

# Muscle Wasting in Cancer and Ageing: Cachexia Versus Sarcopenia

Josep M. Argilés, Sílvia Busquets, Marcel Orpi, Roberto Serpe,  
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**Abstract** The aim of this chapter is to summarize and evaluate the different mechanisms and catabolic mediators involved in cancer cachexia and ageing sarcopenia since they may represent targets for future promising clinical investigations. Cancer cachexia is a syndrome characterized by a marked weight loss, anorexia, asthenia and anemia. In fact, many patients who die with advanced cancer suffer from cachexia. The degree of cachexia is inversely correlated with the survival time of the patient and it always implies a poor prognosis. Unfortunately, at the clinical level, cachexia is not treated until the patient suffers from a considerable weight loss and wasting. At this point, the cachectic syndrome is almost irreversible. The cachectic state is often associated with the presence and growth of the tumour and leads to a malnutrition status due to the induction of anorexia. In recent years, age-related diseases and disabilities have become of major health interest and importance. This holds particularly for muscle wasting, also known as sarcopenia, that decreases the quality of life of the geriatric population, increasing morbidity and decreasing life expectancy. The cachectic factors (associated with both depletion of fat stores and muscular tissue) can be divided into two categories: of tumour origin and humoral factors. In conclusion, more research should be devoted to the understanding of muscle wasting mediators, both in cancer and ageing, in particular the identification of common mediators may prove as a good therapeutic strategies for both prevention and treatment of wasting both in disease and during healthy ageing.

**Keywords** Cancer cachexia • Mediators • Muscle wasting • Metabolic changes • Cytokines • Ageing • Sarcopenia

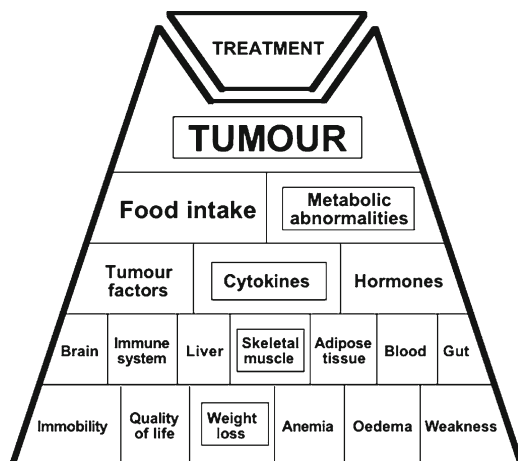
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# 1 Introduction

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 (Warren 1932). The abnormalities associated with cancer cachexia include anorexia, weight loss, muscle loss and atrophy, anemia and alterations in carbohydrate, lipid and protein metabolism (Argiles et al. 1997). The degree of cachexia is inversely correlated with the survival time of the patient and it always implies a poor prognosis (Harvey et al. 1979; Nixon et al. 1980; DeWys 1985). Perhaps one of the most relevant characteristics of cachexia is that of asthenia (or lack of muscular strength), which reflects the great muscle waste that takes place in the cachectic cancer patient (Argiles et al. 1992). Asthenia is also characterized by a general weakness as well as physical and mental fatigue (Adams and Victor 1981). In addition, lean body mass depletion is one of the main trends of cachexia, and it involves not only skeletal muscle but it also affects cardiac proteins, resulting in important alterations in heart performance.

At the biochemical level, different explanations can be found to account for cancer-induced cachexia (Fig. 1). First, the presence and growth of the tumour is invariably associated with a malnutrition status due to the induction of anorexia (decreased food intake). In addition, the presence of the tumour promotes important metabolic disturbances, which include a considerable nitrogen flow from the skeletal muscle to the liver. Amino acids are used there for both acute-phase protein (APP) synthesis and gluconeogenesis. Both tumoural and humoral (mainly



**Fig. 1** Cancer cachexia: the pyramid. Cancer cachexia is a complex pathological condition characterized by many metabolic changes involving numerous organs. These changes are triggered by alterations in the hormonal milieu, release of different tumour factors and a systemic inflammatory reaction characterized by cytokine production and release

cytokines) factors are associated with depletion of fat stores and muscular tissues. Indeed cells of the immune system release cytokines that act on multiple target cells such as bone marrow cells, myocytes, hepatocytes, adipocytes, endothelial cells and neurons, where they produce a complex cascade of biological responses leading to the wasting associated with cancer cachexia. Among the cytokines that have been involved in this cachectic response are tumour necrosis factor- $\alpha$  (TNF), interleukin-1 (IL-1), interleukin-6 (IL-6) and interferon- $\gamma$  (IFN- $\gamma$ ). Interestingly, these cytokines share the same metabolic effects and their activities are closely interrelated, showing in many cases synergistic effects.

The aim of the present chapter is to summarize and evaluate the different mechanisms and catabolic mediators (both humoral and tumoural) involved in cancer cachexia and ageing sarcopenia since they may represent targets for future promising clinical investigations.

## **2 Cancer: An Inflammatory Disorder**

The presence of the tumour clearly elicits a systemic inflammatory response that triggers anorexia and hypermetabolism and neuroendocrine alterations. This systemic inflammatory response is triggered by different mediators either generated by the tumour or by non-tumoural cells of the patient. Mainly, two basic hypotheses can explain this phenomenon. First, the so-called endotoxic hypothesis, by which the tumour burden results in an enhanced translocation of intestinal bacteria into the peritoneum and consequently a release of endotoxin which finally triggers the cytokine cascade. Second, the tumour hypothesis involves either specific tumour-derived compounds or cytokines produced by the tumour which trigger the inflammatory response.

All together, the systemic inflammatory response generates many alterations that affect the patient's metabolism activating among others muscle protein breakdown, and consequently, wasting.

### **2.1 *Hypermetabolism***

As 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, during cachectic states there is an increase in brown adipose tissue (BAT) thermogenesis in both humans and experimental animals. Until recently, the uncoupling protein-1 (UCP1) protein (present only in BAT) was considered to be the only mitochondrial protein carrier that stimulated heat production by dissipating the proton gradient generated during respiration across the inner mitochondrial membrane and therefore uncoupling respiration from adenosine-5'-triphosphate (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 tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) is able to mimic the increase in gene expression (Busquets et al. 1998). Indeed, injection of low doses of TNF- $\alpha$  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 BAT, associated with UCP1. In addition, TNF- $\alpha$  is able to induce uncoupling of mitochondrial respiration as shown in isolated mitochondria (Busquets et al. 2003).

