

### Chemotherapy-induced muscle wasting: an update

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#### Abstract

The majority of cancers are associated to cachexia, a severe form of weight loss mostly accounted for by skeletal muscle wasting. Cancer patients are often treated with chemotherapy, whose side effects are at times neglected or underestimated. Paradoxically, chemotherapy itself can induce muscle wasting with severe, cancer-independent effects on muscle homeostasis. Since muscle wasting is a primary marker of poor prognosis for cancer patients and negatively affects their quality of life, the systemic consequences of chemotherapy in this context must be fully characterized and taken into account. Ten years ago a precursor study in an animal cancer model was published in the *European Journal of Translation Myology* (back then, *Basic and Applied Myology*), highlighting that the side effects of chemotherapy include muscle wasting, possibly mediated by NF- $\kappa$ B activation. This paper, entitled «Chemotherapy-induced muscle wasting: association with NF- $\kappa$ B and cancer cachexia», is now being reprinted for the inaugural issue of the «Ejtm Seminal Paper Series». In this short review we discuss those results in the light of the most recent advances in the study of chemotherapy-induced muscle wasting.

**Key Words:** cancer cachexia, skeletal muscle atrophy, cisplatin, Folfiri, colon cancer C26

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Cancer-cachexia is a syndrome characterized by a severe decrease of body weight, accounted for by specific loss of skeletal muscle and adipose tissues. Cachexia, which is distinct from anorexia, is due to a combination of reduced food intake and metabolic changes, including high energy expenditure, excess catabolism and inflammation.<sup>1</sup> The latter is linked to the production of cytokines by the tumor itself or the immune system of the host and plays a major role in the regulation of cancer cachexia.<sup>2</sup> Pro-inflammatory cytokines, such as IL-6, act as double-edged swords since they recruit NK cells to attack the tumor cells,<sup>3</sup> but also induce a systemic metabolic stress response that blocks the effects of anti-cancer immunotherapy.<sup>4</sup> The pivotal role of fat tissue in driving the chronic inflammation that triggers cachexia was recently recognized.<sup>5,6</sup> Skeletal muscle tissue is enriched in various stem cells but not in inflammatory cells in cachexia;<sup>7</sup> nonetheless, it is a primary target of pro-inflammatory cytokines, which induce muscle fiber atrophy and stem cell dysregulation and apoptosis.<sup>8-10</sup> Cachexia is associated to a large extent with cancers of the pancreas, oesophagus, stomach, lung, liver and bowel; this group of malignancies is responsible for 50% of all cancer deaths worldwide<sup>1</sup> and cachexia is directly accountable for the death of about 20% of all cancer

patients.<sup>11</sup> Being associated with poor prognosis and a lower quality of life for patients, cachexia remains a major challenge in the management of cancer patients to date. Muscle wasting in cachexia affects both striated muscles,<sup>12,13</sup> with important gender differences, likely linked to sex hormones.<sup>14</sup> Great progress is being made in the understanding of the molecular mechanisms underlying muscle wasting, with a central role played by proteasome-mediated protein degradation.<sup>15</sup> As a consequence, several treatments are now proposed to specifically counteract muscle wasting.<sup>16-18</sup> Chemotherapy remains the elective treatment for different cancers since it directly induces the death of tumor cells and it helps endogenous host responses against cancer.<sup>19</sup> However, loss of skeletal muscle during chemotherapy is prognostic of poor survival<sup>20</sup>. Consequently controlling muscle wasting especially in chemotherapy-treated patients is of the greatest importance. In spite of the significant effects of chemotherapy-induced muscle wasting, few studies have investigated this phenomenon up to date. When comparing the papers in PubMed containing the MeSH cachexia AND «muscle wasting» versus those containing the MeSH chemotherapy AND cachexia AND «muscle wasting» a striking difference appears: while the number

of studies dealing with cachexia is increasing exponentially, the number of studies addressing chemotherapy effects in this context is far behind and adds up to a few per year. In this concise review the effects of chemotherapy on muscle wasting are discussed. One of the first papers describing chemotherapy-induced muscle wasting, by Damrauer et al., was first published in *Basic and Applied Myology* (BAM) ten years ago.<sup>21</sup> On the ten anniversary of this publication, it is published again in this issue of *European Journal of Translation Myology* (EJTM), the rationale being that the results of that study are still valid and highly significant today; they will be discussed here along with more recent studies, which confirmed those findings and further characterized the underlying molecular mechanisms of chemotherapy-induced muscle wasting.

### Primordial studies on chemotherapy-induced muscle wasting

In the paper entitled «Chemotherapy-induced muscle wasting: association with NF- $\kappa$ B and cancer cachexia» the group headed by Denis Guttridge, at the Ohio State University, studied the effects of cisplatin, a common anti-cancer therapeutic agent, in a cancer cachexia animal model. The latter consisted in mice bearing a subcutaneously grafted colon carcinoma, the C26 tumor.<sup>21</sup> Guttridge and co-workers found that «although cisplatin is able to reduce tumor burden as expected, muscle wasting in mice nevertheless persists. Strikingly, cisplatin alone was seen to regulate muscle atrophy, which was independent of the commonly implicated ubiquitin proteasome system» (Damrauer et al.).<sup>21</sup> It is worth noting that then another group had reported opposite findings, i.e. that chemotherapy inhibits protein breakdown and promotes protein synthesis<sup>24,25</sup>, however, both studies showed that cisplatin induced body weight loss and muscle wasting in healthy mice, suggesting that chemotherapy does indeed induce muscle loss. Very likely, cisplatin triggers multiple responses in muscle tissue, which ultimately lead to muscle fiber atrophy while the role of protein ubiquitination and proteasome-mediated degradation remains controversial (see also below). Clearly these studies were relevant in addressing cancer cachexia in the presence of chemotherapy, which contributes to mimicking clinical settings better.

