Recent developments in the treatment of cachexia: highlights from the 6th Cachexia Conference

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1 Introduction

The term cachexia embraces a complex metabolic syndrome characterized by loss of body weight that may develop as a consequence of loss of muscle mass with or without loss of fat mass; bone mineral density may be affected as well [1]. Over the last 10 years, the Cachexia Conference has developed a forum for researchers from the fields of cachexia and wasting disorders. It is unique in several ways as it provides a platform for both clinicians and basic researchers to meet and discuss pathways and potential therapeutic targets as well as recent evidence from clinical trials. The 6th Cachexia Conference was held in Milan, Italy, from 8 to 10 December 2012 with over 400 participants from more than 25 countries attending [2].

Cachexia remains underdiagnosed and undertreated, even though it is prevalent among many patients presenting with cancer, chronic heart failure, chronic obstructive pulmonary disease, human immunodeficiency virus infection or chronic kidney disease. Creating awareness for cachexia is one of the major aims of the Cachexia Conference as well as the improvement of patients’ morbidity, mortality and quality of life. A more thorough understanding of the underlying mechanisms and pathophysiology may help in achieving these aims. The identification of such mechanisms may help to identify therapeutic targets and potential biomarkers that help to detect loss of tissue as early as possible. Many excellent animal and clinical studies were presented at the meeting in Milan, and the following overview seeks to highlight some major research areas in the field of cachexia and body wasting.

2 Muscle mitochondrial dysfunction

A number of elegant models were presented in order to improve our understanding of pathways involved in the wasting process. Muscle wasting has received increasing research efforts in recent years. Thus, one of the hot topics of the meeting was the investigation of muscle proteolytic pathways. Slimani et al. from Didier Attaix’s group (Clermont University, Clermont-Ferrand, France) used a rat model of immobilisation-induced muscle atrophy to examine underlying pathomechanisms. They demonstrated that proteolysis via the ubiquitin proteasome system (UPS) and mitochondrion-associated apoptosis are involved in muscle remodelling during early recovery in immobilised muscle [3]. In addition, these authors demonstrated that the muscle-specific E3 ubiquitin ligase muscle RING-finger protein 1 (MuRF1) is up-regulated during catabolic conditions and that it is involved in the polyubiquitinylation of components of the thick...
filament. Interestingly, actin is being degraded in a specific pattern despite myosin degradation. Thick actin filaments degrade earlier than thin actin filaments. Unfortunately, the question of whether the order of actin filament degradation is clinically relevant with regards to the reversibility of the muscle wasting process remains unanswered. Importantly, the abundant contractile protein actin is a target of the UPS in skeletal muscle both in vitro and in vivo, further supporting the need for new strategies to block specifically the activation of this pathway in muscle wasting conditions [4].

Several investigators studied mitochondrial dysfunction and its role in muscle wasting. The current conclusion of these reports is that mitochondrial dysfunction seems to be the principal pathway in sarcopenia, i.e. age-related loss of muscle mass [5]. It may be important to differentiate between muscle wasting as part of ‘healthy ageing’ in contrast to muscle loss in chronic disease, as the involved processes could be fundamentally different [6]. At the meeting, special emphasis was put on possible steps involved in sarcopenia during the ageing process. Chikwendu Ibebunjo et al. (Novartis Institutes for Biomedical Research, Cambridge, Massachusetts, USA) subjected muscle samples to microarray and proteomic analysis in a rat sarcopenia model. The phenotypic, genomic and proteomic features of sarcopenia in these rats were similar to those of human sarcopenia and suggest that the animals may provide a suitable model for mechanistic studies of sarcopenia. Indeed, whilst pathways of mitochondrial energy metabolism (tricarboxylic acid cycle and oxidative phosphorylation) were significantly down-regulated in sarcopenic rats, genes associated with the neuromuscular junction were up-regulated [7]. Therefore, intervention strategies that counteract these dysregulations may be beneficial for prevention or treatment of sarcopenia. In line with this observation is the work of the group by Siegfried Labeit (Medical Faculty of Mannheim, Mannheim, Germany) that used MuRF1-knockout mice to analyse the role of E3 ligase MuRF1 in sarcopenia. Gene inactivation of MuRF1 resulted in potent protection from muscle atrophy induced by stimuli such as denervation, hindlimb suspension or injection of tumour necrosis factor-α (TNFα) [8]. They noted that fast fibre types were preferentially protected. Furthermore, in line with systemic regulatory effects of MuRF1 in muscle atrophy, metabolic effects on lipid and glucose oxidation and circulating amino acid levels could be detected. Therefore, future studies are warranted to identify additional pathways that are regulated by MuRF1.

