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Review

The pivotal role of cytokines in muscle wasting during cancer

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Abstract

The cachectic syndrome, characterized by a marked weight loss, anorexia, asthenia and anemia, is invariably associated with the presence and growth of the tumour and leads to a malnutrition status due to the induction of anorexia or decreased food intake. In addition, the competition for nutrients between the tumour and the host leads to an accelerated catabolic state, which promotes severe metabolic disturbances in the host, including hypermetabolism, which leads to an increased energetic inefficiency. Although the search for the cachectic factor(s) started a long time ago, and although many scientific and economic efforts have been devoted to its discovery, we are still a long way from knowing the whole truth. Present investigation is devoted to unrevealing the different signaling pathways (particulary transcriptional factors) involved in muscle wasting. The main aim of the present review is to summarize and evaluate the different molecular mechanisms and catabolic mediators involved in cancer cachexia since they may represent targets for future promising clinical investigations.

Keywords: Cancer cachexia; Mediators; Cytokines

Contents

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1. Wasting in cancer: introductory remarks

The cachectic syndrome, characterized by a marked weight loss, anorexia, asthenia and anemia, is often associated with the presence and growth of the tumour and leads to a malnutrition status due to the induction of anorexia or decreased food intake. In addition, sometimes the competition for nutrients between the tumour and the host leads to an accelerated starvation state, which promotes severe metabolic disturbances in the host, including hypermetabolism, which leads to a decreased energetic efficiency. Although the search for the cachectic factor(s) started a long time ago, and although many scientific and economic efforts have been devoted to its discovery, we are still a long way from knowing the whole truth.

Perhaps the most common manifestation of advanced malignant disease is the development of cancer cachexia. Indeed, cachexia occurs in the majority of cancer patients before death, and it is responsible for the deaths of 22% of cancer patients. The abnormalities associated with cancer cachexia include anorexia, weight loss, muscle loss and atrophy, anemia and alterations in carbohydrate, lipid and protein metabolism (see Costelli & Baccino, 2000; Fearon & Moses, 2002 for a review). The degree of cachexia is inversely correlated with the survival time of the patient and it always implies a poor prognosis.

The aim of the present review is to summarize and update the role of catabolic mediators (cytokines and tumour-derived factors) in cancer cachexia since research based on these compounds may be of great relevance in future clinical investigations.

2. Cytokines mediate anorexia and muscle wasting

Cytokines have a key role as the main humoural factors involved in cancer cachexia. Thus, a large number of them may be responsible for the metabolic changes associated with cancer wasting.

Anorexia may play an important role in accounting for malnutrition, invariably associated with cancer cachexia. But, are cytokines involved in the induction of anorexia? Cytokines such as interleukin-1 (IL-1) and tumour necrosis factor-α (TNF) have been suggested as involved in cancer-related anorexia, possibly by increasing the levels of corticotropin-releasing hormone (CRH), a central nervous system neurotransmitter that suppresses food intake, and the firing of glucose-sensitive neurons, which would also decrease food intake (Watanobe & Takebe, 1992). However, many other mediators have been suggested as involved in cancer-induced anorexia. Thus, leptin (an adiposity signal to the hypothalamus that it is a member of the cytokine family) does not seem to play a role, at least in experimental models (López-Soriano, Carbó, Tessitore, López-Soriano, & Argilés, 1999; Sato, Meguid, Miyata, Chen, & Hatakeyama, 2002). In human subjects, cancer anorexia does not seem to be due to a dysregulation of leptin production (Kowalczuk, Wiecek, Franek, & Kokot, 2001). Indeed, leptin concentrations are not elevated in weight-losing cancer patients (Brown, Berkowitz, & Breslow, 2001; Tessitore et al., 2000) and are inversely related to the intensity of the inflammatory response (Aleman et al., 2002) and the levels of inflammatory cytokines (Mantovani et al., 2000, 2001). The concentrations of the peptide seem to be dependent only on the total amount of adipose tissue present in the patient. Cytokines can have a role in cancer-induced anorexia since they modulate gastric motility and emptying, either directly in the gastrointestinal system or via the brain, by altering efferent signals that regulate satiety. IL-1, in particular, has been clearly associated with the induction of anorexia (Plata-Salaman, 2000), by blocking neuropeptide Y (NPY)-induced feeding. The levels of this molecule (a feeding-stimulating peptide) are reduced in anorectic tumour-bearing rats (Chance, Balasubramaniam,