## 2.2 Muscle Wasting

The loss of muscle mass is a hallmark of cancer cachexia and it is essentially caused by an increase of myofibrillar protein (especially myosin heavy-chain (Acharyya et al. 2004) degradation (Llovera et al. 1994, 1995; Busquets et al. 2004), sometimes accompanied by a decrease in protein synthesis (Smith and Tisdale 1993; Eley and Tisdale 2007). The enhanced protein degradation is caused by an activation of the ubiquitin-dependent proteolytic system (Temparis et al. 1994; Baracos et al. 1995; Costelli et al. 1995). This enhanced proteolysis may be caused by tumour factors such as proteolysis-inducing factor (Lorite et al. 1998; Belizario et al. 1991) or by cytokines (Mahony et al. 1988; Tracey et al. 1990). Thus, administration of TNF- $\alpha$  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 (Bossola et al. 2001) and humans (Baracos 2000). Other cytokines such as interleukin-1 or interferon- $\gamma$  are also able to activate ubiquitin gene expression. Therefore, TNF- $\alpha$ , 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 (Pajak et al. 2008). In addition to the massive muscle protein loss, and similar to that observed in skeletal muscle of chronic heart failure patients suffering from cardiac cachexia (Sharma and Anker 2002), muscle DNA is also decreased during cancer cachexia, leading to DNA fragmentation and, thus, apoptosis (van Royen et al. 2000; Belizario et al. 2001). Interestingly, TNF- $\alpha$  can mimic the apoptotic response in the muscle of healthy animals (Carbo et al. 2002).

The therapy against wasting during cachexia has concentrated on either increasing food intake or normalizing the persistent metabolic alterations that take place in the patient. It is difficult to apply a therapeutic approach based on the neutralization of the potential mediators involved in muscle wasting (i.e. TNF- $\alpha$ , IL-6, IFN- $\gamma$ , proteolysis-inducing factor) because many of them are simultaneously involved in promoting the metabolic alterations and the anorexia present in the cancer patients (Argilés et al. 2007). Bearing this in mind, it is obvious that a good

understanding of the molecular mechanisms involved in the signalling of these mediators may be very positive in the design of the therapeutic strategy. This is especially relevant because different mediators may be sharing the same signalling pathways. There are currently few studies describing the role of cytokines and tumour factors in the signalling associated with muscle wasting. Penner et al. (2001) reported an increase in both NF- $\kappa$ B and AP-1 transcription factors during sepsis in experimental animals. The increase in NF- $\kappa$ B observed in skeletal muscle during sepsis can be mimicked by TNF- $\alpha$ . Indeed, TNF- $\alpha$  addition to C2C12 muscle cultures results in a short-term increase in NF- $\kappa$ B (Fernandez-Celemin et al. 2002; Li et al. 1998). Whether or not this increase in NF- $\kappa$ B promoted by TNF- $\alpha$  is associated with increased proteolysis and/or increased apoptosis in skeletal muscle remains to be established. In relation to AP-1 activation, TNF- $\alpha$  has been shown to increase c-jun expression in C2C12 cells (Brenner et al. 1989). Interestingly, overexpression of c-jun mimics the observed effect of TNF- $\alpha$  upon differentiation; indeed, it results in decreased myoblast differentiation (Thinakaran et al. 1993). Tumour mediators, proteolysis-inducing factor (PIF) in particular, also seem to be able to increase NF- $\kappa$ B expression in cultured muscle cells, this possibly being linked with increased proteolysis (Wyke and Tisdale 2005). Other reports, using experimental cancer models, have also suggested that NF- $\kappa$ B is involved in the signalling of muscle wasting (Wyke et al. 2004; Cai et al. 2004). In our laboratory, we have recently demonstrated increased activation of AP-1 in the skeletal muscle of tumour-bearing rats, therefore suggesting that this factor is involved in the muscle events that take place during cancer cachexia (Costelli et al. 2005a). Indeed, the intramuscular administration of adenoviruses carrying TAM 67 (a negative-dominant of c-jun [AP-1]) resulted in an improvement of the muscle weight during tumour growth (Moore-Carrasco et al. 2006). Other transcriptional factors that have been reported to be involved in muscle changes associated with catabolic conditions include c/EBP $\beta$  and  $\delta$  (which are increased in skeletal muscle during sepsis (Penner et al. 2002), PW-1 and PGC-1. TNF- $\alpha$  decreases MyoD content in cultured myoblasts (Guttridge et al. 2000) and blocks differentiation by a mechanism which seems to be independent of NF- $\kappa$ B and which involves PW-1, a transcriptional factor related to p53-induced apoptosis (Coletti et al. 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 both UCP-2 and UCP-3 and increased oxygen consumption by cytokines in cultured myotubes (Puigserver et al. 2001). This transcription factor is involved as an activator of peroxisomal proliferator-activated receptor (PPAR)- $\gamma$  in the expression of uncoupling proteins. Very recent investigations have revealed a role for PPAR- $\gamma$  and PPAR- $\delta$  in experimental muscle wasting (Fuster et al. 2007).

Muscle wasting is invariably associated with DNA fragmentation in many catabolic states. One of the first reports showing apoptosis in skeletal muscle was in experimental cancer cachexia (van Royen et al. 2000; Sumi et al. 1999). Recently, the same phenomenon has been observed in cancer patients (Busquets et al. 2007). Our laboratory has also described the activation of muscle apoptosis during sepsis

(Almendro et al. 2003). In diabetes (Lee et al. 2004), chronic heart failure (Vescovo and Dalla Libera 2006) and chronic obstructive pulmonary disease (Agusti et al. 2002), apoptosis is also activated in muscle tissue. Recent work on the molecular mediators involved in the intracellular activation of the proteasome has clearly shown that caspase-3 is essential for the activation of proteolysis (Lee et al. 2004; Agusti et al. 2002). Indeed, caspase-3 cleaves actomyosin to actin, which can be degraded by the ubiquitin-proteasome-dependent system (Du et al. 2004). In this cleavage, caspase-3 generates a characteristic 14-kDa actin fragment, which is a marker for muscle proteolysis (Workeneh et al. 2006). In this way, the activation of caspase-3 seems to be associated with myofibril degradation, a process that precedes active protein degradation by the proteasome. Interestingly, caspase-3 is an enzyme involved in apoptosis which is activated by caspase-8 as a result of an apoptotic stimulus such as TNF- $\alpha$  (Benn and Woolf 2004; Adams et al. 2001). In this activation process, the apoptosome (cytochrome c, APAF-1 and caspase-9) is also involved, along with caspase-12 (Benn and Woolf 2004). Interestingly, Fernando et al. (2002) have shown that caspase-3 activity is required for skeletal muscle differentiation. Indeed, during differentiation, reorganization of myofibrillar proteins is essential and possibly linked with the activity of caspase-3. Another interesting observation is that during wasting there is an enhanced myoblast/satellite cell proliferation (Ferreira et al. 2006). All these observations are of utmost importance as inhibitors of caspase-3 in skeletal muscle during wasting could be a potential way of blocking proteolysis (Argiles et al. 2008).