### 3 Cytokines

The activation of pro-inflammatory cytokines and a dysbalance between pro- and anti-inflammatory mediators play important roles in the pathophysiology of cachexia and muscle wasting in chronic illness. Cytokines are currently thought of as among the principal catabolic players in skeletal muscle.

Pedro L. Martinez-Hernandez (Hospital University La Paz, Madrid, Spain) collected data from 21 cancer patients and 8 healthy controls. The authors measured interleukin-15 (IL-15) at weeks 4 and 8, respectively, because IL-15 might be directly associated with changes in body weight [9]. Baseline levels of IL-15 were similar between cancer patients and controls. Whilst cancer patients who gained weight (n=5) had an increase in IL-15 serum levels, this was not the case in patients who lost weight (n=13).

Pro-inflammatory cytokines such as IL-6 have likewise seen increasing research efforts over the last several years. The group of James A. Carson (University of South Carolina, Columbia, South Carolina, USA) used the ApcMin/mouse that develops severe cachexia and reduced muscle oxidative capacity, to study a possible role of IL-6 receptor antagonism and exercise in restoring mitochondrial function in cancer cachexia [10]. They found that whilst loss of muscle oxidative capacity occurs late in the course of cachexia development, decreased expression of regulators of mitochondrial biogenesis and dynamics occur rather early. These data demonstrate clearly that blockade of IL-6 dependent signalling can reverse deteriorated mitochondrial function in this model of severe cachexia.

Andrea Bonetto (Thomas Jefferson University, Philadelphia, USA) and his group concentrated their research on the signalling of IL-6 and of signal transducer and activators of transcription 3 (STAT3), which is known to induce muscle wasting in cancer cachexia [11]. Since the suppressor of cytokine signalling 3 (SOCS3) is one of the inhibitors of the IL-6/STAT3 pathway, SOCS3 over-expression in C2C12 myotubes by means of in vitro adenoviral infection was used to counteract this pathway. Indeed, C2C12 myotubes that over-express SOCS3 proved resistant to IL-6-induced wasting. Furthermore, transgenic mice (MLC-SOCS3 C57BL/6) served to isolate the effects of SOCS3 on skeletal muscle. Interestingly, muscle weight was increased in female MLC-SOCS3 transgenic animals only, suggesting a gender-specific function of SOCS3. In cancer cells, over-active receptor and non-receptor-bound tyrosine kinases cause persistent STAT3 phosphorylation (p-STAT3) and hence, STAT3 activation. Mice bearing the colon-26 adenocarcinoma (C26) exhibit severe muscle wasting that was associated with increased levels of p-STAT3. The researchers demonstrated elegantly that localized over-expression of SOCS3 in the tibialis muscle inhibits STAT3 activation and thus prevents muscle wasting in C26 mice. Therefore, SOCS3 seems to be a possible therapeutic target in cachexia induced by tumours with high IL-6/STAT3 signalling [11].
4 Therapeutic interventions targeting deleterious cytokine signalling

A very impressive example of the clinical importance of deleterious IL-6 signalling in cancer cachexia was reported by Miho Murakami and colleagues (Wakayama Medical University, Ibaraki, Japan). They used tocilizumab (TCZ), a humanized anti-human IL-6 receptor antibody, in a patient with advanced malignant mesothelioma [12]. In their case report, a 76-year old man with recurrent malignant mesothelioma of the pleura was treated with tocilizumab at a dose of 8 mg/kg of body weight every other week. The tumour had been refractory to standard polychemotherapy and radiation, and therefore treatment with tocilizumab was commenced. The drug lowered subfebrile temperatures and normalized IL-6-dependent plasma markers of cachexia like C-reactive protein, vascular endothelial growth factor and ghrelin within 2 weeks. Whilst tocilizumab increased pre-albumin and retinol binding protein, leptin levels were not changed. The general status of the patient was considerably improved as documented by the Eastern Cooperative Oncology Group performance status (ECOG PS scale). Since the patient suffered from radiation pneumonitis caused by previous treatment, tocilizumab had eventually been discontinued. Unfortunately, tumour growth increased rapidly thereafter [12]. Thus, further studies are warranted to elucidate whether blockade of IL-6 action in patients with malignant mesothelioma can improve outcomes and possibly the course of cancer cachexia.

Vasilis Paspaliaris (Itis Pharmaceuticals Pty Ltd., Melbourne, Australia) presented data from a phase I/II study of IP-1510, a novel interleukin-1 (IL-1) receptor antagonist that was used in 26 patients with cachexia caused by advanced gynaecological cancer. They measured stabilization and increases in body weight in 17 patients who were treated with IP-1510 at a dose of 1 mg twice daily over 28 days [13]. IP-1510 was well tolerated and safe in patients with advanced cancer. The interpretation of the current data is limited because the study was neither randomised nor blinded or controlled. Large-scale clinical studies are needed to prove whether neutralization of deleterious cytokines or direct receptor antagonism is an effective therapeutic approach to improve patient outcomes or to reverse muscle loss in cachexia.