Dayal, Brown, & Fischer, 1994), and a correlation between food intake and brain IL-1 has been found in anorectic rats with cancer. The mechanism involved in the attenuation of NPY activity by cytokines may be related to an inhibition of cell firing rates or to an inhibition of NPY synthesis or an attenuation of its postsynaptic effects (King, Widdowson, Doods, & Williams, 2000). Other mediators have been proposed (Laviano, Russo, Freda, & Rossi-Fanelli, 2002) including changes in the circulating levels of free tryptophan; these may induce changes in serotonin brain concentrations and, consequently, cause changes in food intake. Bing, Taylor, Tisdale, and Williams (2001) have also suggested that some tumour-derived compounds may mediate the anorexia associated with tumour burden.

Different experimental approaches have demonstrated that cytokines are able to induce weight loss. Nevertheless, the results obtained have to be carefully interpreted. Thus, episodic TNF administration has proved unsuccessful at inducing cachexia in experimental animals. Indeed, repetitive TNF administrations initially induce a cachectic effect, although tolerance to the cytokine soon develops and food intake and body weight return to normal. Other studies have shown that escalating doses of TNF are necessary to maintain the cachectic effects. In an elegant experiment, Oliff et al. (1987), after transfecting the human TNF gene in CHO cells that were later implanted in nude mice, clearly showed that the expression and release of the cytokine led to a massive body weight loss that was characterized by a profound anorexia.

Strassmann et al. (1993) have shown that treatment with an anti-mouse interleukin-6 (IL-6) antibody was successful in reversing the key parameters of cachexia in murine colon adenocarcinoma tumour-bearing mice. These results seem to indicate that, at least in certain types of tumours, IL-6 could have a more direct involvement than TNF in the cachectic state. In addition, Enomoto et al. (2004) found very effective in the treatment of C26 colon carcinoma-induced cachexia the utilization of a novel nonpeptide IL-6 receptor antagonist. Similar results were obtained in a mouse model that reproduces the cachexia associated with multiple myeloma (Barton, Cullison, Jackson, & Murphy, 2000; Barton & Murphy, 2001), in a murine model of intracerebral injection of human tumours (Negri et al., 2001) and using CNTO 328, a monoclonal antibody to IL-6, where inhibition of tumour-induced cachexia was observed in nude mice (Zaki, Nemeth, & Trikha, 2004) Conversely, studies using incubated rat skeletal muscle have clearly shown that IL-6 had no direct effect on muscle proteolysis (García-Martínez, López-Soriano, & Argilés, 1994).

Another interesting candidate for cachexia is interferon-γ (IFN-γ), which is produced by activated T and NK cells and possesses biological activities that overlap with those of TNF. Matthys, Heremans, Opdenakker, and Billiau (1991), using a monoclonal antibody against IFN-γ, were able to reverse the wasting syndrome associated with the growth of the Lewis lung carcinoma in mice, thus indicating that production of IFN-γ occurs in the tumour-bearing mice and is instrumental in bringing about some of the metabolic changes characteristic of cancer cachexia. The same group has also demonstrated that severe cachexia develops rapidly in nude mice inoculated with CHO cells constitutively producing IFN-γ, as a result of the trans-fection of the corresponding gene.

