anti TNF Antiinflammatory cytokines IL-12 IL-15 INF-α Anti NF-κB	 More studies needed Proven benefit in patients with AIDS and lymphoma Proven benefit in animal models Without proven benefit Efficient in animal models-more studies needed Efficient in animal models-more studies needed
17. Proteasome inhibitors	More studies needed

serotonin and CRF. The most commonly used glucocorticoids are prednisolone at a dose of 15 mg daily (divided in 3 doses), dexamethasone at 3-6 mg daily and methylprednisolone at a dose of 125 mg daily. It is important to begin with a trial period of one week, and continue therapy according to the response. Intermediate acting glucocorticoids may cause less suppression of the hypothalamic - pituitary axis, and are usually the first choice. Special care must be taken because of side effects after prolonged treatment, particularly peptic ulceration and immunosuppression.

3. Progestational drugs

Megestrol acetate and medroxyprogesterone acetate are synthetic derivatives of the naturally occurring hormone progesterone. Their mechanism of action seems to be related to glucocorticoid activity, and includes stimulation of NPY in the hypothalamus, modulation of calcium channels and inhibition of proinflammatory cytokines such as IL-1, IL-6 and TNF-α. Megestrol has been used in doses of 160-1600 mg daily, starting with the lower dose and titrating upwards according to the clinical response. It has shown significant benefit compared to placebo in patients with cachexia, and also better results compared with dronabinol [13]. Medroxyprogesterone has been used in doses of 500-4000 mg daily, but side effects increase significantly above 1000 mg. Both drugs can induce thromboembolism, adrenal suppression, hypertension and peripheral edema.

4. Antiserotonergic drugs

Cyproheptadine is an antiserotonergic drug with antihistamine properties, with appetite stimulatory action in patients with cachexia and other clinical conditions with reduced food intake. Serotonin (5HT) suppresses food intake and might play a critical role in anorexia associated with cancer. 5HT3 antagonists, such as ondasentron, tropisentron and granisentron are widely used as antiemetics in several conditions, and seem to improve the ability of food intake.

5. Branched - chain aminoacids

The administration of aminoacids can theoretically prevent muscle wasting by providing the substrate for muscle metabolism and gluconeogenesis. Branched-chain aminoacids (BCAA: leucine, isoleucine and valine) have been used as parenteral nutrition, and seem to improve protein synthesis and nitrogen balance. They also antagonize the effects of tryptophan (the precursor of serotonin), blocking the effects of 5HT in the hypothalamus.

6. Anabolic agents

The use of recombinant human growth hormone has been studied in patients with cachexia, but is controversial because of its theoretical anabolic effect on the tumor itself. Other anabolic agents, such as oxandrolone in doses up to 20 mg daily have better results regarding weight gain.

7. Prokinetic agents

Metoclopramide in doses of 10 mg orally before meals is particularly effective and results in appetite and nausea improvement. Slow-release formulas of the drug taken every 12 hours have better results because of continued gastric stimulation.

8. Eicosapentanoic acid

EPA is a polyunsaturated fatty acid of the omega-3 family which suppresses mediators of cachexia, especially IL-6 and PIF. In addition, EPA interferes with the ubiquitin proteasome system [14]. Most studies suggest that combination of EPA with a conventional oral nutritional supplement can produce weight and lean body mass gain in cachectic patients [15].

9. Aminoacids

Human aminoacid requirements have not been completely defined in patients with cachexia. It has been suggested that a group of non essential aminoacids, such as glutamine, glutamic acid, arginine, citrulline, proline and others, become essential under conditions of stress including cancer cachexia. These aminoacids are preferentially depleted in cancer, and their supplementation seems to improve nitrogen balance, muscle protein mass and immunity [15]. Glutamine has been widely studied, and seems to be an important substrate for protein synthesis, gluconeogenesis, and glutathione synthesis (a free radical scavenger). On the other hand, it is used directly as an energy source by cells of the immune system and intestinal mucosa. The effects of glutamine, however, in enteral and parenteral nutrition have not been defined [12].

10. Cannabinoids

Dronabinol and nabilone are cannabinoids which have been used as antiemetic agents for many years. Dronabinol is the synthetic derivative of tetrahydrocannabinol, and in doses of 2.5 mg twice daily showed significant improvement in appetite, mood and nausea, but no weight gain [16]. Theoretically, cannabinoids stimulate appetite through hypothalamic cannabinoid-1 receptors, increasing GABA and dynorphin [8].

11. 5'- deoxy-5-fluorouridine

It is a fluorinated pyrimidine nucleoside, which is cytostatic in tumor tissue. The mechanism of action regarding cachexia is probably through inhibition of IL-6 and PIF. Chemotherapy could have a role in improving cachexia, not only by reducing the tumor mass, but also by modulating the production of immune cells and mediators.