5 Therapeutic approaches to counteract immobilisation-induced atrophy

Different studies concentrated on the mechanisms of muscle wasting induced by immobilisation. A study by L. Larsson (Department of Clinical Neurophysiology, Uppsala, Sweden) aimed to improve the understanding of mechanisms underlying the muscle type-specific differences in critically ill patients with acute quadriplegic myopathy. Using a porcine model, they found an up-regulation of UPS activity after 5 days of immobilisation. In addition, up-regulation of heat shock molecular chaperones as well as a concomitant down-regulation of sarcomeric proteins such as MURF2 and growth factors like insulin-like growth factor-1 (IGF-1) or IGF-2 were reported [14].

Several elegant studies either derived from animal data or from cell lines were presented with regards to the role of microRNAs (miRNA) in skeletal muscle wasting during cancer cachexia. Each miRNA has multiple target genes (200–500) and thus represents an attractive tool to study putative genes involved in the development of cancer cachexia. Nathan A. Stephen (University of Edinburgh, Edinburgh, UK) showed that cancer cachexia is associated with significantly increased expression of skeletal muscle miR-29b, miR-143, miR-100, miR-768-3p and miR-193b whereas miR-208a is decreased. Quantitative polymerase chain reaction (PCR) validation of these differentially expressed miRNAs indicated that only miR-29b correlated with weight loss ($r=0.5, p=0.03$) [15, 16]. Therefore, selected miRNAs may represent potential biomarkers for early detection of muscle wasting and targets for future interventions.

Another approach involves expression patterns of mRNA in skeletal muscle. Christopher M. Adams (University of Iowa, Iowa City, Iowa, USA) showed mRNA expression signatures of human skeletal muscle atrophy to identify a small molecular inhibitor of muscle atrophy. Ursolic acid, a naturally triterpene acid present in the fatty layer of several fruits and herbs, was used to demonstrate reduction in muscle atrophy. For this purpose, the authors used three distinct mouse models: fasting, denervation and immobilisation. They identified 63 mRNAs in human and mouse muscle that are regulated by fasting in human and mouse muscle, and 29 mRNAs were regulated by both fasting and spinal cord injury (i.e. denervation). Their data showed that ursolic acid reduced atrophy and stimulated hypertrophy by enhancing skeletal muscle insulin/IGF-1 signalling and inhibiting atrophy-associated mRNA expression. Thus, the authors concluded that ursolic acid and the research on mRNAs may help to prevent and treat muscle atrophy [17].

Jan Vrijbloed (Neurotune AG, Schlieren, Switzerland) presented a new animal model of sarcopenia, the so-called SARCO mouse, a transgenic mouse over-expressing the human enzyme neurotrypsin. This enzyme produces c-terminal agrin fragment from the peptide agrin, a synaptically located key player during initial formation and maintenance of neuromuscular junctions. Levels of c-terminal agrin fragment are significantly elevated in a large number of patients with sarcopenia. The SARCO mouse may therefore offer novel starting points for research of pathogenic
mechanisms in sarcopenia that could be used for pharmaceutical treatments [18].

6 MT-102, an anabolic/catabolic transforming agent

Another intriguing approach to the treatment of muscle wasting was presented by Mareike Pötsch (Charité Medical School, Berlin, Germany) who showed data from an animal model using the new anabolic/catabolic transforming agent MT-102 in order to reverse muscle wasting in cancer cachexia in the rat. Rats that were inoculated intra-peritoneally with 108 Yoshida AH-130 hepatoma cells and were then treated with MT-102 at a dose of 3.0 mg/kg/day resulted in a gain of lean mass and body weight. On day 11, left ventricular ejection fraction \( (p<0.01) \), fractional shortening \( (p<0.05) \), and stroke volume \( (p<0.01) \) were significantly improved by MT-102 [19]. The ACT-ONE trial, a multicentre, randomised, double-blind, placebo-controlled, dose-finding study of the anabolic/catabolic transforming agent MT-102 that has recently commenced recruitment of subjects with cachexia related to stages III and IV non-small cell lung cancer or colorectal cancer needs to confirm whether these animal data can be translated into humans [20].

7 Clinical studies/growth hormone

Several factors have complicated the development of effective therapies for cachexia particularly the many different pathways involved in the development of the disease. The focus of many therapies includes nutritional interventions. There has been little consensus on the primary end point for clinical trials, which has hampered assessment of the efficacy of treatments. Results of randomised, double-blind, placebo-controlled adequately powered clinical trials in the field of cachexia are eagerly awaited.