In skeletal muscle, anabolic signals influence protein synthesis and accumulation by activation of phosphatidylinositol-3-kinase (PI3K) which is involved in the phosphorylation of the Akt-mTOR signalling pathway leading to protein anabolism (Latres et al. 2005). Interestingly, the PI3K activation is also associated with the phosphorylation – and therefore inactivation – of the FOXO transcription factor (Sandri et al. 2004). FOXO is known to participate in the transcription of Atrogin-1 and Murf-1, specific ubiquitin ligases involved in muscle proteolysis (Sandri et al. 2004). Therefore, the PI3K signalling pathway is linked with both synthesis and degradation of muscle proteins. For instance, both insulin-like growth factor-1 (IGF-1) and insulin act by activating PI3K (Latres et al. 2005; Kirwan and del Aguila 2003). In catabolic conditions, muscle insulin sensitivity is often hampered (type II diabetes) (Wang et al. 2006) or muscle IGF-1 expression is reduced (cancer) (Costelli et al. 2006). Interestingly, PI3K is linked with caspase-3; indeed, activation of caspase-3 is associated with a suppressed activity of the kinase (Lee et al. 2004). Thus, when PI3K activity is low, both apoptotic and ubiquitin-proteasome proteolysis pathways are activated, suggesting that PI3K participates in the inhibition of caspase-3. Apparently normal protein turnover in skeletal muscle under healthy conditions does not seem to be linked with a protein breakdown activated by caspase-3 (Du et al. 2004). Indeed, inhibition of caspase-3 with the specific compound Ac-DEVD-CHO in isolated epitrochlearis muscle from rats, does not lead to an inhibition of basal proteolysis (Du et al. 2004). The excessive protein breakdown of myofibrillar proteins in catabolic conditions can, however, be

blocked with the mentioned inhibitor. This idea is supported by experiments carried out in muscles from acutely-induced diabetes (Du et al. 2004). Bearing all this in mind, it seems clear that excessive proteolysis (the fraction of protein breakdown which is activated during catabolic conditions) is linked with activation of the apoptotic enzyme caspase-3 and, as mentioned above, inhibition of this enzyme could be a potential therapeutic target for the treatment of muscle wasting associated with chronic diseases.

In addition to the abovementioned PI3K signalling pathway, other factors are related to the activation/inhibition of caspase-3. Indeed, the intracellular levels of calcium have a role in proteolysis not only by activating the calpain-dependent system (specific calcium-dependent proteases) (Costelli et al. 2005b) but also in the activation of caspase-3 (Benn and Woolf 2004; Choi et al. 2006). From this point of view, some studies have shown that calcium can either directly activate caspase-3 or indirectly by favouring a release of mitochondrial cytochrome c, which, in turn, activates the apoptosome, which then acts on caspase-3 (Benn and Woolf 2004). From this point of view, an increased entry of calcium into the mitochondria, either by the calcium release from the endoplasmic reticulum or by the entry of extracellular calcium, results in an activation of caspase-3, apoptosis and finally skeletal muscle proteolysis (Benn and Woolf 2004; Hajnoczky et al. 2006). Interestingly, there is another way that calcium can activate caspase-3; indeed, calcium is essential for calpain activation and calpains are able to activate caspase-12, which acts on caspase-3 (Benn and Woolf 2004; Bajaj and Sharma 2006). From the point of view of proteolysis, calpains have been shown to also act before the ubiquitin-proteasome-dependent proteolytic pathway, in a similar manner to that described for caspase-3 (Costelli et al. 2005b; Williams et al. 1999). In fact, calpains have been proposed to act on myofibrils to promote their breakage to myosin, which is then degraded by the proteasome (Costelli et al. 2005b). In a way, therefore, both calpain and caspase-3 activation seem to be essential for ATP-dependent degradation of myofibrillar proteins.

Recent studies have shown that alterations in the muscular dystrophy-associated dystrophin glycoprotein complex may have an important role in muscle wasting during cancer (Acharyya et al. 2005; Glass 2005). Finally, necdin, a protein which has a key role in fetal and postnatal physiological myogenesis is selectively expressed in muscles of cachectic mice and this seems to be linked to a protective response of the tissue against tumour-induced wasting, inhibition of myogenic differentiation and in muscle regeneration (Sciorati et al. 2009).

Moreover, myostatin, a transforming growth factor- $\beta$  super-family member well characterized as a negative regulator of muscle growth and development, has been implicated in several forms of muscle wasting including the severe cachexia observed as a result of conditions such as AIDS and liver cirrhosis. McFarlane et al. (2006) have demonstrated that myostatin induces cachexia through a NF- $\kappa$ B independent mechanism, by antagonizing hypertrophy signalling through regulation of the AKT-FoxO1 pathway. Antimyostatin strategies are therefore promising and should be considered in future clinical trials involving cachectic patients (Patel and Amthor 2005; Bonetto et al. 2009).

### 2.3 *Adipose Tissue Dissolution and Hypertriglyceridaemia*

Lipid metabolism in cancer has been extensively studied, the main trends being an important reduction in body fat content (particularly white adipose tissue) together with a clear hyperlipaemia. The dissolution of the fat mass is the result of three different altered processes. First, there is an increase in lipolytic activity (Thompson et al. 1981), which results in an important release of both glycerol and fatty acids. Recent studies have shown that the mechanism of increased lipolysis is associated with activation of hormone-sensitive lipase in adipose tissue. In addition, in human cancer cachexia there is a decreased antilipolytic effect of insulin on adipocytes together with an increased responsiveness to catecholamines and atrial natriuretic peptide (Agustsson et al. 2007). Second, an important decrease in the activity of lipoprotein lipase (LPL), the enzyme responsible for the cleavage of both endogenous and exogenous triacylglycerols (present in lipoproteins) into glycerol and fatty acids, occurs in white adipose tissue (Thompson et al. 1981; Lanza-Jacoby et al. 1984; Noguchi et al. 1991) and, consequently, lipid uptake is severely hampered. Finally, adipose tissue de-novo lipogenesis is also reduced in tumour-bearing states (Thompson et al. 1981), resulting in a decreased esterification and, consequently, a decreased lipid deposition.