Other cytokines, such as the leukemia inhibitory factor (LIF), transforming growth factor-β (TGF-β) or IL-1 have also been suggested as mediators of cachexia. Thus, mice engrafted with tumours secreting LIF develop severe cachexia. Concerning IL-1, although its anorectic andpyrogenic effects are well known, administration of IL-1 receptor antagonist (IL-1ra) to tumour-bearing rats did not result in any improvement in the degree of cachexia (Costelli et al., 1995), thus suggesting that its role in cancer cachexia may be secondary to the actions of other mediators. Interestingly, the levels of both IL-6 and LIF have been shown to be increased in patients with different types of malignancies.

Cyliary neurotrophic factor (CNTF) is a member of the family of cytokines which include IL-6 and LIF and which is produced predominantly by glial cells of the peripheral nervous system; however, this cytokine also seems to be expressed in skeletal muscle. Henderson, Mullen, and Roder (1996) have demonstrated that CNTF induces potent cachectic effects and acute-phase proteins (independent of the induction of other cytokine family members) in mice implanted with C6 glioma cells, genetically modified to secrete this cytokine. The cytokine, however, exerted divergent direct effects dependent on the dose and the time of exposure on in vitro muscle preparations (Wang & Forsberg, 2000).

If anorexia is not the only factor involved in cancer cachexia, it becomes clear that metabolic abnormalities leading to a hypermetabolic state must have a very important role. Interestingly, injection of low doses of TNF either peripherally or into the brain of laboratory animals elicits rapid increases in metabolic rate which are not associated with increased metabolic activity but rather with an increase in blood flow and thermogenic activity of brown adipose tissue (BAT), associated with uncoupling protein (UCP1). Interestingly, during cachectic states there is an increase in BAT thermogenesis both in humans and experimental animals. Until recently, the UCP1 protein (present only in BAT) was considered to be the only mitochon-drial protein carrier that stimulated heat production by dissipating the proton gradient generated during respiration across the inner mitochondrial membrane and therefore uncoupling respiration from ATP synthesis. Interestingly, two additional proteins sharing the same function, UCP2 and UCP3, have been described. While UCP2 is expressed ubiquitously, UCP3 is expressed abundantly and specifically in skeletal muscle in humans and also in BAT of rodents. Our research group has demonstrated that both UCP2 and UCP3 mRNAs are elevated in skeletal muscle during tumour growth and that TNF is able to mimic the increase in gene expression (Busquets et al., 1998). In addition, TNF is able to induce uncoupling of mitochondrial respiration as recently shown in isolated mitochondria (Busquets et al., 2003). In conclusion, it seems clear that, in addition to promoting skeletal muscle protein breakdown, TNF may be responsible for the induction of other events associated with the hypermetabolism state, like those related to uncoupling.

Several cytokines have been shown to mimic many of the metabolic abnormalities found in the cancer patient during cachexia. Among these metabolic disturbances, changes in lipid metabolism, skeletal muscle proteolysis and apoptosis and acute-phase protein synthesis have been described (see Argilés & López-Soriano, 1998 for review). Concerning muscle wasting, it seems that administration of TNF to rats results in an increased skeletal muscle proteolysis associated with an increase in both gene expression and higher levels of free and conjugated ubiquitin, both in experimental animals and humans (Baracos, 2000). In addition, the in vivo action of TNF during cancer cachexia does not seem to be mediated by IL-1 or glucocorticoids. Other cytokines such as IL-1 or IFN-γ are also able to activate ubiquitin gene expression. Therefore, TNF, alone or in combination with other cytokines (Alvarez et al., 2002), seems to mediate most of the changes concerning nitrogen metabolism associated with cachectic states. In addition to the massive muscle protein loss, during cancer cachexia (similar to that observed in skeletal muscle of chronic heart failure patients suffering from cardiac cachexia (Sharma & Anker, 2002)) muscle DNA fragmentation is increased and, thus, apoptosis (Belizario, Lorite, & Tisdale, 2001; Van Royen et al., 2000). Interestingly, TNF can mimic the apoptotic response in muscle of healthy animals (Carbó et al., 2002).