A promising approach was presented by John Friend (Helsinn Therapeutics Inc, Bridgewater, New Jersey, USA) who provided insight into the design of a randomised, double-blind, placebo-controlled, multicenter phase III study to evaluate the safety and efficacy of anamorelin in patients with non-small-cell lung carcinoma (NSCLC). Anamorelin is an orally active ghrelin receptor agonist. Ghrelin is a physiological ligand of the growth hormone secretagogue receptor that stimulates food intake. Anamorelin as a potential ghrelin-analog seems to be a therapeutic agent with possible effects during all stages of cachexia. Study results are estimated to be presented at the 7th Cachexia Conference in Kobe in December 2013.

Plasma ghrelin levels are elevated in cachectic patients with chronic heart failure possibly through a compensatory mechanism to a catabolic/anabolic imbalance [21, 22]. Exogenously administered ghrelin has been shown to improve left ventricular dysfunction and to attenuate the development of cardiac cachexia in rats with heart failure. Thus, supplementation of ghrelin could be a therapeutic approach in the treatment of chronic heart failure [23, 24]. A naturally occurring splice variant of ghrelin (Dln-101) with 57% homology to ghrelin was presented. Liat Mintz (DiaLean Ltd., East Brunswick, New Jersey, USA) conducted extensive preclinical studies showing that Dln101 acts similarly to ghrelin in increasing food intake, promoting weight gain and increasing growth hormone release. In addition, Dln-101 suppresses inflammation and has beneficial effects on the metabolic profile in terms in reducing cholesterol and glucose levels. Thus, Dln-101 has received approval to start phase I clinical trials [25].

8 Erythropoietin

Yulia Elkina (Charité Medical School, Berlin, Germany) and colleagues showed the tissue-protective effect of the non-hematopoietic erythropoietin analogues ARA284 and ARA286 in the treatment of cancer cachexia in a rat cancer cachexia model. ARA284 and ARA286 in high concentrations (5,000 units/kg/day) were shown to be effective in reducing tissue wasting in rat cancer cachexia model. These compounds should be seen as prospective drugs for human cancer cachexia [26].

9 Selective androgen receptor modulators

Selective androgen receptor modulators (SARMs) belong to a relatively new class of therapeutics that possesses anabolic properties. SARMs are currently in the early stages of development [27]. A double-blind, placebo-controlled phase II clinical trial with GTx-024 (enobosarm) in 120 healthy elderly men and women showed a dose-dependent (3 mg of enobosarm) improvement in total lean body mass and physical function [28]. Shontelle Dodson (GTx Inc., Memphis, USA) and colleagues analysed enobosarm that was used in the treatment of 159 patients with NSCLC with muscle wasting [29]. The group that received enobosarm showed positive effects on quality of life. Additionally, they found a benefit with regards to stair climbing power, a readily available measure of exercise capacity, frequently used by geriatricians. Moreover, stair climbing power benefit (defined as 10% improvement) correlated with quality of life (measured with functional assessment of cancer therapy). According to that, enobosarm had an impact on physical function, quality of life, and it had the ability to overcome the negative prognostic effect of >8% weight loss on overall survival [30]. Eric Vajda (Ligand Pharmaceuticals, La jolla, California, USA) presented
data from another novel SARM termed LGD-4033 that was used in healthy young men. In this randomised, placebo-controlled study, the dose of 0.1, 0.3 or 1 mg LGD-4033 daily was studied over a time of 21 days. This treatment phase was followed by a 5-week observation period. The study showed a dose-dependent increase in lean body mass (about 1.2 kg) in patients who were treated with 1 mg LGD-4033 [31]. The investigators are planning a phase II study to evaluate LGD-4033 in conditions such as muscle wasting associated with cancer and acute illness. The mechanism by which steroidal and non-steroidal SARMs produce selective tissue-specific anabolic responses has not been fully elucidated. However, further studies are necessary to evaluate the mechanism and long-term effect of SARMs in patients with cachexia.

10 Conclusions

Several pathways have been shown to play important roles in muscle wasting in the muscle wasting process: actin as a target of UPS, MuRF-regulated pathways or IL-15 that may be directly associated with loss of body weight. Potential biomarkers for cachexia are currently under investigation. There is further need for attractive biomarkers as therapeutic targets in the context of cachexia. The outcome criteria of drug studies in cancer cachexia need to focus not only on mortality, but also on symptoms and quality of life rather than simply on nutritional end-points, since the survival of cachectic cancer patients is usually limited to weeks or months due to the incurable nature of the underlying malignancy. In summary, cachexia and sarcopenia need more attention in clinical work and research and prospective clinical randomised, double blinded, placebo-controlled studies are needed. Prospective large-scale studies are warranted, such as the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF), a multicenter pathophysiological observational study which is particular looking at cachexia and obesity prevalence in chronic heart failure [32]. The results thereof will be presented in Kobe in 2013.

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Conflict of interest The authors declare that they have no conflict of interest.

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