Hyperlipaemia in cancer-bearing states seems to be the result of an elevation in both triacylglycerols and cholesterol. Hypertriglyceridaemia is the consequence of the decreased LPL activity, which results in a decrease in the plasma clearance of both endogenous (transported as very low-density lipoproteins) and exogenous (transported as chylomicra) triacylglycerols. Muscaritoli et al. (1990) have clearly demonstrated that both the fractional removal rate and the maximum clearing capacity (calculated at high infusion rates when LPL activity is saturated) are significantly decreased after the administration of an exogenous triacylglycerol load to cancer patients. In tumour-bearing animals with a high degree of cachexia, there is also an important association between decreased LPL activity and hypertriglyceridaemia (Lopez-Soriano et al. 1996; Evans and Williamson 1988). Another factor that could contribute to the elevation in circulating triacylglycerols is an increase in liver lipogenesis (Mulligan and Tisdale 1991).

Hypercholesterolaemia is often seen in both tumour-bearing animals and humans with cancer (Dessi et al. 1991, 1992, 1995). Interestingly, most cancer cells show an altered regulation in cholesterol biosynthesis showing a lack of feedback control on 3-hydroxy-3-methylglutaryl CoA reductase, the key enzyme in the regulation of cholesterol biosynthesis. Cholesterol perturbations during cancer include changes in lipoprotein profiles, in particular an important decrease in the amount of cholesterol transported in the high-density lipoproteins (HDL) fraction. This finding has been observed in both experimental animals and human subjects (Dessi et al. 1991, 1992, 1995). HDL plays an important role in the transport of excess cholesterol from extrahepatic tissues to the liver for reutilization or excretion into bile (reverse cholesterol transport). It is thus conceivable that the

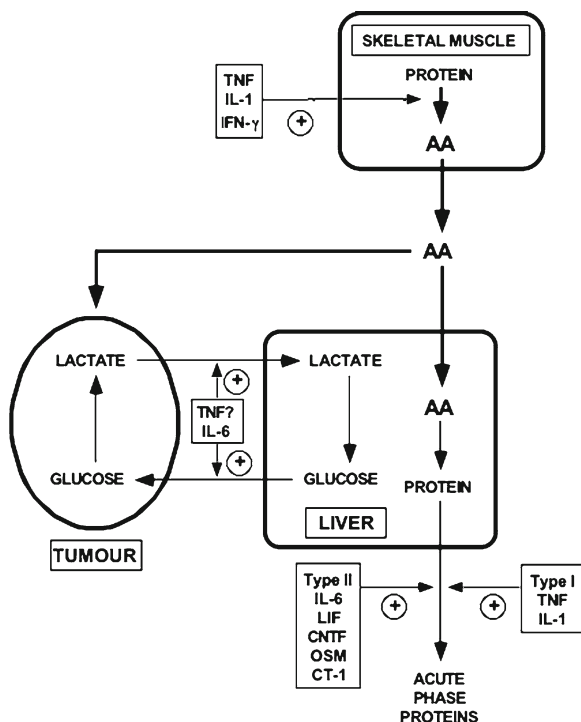
observed low levels of HDL-cholesterol may be related, at least in part, to a decreased cholesterol efflux to HDL as a consequence of increased utilization and/or storage in proliferating tissues, such as neoplasms. As precursor particles of HDL are thought to derive from lipolysis of triacylglycerol-rich lipoproteins such as very low-density lipoproteins and chylomicra (Eisenberg 1984), and as a significant positive correlation between plasma HDL-cholesterol and LPL activity in adipose tissue has also been reported (Eisenberg 1984), one must also consider the possibility that low HDL-cholesterol concentrations observed during tumour growth may be secondary to the decreased triacylglycerol clearance from plasma, as a result of LPL inhibition. Consequently, elevation of circulating lipid seems to be a hallmark of cancer-bearing states to the extent that some authors have suggested that plasma levels may be used to screen patients for cancer (Rossi Fanelli et al. 1995).

Finally, both cytokines – TNF- $\alpha$  in particular (Zhang et al. 2002; Ryden et al. 2002, 2004) – and tumour factors – lipid-mobilising factor (LMF) (Russell and Tisdale 2005; Russell et al. 2004) and toxohormone L – have been related to all the commented alterations in lipid metabolism during cancer cachexia.

## **2.4 Liver Inflammatory Response**

The result of the enhanced muscle proteolysis is a large release of amino acids from skeletal muscle which takes place specially as alanine and glutamine (Fig. 2). The release of amino acids is also potentiated by an inhibition of amino acid transport into skeletal muscle. While glutamine is basically taken up by the tumour to sustain both its energy and nitrogen demands, alanine is mainly channelled to the liver for both gluconeogenesis and protein synthesis. Increased hepatic production of APP has been suggested to be partly responsible for the catabolism of skeletal muscle protein, the essential amino acids being indeed required for APP synthesis. Despite the increased synthesis of APP, hypoalbuminemia is common in cancer patients, although this does not appear to be due to a decreased in albumin synthesis (Fearon et al. 1998).

The acute-phase response is a systemic reaction to tissue injury, typically observed during infection, inflammation or trauma, characterized by the increased production of a series of hepatocyte-derived plasma proteins known as acute-phase reactants (including C-reactive protein (CRP), serum amyloid A (SAA),  $\alpha$ 1-antitrypsin, fibrinogen, and complement factors B and C3) and by decreased circulating concentrations of albumin and transferrin. An APP response is observed in a significant proportion of patients with the type of cancer frequently associated with weight loss (i.e. pancreas, lung, esophagus). The proportion of pancreatic patients exhibiting an acute-phase response increases with disease progression (Falconer et al. 1994; Stephens et al. 2008). For many years investigators have been searching for mediators involved in the regulation of APP synthesis. Interestingly the cytokines IL-6, IL-1 and TNF are now regarded as the major mediators of APP induction



**Fig. 2** Cytokines can mimic most metabolic alterations. Most of the metabolic alterations present during cancer cachexia can be mimicked by pro-inflammatory cytokines

in the liver (Moshage 1997; Moses et al. 2009). In fact, APP can be divided into two groups: type I and type II. Type I proteins include SAA, CRP, C3, haptoglobin (rat) and  $\alpha$ 1-acid glycoprotein, and are induced by IL-1 and TNF. Type II proteins include fibrinogen, haptoglobin (human),  $\alpha$ 1-antichymotrypsin and  $\alpha$ 2-macroglobulin (rat), and are induced by IL-6, LIF, OSM (oncostatin M), CNTF and CT-1 (cardiotrophin-1). Unfortunately, the role of APP during cancer growth is still far from understood.