3. Intracellular signaling in skeletal muscle

At the moment, there are few studies describing the involvement of different transcriptional factors in muscle wasting. Penner, Gang, Wray, Fischer, and Hasselgren (2001) reported an increase in both NFκB and AP-1 transcription factors during sepsis in experimental animals. Recent data from our laboratory do not support an involvement of NFκB in skeletal muscle during cancer cachexia (Busquets et al., 2004). However, tumour burden results in a significant increase in the binding activity of AP-1 (Costelli et al., 2005). In addition, in vivo experiments using a potent AP-1 inhibitor result in an amelioration of muscle wasting in cachectic tumour-bearing rats (Moore-Carrasco et al., in press). Interestingly, inhibition of NFκB (Busquets et al., 2001) is not able to revert muscle wasting in cachectic tumour-bearing animals. The increase in NFκB observed in skeletal muscle during sepsis can be mimicked by TNF. Indeed TNF addition to C2C12 muscle cultures results in a short-term increase in NFκB (Fernández-Celemin, Pasko, Blomart, & Thissen, 2002; Li, Schwartz, Waddell, Holloway, & Reid, 1998). Whether or not this increase in NFκB promoted by TNF is associated with increased proteolysis and/or increased apoptosis in skeletal muscle remains to be established. In addition, the referred experiments with the transcription factor do not necessary imply an increased nuclear translocation of NFκB activity. Therefore, further studies are needed to clarify this point. In relation with AP-1 activation,

TNF has been shown to increase c-jun expression in C2C12 cells (Brenner, O'Hara, Angel, Chojkier, & Karin, 1989). Interestingly, overexpression of c-jun mimics the observed effect of TNF upon differentiation. Indeed, it results in decreased myoblast differentiation (Thinakaran, Ojala, & Bag, 1993). Tumour mediators,

PIF in particular, also seem to be able to increase NFκB expression in cultured muscle cells, this possibly being linked with increased proteolysis (Smith, Wyke, & Tisdale, 2004). In a very interesting investigation, Cai et al. (2004) conclude, using an IκB kinase beta trans-genic model, that NFκB has a marked role in muscle wasting. Therefore, it seems likely that at least in some experimental models, this transcription factor does play a role in cachexia. However, it has to be considered that in vitro experiments, even when undertaken with different approaches (cell cultures, isolated muscle fibers), do not necessary reflect the situation that may be encountered in muscle in vivo (Acharyya et al., 2004). In addition, in the case of muscle wasting associated with cancer, there could be a selective targeting of skeletal muscle gene products by different cachectic factors like cytokines and tumour-derived compounds. As a result, wasting has to be interpreted more as a general degradation of muscle proteins rather than a highly selective process involving specific proteins (Acharyya et al., 2004). Other transcriptional factors that have been reported to be involved in muscle changes associated with catabolic conditions include c/EBPβ and δ (which are increased in skeletal muscle during sepsis (Penner, Gang, Sun, Wray, & Hasselgren, 2002)), PW-1 and PGC-1. TNF decreases MyoD content in cultured myoblasts (Guttridge, Mayo, Madrid, Wang, & Baldwin, 2000) and blocks differentiation by a mechanism which seems to be independent of NFκB and which involves PW-1, a transcriptional factor related to p53-induced apoptosis (Coletti, Yang, Marazzi, & Sassoon, 2002). The action of the cytokines on muscle cells, therefore, seems to rely most likely on satellite cells blocking muscle differentiation or, in other words, regeneration.

Finally, the transcription factor PGC-1 has been associated with the activation of UCP-2 and UCP-3 and increased oxygen consumption by cytokines in cultured myotubes (Puigserver et al., 2001). This transcriptional factor is involved as an activator of PPAR-γ in the expression of uncoupling proteins.

4. Cytokines may be used as targets for muscle wasting

Bearing in mind the fact that both anorexia and metabolic disturbances are involved in cancer cachexia, the development of different therapeutic strategies has focused on these two factors. Unfortunately, counteracting anorexia either pharmacologically or nutritionally has led to rather disappointing results in the treatment of cancer cachexia. It is basically for this reason that the strategies mentioned below rely on neutralizing the metabolic changes induced by the tumour, which are ultimately responsible for the weight loss. Therefore, taking into account the involvement of cytokines in cachexia, different therapeutic strategies have been based on either blocking their synthesis or action.