12. Emerging drugs

Melatonin can decrease the level of TNF-α in patients with advanced cancer, and it seems to improve survival rate, neuropathy and cachexia. Thalidomide is known to inhibit selectively the production of TNF-α and IL-6. It also inhibits tumor growth through inhibition of neoangiogenesis, and improves appetite, insomnia and restlessness in cachectic patients.

13. Adrenergic agents

The sympathetic nervous system mediates anabolism in the skeletal muscles, inhibiting protein degradation and increasing protein synthesis. Clenbuterol, is a β2 adrenergic agonist, and can decrease the degree of muscle mass loss in patients with disuse atrophy. Until now, no study can prove the benefit of β2 agonists in critical illness [12].

14. Non steroidal antiinflammatory drugs

Ibuprofen has been used in doses up to 400 mg 3 times daily. It has been shown to reduce IL-6 levels, acute phase proteins and cortisol, and, in addition, to normalize protein metabolism in cachectic patients. In the same way, indomethacin at a dose of 50 mg twice daily, stabilizes performance status and prolongs survival. All NSAIDs act through inhibition of prostaglandin synthesis, blocking the activity of cyclooxygenases (COX) 1 and 2. Selective COX-2 inhibitors have a high antiinflammatory activity, with antiangiogenic and antitumor action in animal models [7].

15. Erythropoietin

Erythropoietin, combined with NSAIDs, causes weight gain and increased appetite in patients with

advanced cancer. Its mechanism of action seems to be an increase in serum NPY concentrations [8].

16. Muscle stimulation

Physiotherapy can provide improvement in flexibility and also offers mild exercise and encourages activity [4]. Mobilization can improve muscle atrophy, tendon retraction and prevent pressure ulcers. Electrical stimulation of muscles can also prevent the skeletal muscle protein loss associated with immobility.

17. Cytokine inhibition

Inhibition of pro-inflammatory cytokine activity can decrease protein degradation *in vitro* [17,18]. Some agents already in use have anticytokine properties, such as megestrol acetate, medroxyprogesterone and dronabinol.

a) *TNF synthesis inhibitors:* many different TNF synthesis inhibitors have been used therapeutically. Pentoxifylline, a methylxanthine derivative, can decrease the cytokine-induced toxicity of antineoplastic agents, preserving at the same time their efficacy. On the other hand, pentoxiffyline failed to improve appetite, or to increase weight in cachectic patients [19]. Rolipram is a phosphodiesterase inhibitor that seems to reduce TNF production in endotoxinaemia. Thalidomide also suppresses TNF production in monocytes, and normalizes TNF levels *in vivo* [19,20].

b) *Anticytokine antibodies:* the use of mono or poly-clonal anticytokine antibodies and cytokine receptor antagonists has led to interesting results. Anti IL-6 therapy with the drug suramine was proved effective in improving cancer-induced cachexia. Suramine partially blocks the binding of IL-6 to its cell surface receptor, and had successful results in humans suffering from AIDS and lymphoma [19]. Anti INF-γ therapy has also been effective in reverting cachexia in animal models with carcinoma, but more studies are needed to prove this effect. On the other hand, anti TNF therapy in humans has produced poor results in preventing cachexia due to sepsis.

c) *Antiinflammatory cytokines:* many studies have been made concerning the use of antiinflammatory cytokines, in order to block the pathogenesis of cachexia. IL-12 seems to decrease the levels of IL-6 and has been used in animal models with promising results. A similar action has been described for INF-α, which produces a decrease in IL-6 mRNA expression and also in IL-6 serum levels. IL-15 is an anabolic factor for skeletal muscle and achieved some reversal of cancer cachexia in animal models [21].

d) *NF-κB inhibitors:* NF-κB is another possible target against cancer cachexia. An oligonucleotide has been used which competes with NF-κB binding site and is able to revert cachexia in animal models [19].

18. Proteasome inhibitors

Recently, studies with proteasome inhibitors have started. Four classes of inhibitors have already been described: a) peptide aldehydes; b) lactacystine and its active derivative b-lactone; c) vinyl sulfone; and d) dipeptide boronic acid analogs. All 4 potential therapies have been shown to block up to 90% of the degradation of abnormal proteins and short-lived proteins of the cell [22,23].

Conclusions

Cachexia is now considered to be a complex multidimensional process due to metabolic and immunological abnormalities. Understanding the molecular mechanisms of protein wasting in cancer cachexia is essential in order to design new therapeutic strategies. Except of the primary goal of treating the underlying illness, further therapies against the molecular mediators of cachexia are being studied. Nutritional support will continue to develop in combination with new appetite stimulants and anabolic factors. Cytokines, transcription factors, and ubiquitin proteasome pathway mediators, seem to be the most interesting field of research.

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