### 3 Ageing, Inflammation and Sarcopenia

#### 3.1 The Problem

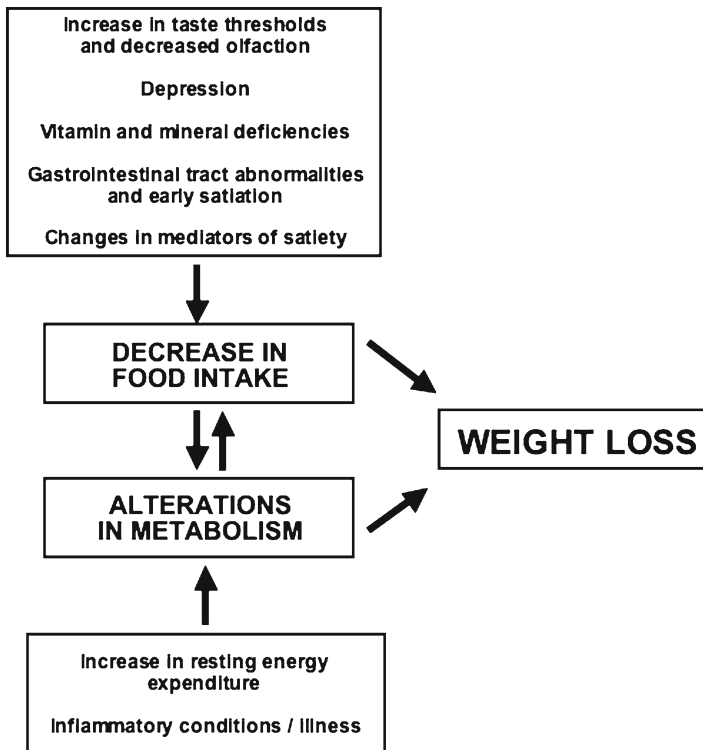
Ageing is an extremely complex biological phenomenon of immense importance. Currently, we have a poor, incomplete understanding of the fundamental molecular mechanisms involved. Discussions on ageing invariably begin by establishing a satisfactory definition for the term ageing and the related word senescence.

Although the term ageing is commonly used to refer to postmaturational processes that are deteriorative and lead to an increased vulnerability, the more correct term for this is senescence. Ageing could refer to any time-dependent process. In this proposal, the terms ageing and senescence are used interchangeably. All aging changes have a cellular basis, and ageing is perhaps best studied, fundamentally at the cellular level under defined and controlled environmental conditions.

In recent years, age-related diseases and disabilities have become of major health interest and importance. This holds particularly for the Western community, where the dramatic improvement of medical health, standard of living and hygiene have reduced the main causes of death prevalent in previous eras, most notably infectious diseases. Thanks to the discovery and development of antibiotics, vaccines and improved hygiene, the average life span has dramatically increased and has resulted in a conversion of the age-pyramid structure from a population numerically dominated by the younger generations to one in which the elderly have become of significant importance. Simple prediction of human life span from the average decline in kidney function results in a maximum life span of 120–140 years. Although the age statistics are inaccurate and records of previous centuries are missing, anecdotal evidence does not indicate a change in maximum life span.

Weight loss is a major problem that increases mortality in the geriatric population. Feelings of well-being and the pleasure derived from eating affect the quality of older individuals' lives positively. The connection between eating and good health has been understood for hundreds of years and transcends all cultures. Furthermore, it is understood that when elderly people stop eating their death is imminent. Treating malnutrition and weight loss can help to ameliorate many medical conditions. Rehabilitation time after hip fractures has been shown to be shortened with nutritional support (Bastow et al. 1983). In hospitalized geriatric patients, low serum albumin concentrations with weight loss predict those patients at highest risk of death (McMurtry and Rosenthal 1995).

Weight loss in geriatric patients is not unusual (Fig. 3). Of nursing home residents, 30–50% have substandard body weight and midarm muscle circumferences, and low albumin concentrations (Abbasi and Rudman 1994). Morley and Kraenzle (1994) found that 15–21% of 1,156 nursing home residents had lost more than 5 lb over a period of 3–6 months. According to Schneider et al. (2002) weight loss in the elderly leads to cachexia with a preferential loss of lean versus adipose tissue. The same authors report that the elderly show an increased resting energy expenditure that may be one of the underlying causes of the weight loss. Wasting and cachexia are associated with severe physiological, psychological, and immunological consequences, regardless of the underlying causes (Chandra 1983). Cachexia has been associated with an increased number of infections, decubitus ulcers, and even deaths (Pinchcofsky-Devin and Kaminski 1986). Wallace et al. (1995) reported that involuntary weight loss exceeded 13% in a group of 247 community-residing male veterans of 65 years of age or older. They also found involuntary weight loss of more than 4% of body weight to be an important independent predictor of increased mortality (Wallace et al. 1995). Goodwin et al. (1983),

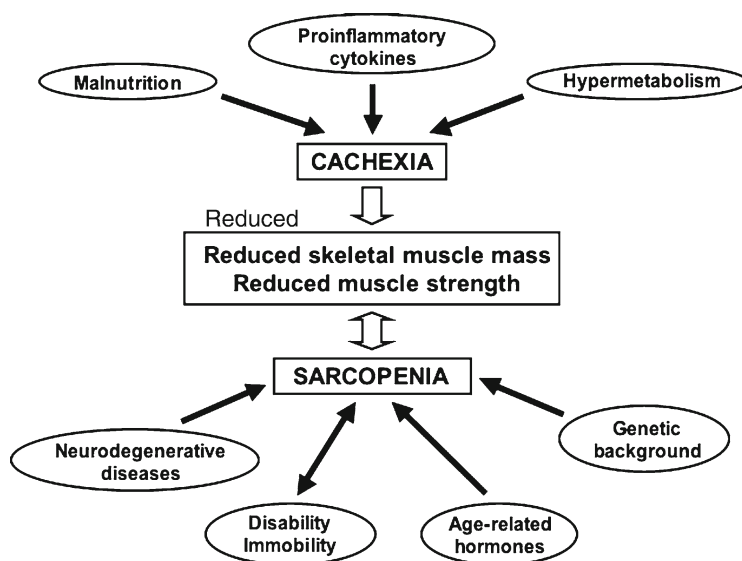


**Fig. 3** Factors involved in ageing malnutrition. The main factors that contribute to the malnutrition commonly observed in geriatric patients

Braun et al. (1988) and Morley and Silver (1988) found that malnutrition may also cause or exacerbate cognitive and mood disorders. Others have found that weight loss and cachexia are also predictive of morbidity and mortality (Marton et al. 1981; Rabinovitz et al. 1986). In the elderly, medical, cognitive and psychiatric disorders may diminish self-reliance in activities of daily living, thus reducing quality of life and increasing the frequency of secondary procedures, hospitalizations, and the need for skilled nursing care (Aubertin-Leheudre et al. 2008). Therefore, adequate weight and nutrition are necessary for a good quality of life and for optimal health in nursing home settings.