As previously mentioned, the cytokines that have been implicated in this cachectic response are TNF, IL-1, IL-6 and IFN-γ. Interestingly, these cytokines share the same metabolic effects and their activities are closely interrelated. In many cases these cytokines exhibit synergic effects when administered together (Evans, Argilés, & Williamson, 1989). Therefore, therapeutic strategies have been based on either blocking their synthesis or their action (Yamamoto et al., 1998; Fig. 1).

4.1. Interfering with synthesis

4.1.1. Pentoxifylline

Pentoxifylline, a methylxantine derivative, is a phosphodiesterase inhibitor that inhibits TNF synthesis by decreasing gene transcription. This drug was originally used for the treatment of various types of vascular insufficiency because of its haemorheological activity, thought to be based on its ability to reduce blood viscosity and increase the filterability of blood cells. While several studies using animal models suggest that pentoxifylline is able to decrease the cytokine-induced toxicity of antineoplasic agents while preserving antitumour treatment efficacy (Balazs & Kiss, 1994), clinical studies have shown that the drug failed to improve appetite or to increase the weight of cachectic patients (Goldberg et al., 1995). In addition, pentoxifylline has also been used in the treatment of cachectic AIDS patients with very poor results since it did not influence the weight of the subjects (Dezube et al., 1993); in fact, the patients frequently reported

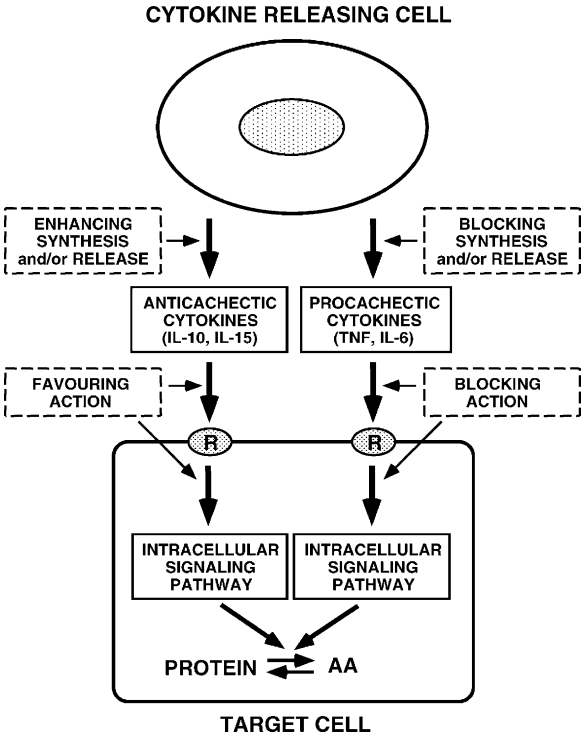

Fig. 1. Therapeutic strategies based on cytokines. The main possibilities are based on either acting on synthesis or intracellular action.

gastrointestinal side effects. However, the reported clinical trials have been relatively small and, therefore, larger randomized studies are necessary to assess the efficacy of pentoxifylline in the treatment of cancer cachexia.

4.1.2. Rolipram

Rolipram is a type IV phosphodiesterase inhibitor that has been shown to decrease TNF production by LPS-stimulated human monocytes (Semmler, Wachtel, & Endres, 1993). This compound has previously been used in the treatment of endogenous depression in both animals and man, and it may have therapeutic activity in disease states where TNF seems to play a role in the pathogenesis, such as in endotoxic shock (Badger, Olivera, & Esser, 1994).