### 3.2 Cachexia and Sarcopenia are Driven by Different Factors

As can be seen in Fig. 4, the factors involved in the etiology of cachexia are different from those involved in sarcopenia. While proinflammatory cytokines, hypermetabolism and malnutrition play an important role in cachexia, hormonal changes and physical inactivity are the main triggering factors in sarcopenia.

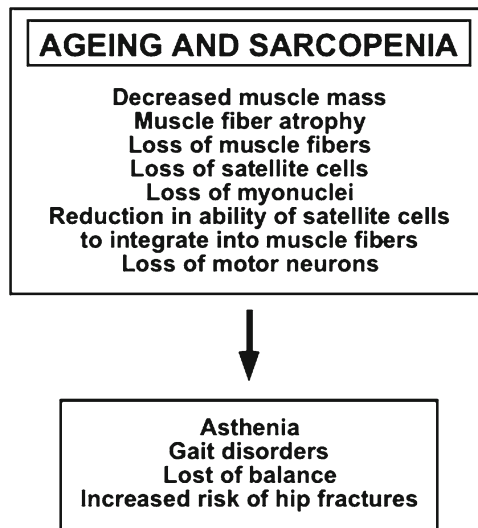


**Fig. 4** Differential factors involved in sarcopenia and cachexia. The factors involved in cancer cachexia are very different from those behind sarcopenia. Thus, in cancer, proinflammatory cytokines play a very important role together with the hypermetabolic state and anorexia, while in sarcopenia endocrine changes and neurodegenerative alterations are very important

### 3.3 Age-Related Muscle Wasting: Mechanisms

Despite numerous theories and intensive research, the principal molecular mechanisms underlying the process of ageing are still unknown. Most, if not all, attempts to prevent or stop the onset of typical degenerative diseases associated with ageing have so far been futile. Solutions to the major problems of dealing with age-related diseases can only come from a systematic and thorough molecular analysis of the ageing process and a detailed understanding of its causes. Thus, effective measures to prevent the onset of age-related disease and disabilities depend on solid fundamental scientific knowledge and a detailed mechanistic insight.

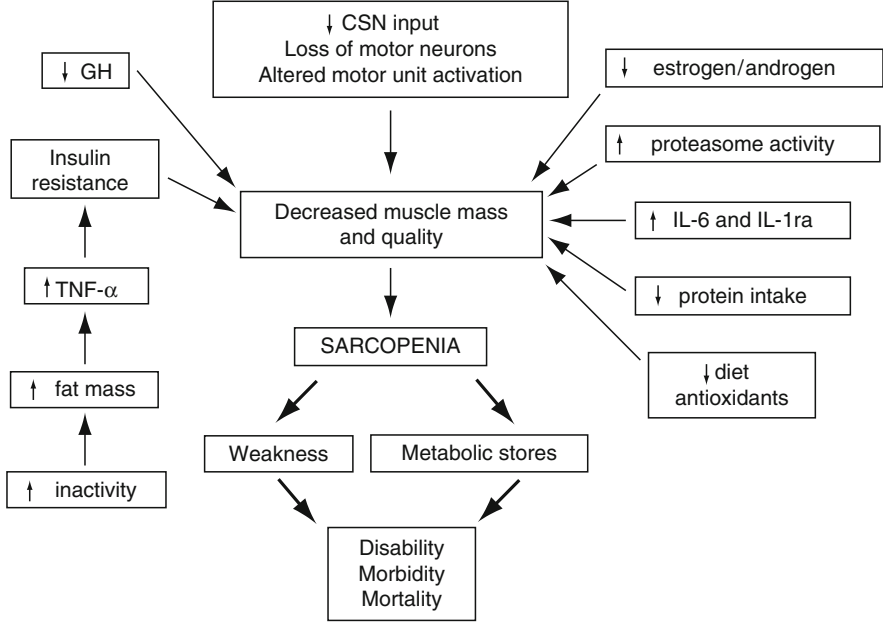
Some of the mechanisms and determinants involved in muscle wasting (Fig. 5) during ageing involve hormonal changes. Glucocorticoids seem to be involved in the emergence of muscle atrophy with advancing age (Dardevet et al. 1995, 1998; Savary et al. 1998). These hormones seem to interfere with other anabolic ones such as insulin or IGF-I (Dardevet et al. 1998, 1996; Vary et al. 1997, 1999, 1998; Sinaud et al. 1999). Some studies have suggested that exercise can delay the onset of muscle wasting in aged experimental animals (Mosoni et al. 1995; Slentz and Holloszy 1993; Lambert et al. 2002). Other investigations have shown that treatment with  $\beta$ 2-agonists can delay the onset of wasting associated with ageing (Carter and Lynch 1994). Bearing in mind the fact that the regenerative potential of skeletal muscle, and overall muscle mass, decline with age, this may be influenced



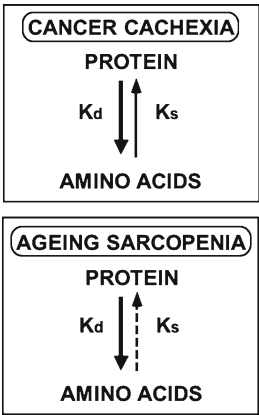
**Fig. 5** Main events that take place in skeletal muscle leading to sarcopenia. The reduction in muscle mass is accompanied by a clear atrophy involving changes that affect not only muscle fibers but also satellite cells, all of it leading to a considerable degree of asthenia

by autocrine growth factors intrinsic to the muscle itself. Extrinsic host factors that may influence muscle regeneration include hormones, growth factors secreted in a paracrine manner by accessory cells, innervation, and antioxidant mechanisms (Cannon 1995) (Fig. 6). An inflammatory response ensues in which distinctive populations of macrophages infiltrate the affected tissue: some of these macrophages are involved in phagocytosis of damaged fibers; other macrophages arriving at later times may deliver growth factors or cytokines that promote regeneration. These include fibroblast growth factor and IGF-I, which are important regulators of muscle precursors cell growth and differentiation, as well as nerve growth factor (NGF), which is essential for maintenance or reestablishment of neuronal contact. Other cytokines, including IL-1, TNF, IL-15 and CNTF, have a strong influence on the balance between muscle protein synthesis and breakdown. Beyond the severe reduction in life quality for a large fraction of the ageing population suffering from muscle wasting, the age-related loss of muscle mass leaves the affected individuals more prone to risk factors that adversely affect their health including social isolation, stress, depression and accidents.

Among the factors that could be involved in modulating protein turnover in skeletal muscle during ageing, hormonal status may play a very important role. From this point of view, alterations in the somatotrophic (GH/IGF-1) axis with a decrease in both mediators during ageing could be either be a symptom of declining neuroendocrine function, a cause of age-related alterations in body composition and functionality or protective mechanism against age-associated disease (Bartke 1992). Thus, insulin resistance phenomena may alter the rates of protein synthesis



**Fig. 6** Etiology of sarcopenia. The etiology of sarcopenia involves many different factors, including hormonal changes, cytokine alterations and alterations in food intake, that result in protein and vitamin deficiencies



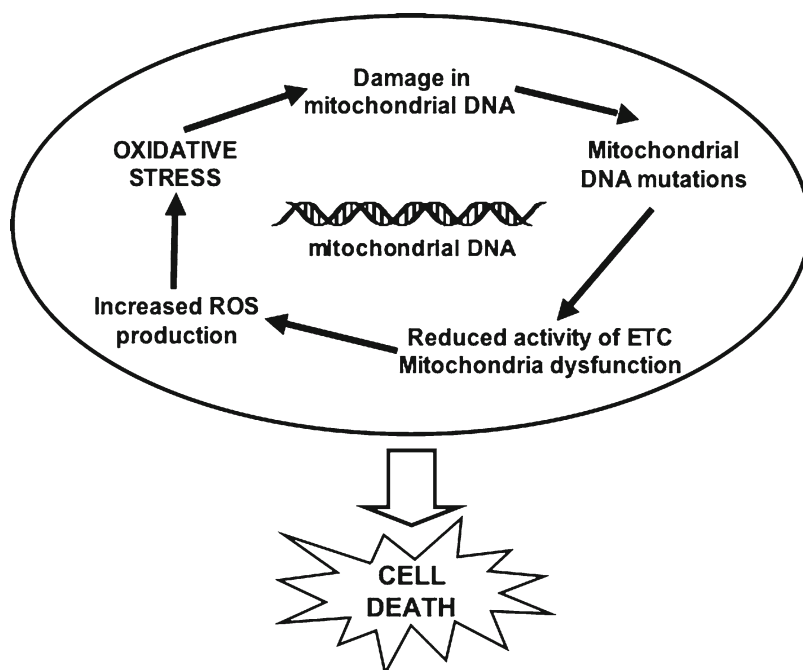
**Fig. 7** Differences in protein turnover in cancer cachexia and muscle sarcopenia. Interestingly, while in cancer cachexia protein degradation is the main factor involved in ageing, sarcopenia includes a dramatic decrease in the rate of myofibrillar protein synthesis

in skeletal muscle. It has been reported that glucocorticoids that induce the ubiquitin-dependent muscle proteolysis in fasted or acidotic young rats, do not induce such proteolysis in aged rats (Dardevet et al. 1995) (Fig. 7). Similarly, a

reduced sensitivity to a variety of hormones and growth factors in aged tissues has been reported (Carlin et al. 1983; Harley et al. 1981; Plisko and Gilchrest 1983). It may then be suggested that a defect in signal transduction could be related to the ubiquitin system in aged cells.

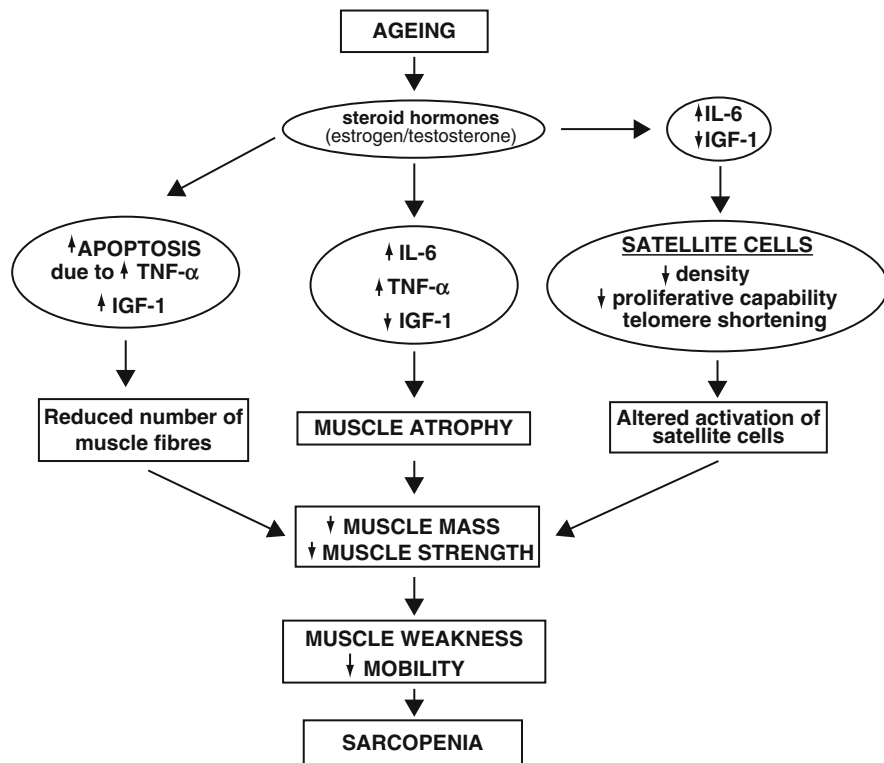
Several other mechanisms have been postulated to explain the skeletal muscle weakness associated with ageing and it appears that sarcopenia is only partially explained by the loss in muscle mass. Thus, apoptosis has been implicated as a mechanism of loss of muscle cells in normal ageing and plays an important role in sarcopenia (Dirks Naylor and Leeuwenburgh 2008). In the apoptotic events, both caspase-2 and oxidative stress seem to play an important role in triggering physiological cell death (Braga et al. 2008). A body of evidence suggests that ion channels and their ability to respond to growth factors such as IGF-I could be a key factor underlying skeletal muscle impairment with ageing (Delbono 2000, 2002; Renganathan et al. 1998). In this context, the reduction in L-type  $\text{Ca}^{2+}$  channels expression in ageing mice reduced peak cytosolic  $\text{Ca}^{2+}$  with subsequent decrease in skeletal muscle force (Delbono 2002). On the other hand,  $\text{K}^{+}$  channels are essential to both induce myogenesis and proliferation of muscle cells (Fischer-Lougheed et al. 2001; Grande et al. 2003).  $\text{K}^{+}$  channels are modulated by IGF-I and the over-expression of human IGF-I exclusively in skeletal muscle increases the number and prevents age-related decline in the sarcoplasmic reticulum dihydropyridine-sensitive voltage-gated L-type  $\text{Ca}^{2+}$  channel (Delbono 2002; Gamper et al. 2002). Taking all of this into consideration, it is clear that ion channels are involved in the age-related decline in muscle force. Concerning neuronal activity important changes in ion channel expression occurs during ageing. It is not clear what is the relationship between the observed changes and the decreased synaptic contacts, ion balances or neuronal loss. However, several hypotheses have been evaluated such as the  $\text{Ca}^{2+}$  theory and the effects of reactive oxygen/nitrogen species in ion channel activity in the aged brain (Foster and Kumar 2002; Dirksen 2002; Annunziato et al. 2002). However, it seems quite clear that changes in nerve ion channel expression may modify behavioral, feeding, learning and cognitive conducts during ageing those affecting muscle wasting in sarcopenia. Di Giulio et al. (2009) have recently found an altered mitochondrial status in skeletal muscles during ageing with a tight correlation between muscle total mitochondrial volume and sarcopenia. Therefore, hypoxia could well be involved in the muscle wasting process associated with ageing. In addition, ageing seems to be related to increased frequency of mutations in mitochondrial DNA. These mutations originate mitochondrial dysfunction and seem to be intimately related with the apoptotic process (Fig. 8). Additionally, the mentioned mutations lead to a decreased rate of electronic transport which results in increased ROS production, therefore increasing even more the mitochondrial damage (Fig. 8) (Thompson 2009; Hiona and Leeuwenburgh 2008).