4.1.3. Thalidomide

Thalidomide (α-*N*-phthalimidoglutaramide) is a drug unfortunately associated with tragedy. Indeed, its use as a sedative in pregnant women caused over 10,000 cases of severe malformations in newborn children. However, a certain revival has affected the drug since it has been demonstrated to suppress TNF production in monocytes in vitro (Sampaio, Sarno, Galilly, Cohn, & Kaplan, 1991) and to normalize elevated TNF levels in vivo (Sampaio et al., 1993). Apparently, thalidomide activity is due to a selective destabilization of the TNF mRNA (Moreira et al., 1993). The drug has certainly been used to counteract high cytokine levels in tuberculosis patients (Klausner et al., 1996). A significant improvement in quality of life and weight gain occurs in AIDS patients given relatively low doses of thalidomide (Klausner et al., 1996). Its use in cancer cachexia remains to be established, but it could potentially have a certain role in counteracting TNF-mediated metabolic changes. In addition, thalidomide therapy has shown to improve insomnia and restlessness as well as nausea in advanced cancer patients, and it has improved appetite as well, resulting in an enhanced feeling of well-being in one-half to two-thirds of patients studied (Bruera et al., 1999). Indeed, a recent pilot study carried out in 10 patients affected by oesophageal cancer revealed that thalidomide was able to reverse the loss of weight and lean body mass over a 2-week trial period (Khan et al., 2003). In chronic heart failure, a recent study shows that thalidomide is able, in addition to decreasing TNF levels, to increase cardiac performance (Gullestad et al., 2002).

4.2. Blocking action

4.2.1. Antibodies and soluble receptors

The use of anti-cytokine antibodies and cytokine receptor antagonists or soluble receptors has led to very interesting results. Thus, in rats bearing the Yoshida AH-130 ascites hepatoma (a highly cachectic tumour) anti-TNF therapy resulted in a partial reversal of the abnormalities associated with both lipid (Carbó et al., 1994) and protein metabolism (Costelli et al., 1993). In humans, however, clinical trials using anti-TNF treatment have led to poor results in reverting the protein waste associated with sepsis (Reinhart et al., 1996). Concerning chronic heart failure, several clinical trials involving anti-TNF strategies, such as etanercep (fusion protein directing against p75 TNF receptor) or infliximab (monoclonal antibody against TNF) have led to poor results in the clinical output of the patients (Anker & Coats, 2002). Concerning IL-6, experimen-

tal models have proven that the use of antibodies is highly effective in preventing tumour-induced waste (Yasumoto et al., 1995). Strassmann et al. (1993) have demonstrated that the experimental drug suramine (which prevents the binding of IL-6 to its cell surface receptor, as demonstrated by radioreceptor-binding assay and affinity binding experiments) partially blocks (up to 60%) the catabolic effects associated with the growth of the colon-26 adenocarcinoma in mice. In humans, administration of an anti-IL-6 monoclonal antibody to patients with AIDS and suffering from an immunoblastic or a polymorphic large-cell lymphoma, resulted in a very positive effect on fever and cachexia (Emilie et al., 1994). Concerning other cytokines, anti-IFN-γ therapy has also been effective in reverting cachexia in mice bearing the Lewis lung carcinoma (Matthys et al., 1991) but there is a lack of clinical data. On the other hand, blocking IL-1 actions by means of the IL-1 receptor antagonist (IL-1ra) in tumour-bearing rats had no effect on either body weight or reversal of metabolic changes (Costelli et al., 1995).

Although it is clear that a potential use for this type of anti-cytokine antibodies exist, absolutely no data are available concerning the long-term effects of blocking cytokines in the cancer patients. In a way, it may be speculated that some of the beneficial effects may be counteracted by a certain immunosupression since cytokines act as double-bladed knives, on one hand they are likely to induce muscle catabolism, but on the other hand they are involved in promoting the proliferation of immune cells. In fact, some divergent data already exist concerning clinical trials using anti-cytokines strategies. While in sepsis the introduction of anti-TNF antibodies has not been succesful, in patients with inflammatory bowel disease and rheumathoid arthritis, the use of anti-TNF therapy has been more satisfactory, although some minor side effects are observed (Kurtovic & Segal, 2004; Rutgeerts, Van Assche, & Vermeire, 2004). Therefore, it seems absolutely essential that future clinical studies should concentrate on the role of such therapies in cancer.