Cytokines seem to play a key role in muscle wasting, at least during pathological conditions thus, cytokines are best known as mediators of host defense to invasive stimuli (Fig. 9). However, some of them (TNF, IL-1 and IL-6 in particular) may modulate clearance and repair processes in skeletal muscle following injury and may also be involved with the sustained viability of muscle cells. Muscle repair also



**Fig. 8** Mitochondrial mutations and oxidative stress. Mitochondrial DNA mutations may play a key role in triggering sarcopenia. These mutations would generate mitochondrial dysfunction and activation of mitochondrial apoptosis. The problem is under a positive feedback since mitochondrial dysfunction generates an increase in reactive oxygen species (ROS) due to a deficient electron transfer mechanism, and this generates more ROS and, therefore, increased mitochondrial dysfunction

requires neuronal contact influenced by other cytokines (such as NGF and CNTFr) as well as angiogenesis and connective tissue matrix formation. Successful muscle ageing will depend, in part, on how well a muscle repairs itself after damage. Age-related loss of muscle mass or function may be the cumulative result of repeated episodes of incomplete repair. Abnormal production or sensitivity to cytokines by aged cells may contribute to these changes in muscle mass and function. Grounds (Grounds 2002) has recently suggested that inflammatory cytokines could be involved in sarcopenia by interfering with IGF-I signaling in skeletal muscle. Cytokines – interleukins in particular – appears to stimulate both corticotropin-releasing factor (CRF) and prostaglandin  $E_{1\alpha}$  production which behave as powerful anorectic agents, thus contributing to the decrease in food intake associated with aging (Morley 2001). In addition, cytokines inhibit the release of orexigenic peptides such as neuropeptide Y. It becomes thus clear that cytokines alter the balance between orexigenic and anorexigenic signals in brain and therefore contribute significantly to the alterations observed in appetite in the elderly (Morley 2001). Interestingly, many cytokines also cause an elevation in availability of leptin which, in turn, further contributes to the decline in food intake (Morley 2001; Lee et al. 2007).



**Fig. 9** Role of cytokines in myofiber alterations associated with sarcopenia. Some cytokines may influence muscle repair mechanisms following injury, and may, therefore, be involved in the maintenance of muscle integrity

## 4 Conclusions

Cancer cachexia is a complex pathological condition characterized by many metabolic changes involving numerous organs. These changes are triggered by alterations in the hormonal milieu, release of different tumour factors and a systemic inflammatory reaction characterized by cytokine production and release. In fact, the macrophage-derived proinflammatory cytokines (IL-1, IL-6, TNF- $\alpha$ ) have key roles in inducing metabolic changes associated with many pathophysiological conditions, not only immune and inflammatory reactions but also in the development of cachexia. In fact, the balance between these and the anti-inflammatory cytokines such as IL-1ra, IL-10 and TGF is pivotal for the fine tuning of many biochemical processes. For instance, in chronic myelogenous leukemia, high cellular (leukocyte) levels of IL-1 $\beta$  and low levels of IL-1ra are seen in advanced disease and correlate with reduced survival (Harley et al. 1981).

A complex interaction of pro-cachectic and anti-cachectic cytokines or cytokine-neutralizing molecules probably determines the critical presentation and course of

cachexia. Intervening in this sequence of events to modify the host responses may prove to be a beneficial treatment strategy for cachexia. Currently tested anti-proinflammatory cytokines have produced interesting results.

Bearing in mind all the information presented here, it can indeed be concluded that no definite mediator of cancer cachexia has yet been identified. However, among all the possible mediators considered here, TNF- $\alpha$  is one of the most relevant candidates. Indeed, TNF- $\alpha$  can mimic most of the abnormalities found during cancer cachexia: weight loss, anorexia, increased thermogenesis, alterations in lipid metabolism and adipose tissue dissolution, insulin resistance and muscle waste including activation of protein breakdown. However, TNF- $\alpha$  alone cannot explain all the cachectic metabolic alterations present in different types of human cancers and experimental tumours. Another important drawback is the fact that TNF- $\alpha$  circulating concentrations are not always elevated in cancer-bearing states and, although it may be argued that in those cases local tissue production of the cytokine may be high, cachexia does not seem to be a local tumour effect. Consequently, both tumour-produced and humoral factors must collaborate in the full induction of the cachectic state. In the particular case of ageing sarcopenia, investigations are needed to elucidate not only mechanisms involved in the wasting process but also to clarify the role of the different factors involved in the complex etiology of sarcopenia.

In conclusion, and because metabolic alterations often appear early 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 humoral factors regulate this process. A better understanding of the role of cytokines 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 humoral response to inflammation and modifying cytokine actions pharmacologically may prove very effective, and no doubt future research will concentrate on this interesting field.

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