It has to be pointed out here that the routine use of anti-cytokine antibodies is, at present, too expensive due to the fact that this type of therapy requires a very large number of antibody molecules in order to block cytokine action completely.

4.2.2. *Anti-inflammatory cytokines*

The degree of the cachectic syndrome is dependent not only on the production of the above-mentioned cytokines, known as catabolic pro-inflammatory cytokines, but also on the so-called anti-inflammatory cytokines, such as IL-4, IL-10 and IL-12.

Mori et al. (1996) have demonstrated that the administration of IL-12 to mice bearing the colon-26 carcinoma alleviates the body weight loss and other abnormalities associated with cachexia, such as adipose tissue wasting and hypoglycaemia. The anticachectic properties are seen at low doses of IL-12, insufficient to inhibit tumour growth. The effects of IL-12 seem to be dependent on an important decrease of IL-6 (Mori et al., 1996), a cytokine, which has been responsible for the cachexia associated with this tumour model (Fujimoto-Ouchi, Tamura, Mori, Tanaka, & Ishitsuka, 1995; Tanaka et al., 1990). A similar action has been described for INF-γ. Administration of this cytokine promoted a decrease in both IL-6 mRNA expression in the tumour and serum IL-6 levels, resulting in an amelioration of the cachexia in a murine model of malignant mesothelioma (Bielefeldt-Ohmann et al., 1995).

Interleukin-15 (IL-15) has been reported to be an anabolic factor for skeletal muscle (Quinn, Haugk, & Grabstein, 1995), and experiments carried out in our laboratory clearly demonstrate that the cytokine is able to reverse most of the abnormalities associated with cancer cachexia in a rat tumour model (Carbó et al., 2000).

4.3. *Interfering with transcription factors*

Concerning therapeutical strategies based on the events related to transcriptional factors in muscle wasting, several points could be raised. First, Kawamura et al. (1999, 2001) reported that the use of an oligonucleotide that competes with a NFκB-binding site can revert cachexia in a mouse experimental model without affecting the growth of the primary tumour. This treatment, however, reduces the metastasic capacity in the colon-26 adenocarcinoma model. In spite of this, administration of curcumine to tumour-bearing rats was unable to block muscle wasting, therefore which means that NFκB is not involved in the cachectic response in this tumour model (Busquets et al., 2001).

As we have previously said, AP-1 is clearly involved in muscle wasting during sepsis (Penner et al., 2001)

and also in cancer. Interestingly, administration of an inhibitor of both (NFκB and AP-1) results in a partial blockade of muscle wasting in rats bearing the AH-130 Yoshida ascites hepatoma, a highly cachectic rat tumour (Moore-Carrasco et al., in press).

5. Conclusions

In conclusion, and because metabolic alterations often appear soon after the onset of tumour growth, the scope of appropriate treatment, although not aimed at achieving immediate eradication of the tumour mass, could influence the course of the patient's clinical state or, at least, prevent the steady erosion of dignity that the patient may feel in association with the syndrome. This would no doubt contribute to improving the patient's quality of life and, possibly, prolong survival. Although exploration of the role that cytokines play in the host response to invasive stimuli is an endeavour that has been underway for many years, considerable controversy still exists over the mechanisms of lean tissue and body fat dissolution that occur in the patient with either cancer or inflammation and whether humoural factors regulate this process. A better understanding of the role of cytokines, both host- and tumour-derived, interfering with the molecular mechanisms accounting for protein wasting in skeletal muscle, is essential for the design of future effective therapeutic strategies. In any case, understanding the humoural response to cancer and modifying cytokine actions pharmacologically may prove very suitable and no doubt future research will concentrate on this interesting field. Finally, understanding the intracellular signalling mechanisms, particulary transcriptional factors, may also be very important for the designing of effective therapeutic approaches.

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