### Mechanisms underlying chemotherapy-induced muscle wasting

As mentioned above, Guttridge's laboratory did not suggest a role for proteasome-mediated protein degradation during chemotherapy, while Attaix's group found that chemotherapy reduced proteasome-dependent protein degradation, both in the absence or presence of a tumor (see Damrauer et al., this issue).<sup>21</sup> A possible explanation is that the first group did not directly measure proteasome activity, but rather Murf1 expression. Murf1 is a muscle specific ubiquitin ligase which leads proteins

to the proteasome, but it is not unique in its role and it could be redundant with other ubiquitin-ligases, such as Atrogin1. In addition Murf1 provides an indirect estimate of protein degradation.

Interestingly, although, cisplatin induces Nf-KB expression, the latter is increased in muscle in the presence of a tumor and NF- $\kappa$ B activity is sufficient to trigger muscle wasting. Taken together these findings provide a possible mechanism whereby chemotherapy induces muscle wasting.<sup>26</sup> In addition, the fact that NF- $\kappa$ B targets not only muscle fibers but also muscle stem cells,<sup>27</sup> suggests that chemotherapy may reach multiple targets, in addition to muscle fiber protein metabolism. The intriguing findings that NF- $\kappa$ B is involved in both tumor- and chemotherapy-induced muscle wasting suggested that common pathways are activated. This has been recently confirmed by the group of Andrea Bonetto, at Indiana University.<sup>28</sup> By using a comprehensive approach based on liquid chromatography followed by mass spectrometry they compared the skeletal muscle proteome in C26-tumor bearing and chemotherapy treated mice (chemotherapy consisting of 5-fluorouracil (5-FU), Leucovorin (LV) and CPT-11, a combination also known as Folfiri). Authors found that cancer and chemotherapy promote the down-regulation of 235 and 345 muscle proteins, respectively, the vast majority of which were modulated in common.<sup>28</sup> Mitochondrial dysfunction, TCA cycle, fatty acid metabolism, and Ca<sup>2+</sup> signaling were among the altered pathways detected.<sup>28</sup> Further insights about muscle mitochondria dysregulation following chemotherapy came from the same group which proved that mitochondrial depletion is MAPK-dependent.<sup>29</sup> This is consistent with previous findings that muscle wasting is associated with up-regulation of ERK1/2 and p38 MAPKs.<sup>30</sup> Taken together these studies provide a rationale for using treatments to both counteract tumor growth and to reduce the side effects of chemotherapy.

### Countermeasures: would exercise be effective against chemotherapy side effects?

In an elegant, recent study Bonetto and co-workers proposed the inhibition of the activin receptor 2B (ACVR2B) signaling to counteract both cancer- and chemotherapy-induced muscle wasting, by using ACVR2B/Fc, a soluble ACVR2B fusion protein and inhibitor of receptor downstream signaling.<sup>31</sup> ACVR2B/Fc was effective not only in counteracting Folfiri-induced skeletal muscle loss, but also the Folfiri negative effects on bone mass.<sup>31</sup> Beside pharmacological treatments, many studies including ours have established that exercise counteracts cachexia and sarcopenia.<sup>32-35</sup> The mechanisms underlying the beneficial effects of exercise against cachexia include autophagic flux regulation,<sup>36</sup> the reduction of Pax7 expression in satellite cells,<sup>37</sup> and the release of Hsp60 from muscle cells.<sup>38</sup> This topic was recently reviewed,<sup>39-41</sup> and it will be not further discussed here.

Given that cancer and chemotherapy activate common pathways in muscle and exercise has proven effective against cancer-induced muscle wasting, several research groups have been prompted to study whether physical activity could have beneficial effects in the presence of chemotherapy as well. Indeed, several epidemiological studies and clinical trials indeed suggest that both resistance and endurance exercise should be an integral part of supportive care for cancer patients undergoing chemotherapy.<sup>42-45</sup>

### The European Journal of Translation Myology Seminal Papers Series

This mini-review represents an update on the most relevant research on chemotherapy-induced muscle wasting. One of the first studies on this topic was the paper by Damrauer et al. in the Cachexia 2008 special issue of *Basic and Applied Myology* (now *European Journal of Translation Myology*).<sup>22</sup> Ten years later, this paper was selected for the inaugural issue of the Seminal Papers Series of the *European Journal of Translation Myology*.<sup>21</sup> This series provides an opportunity to disseminate to a larger audience seminal papers, previously published in BAM or EJTM, that have paved the way for breakthroughs in translational myology and medicine. The *European Journal of Translation Myology* has published many papers related to muscle wasting linked to mobility disorders,<sup>46-52</sup> to muscle atrophy in sarcopenia and disease states,<sup>53-55</sup> and to physical exercise.<sup>33,56</sup> EJTM is now entering in all major databases for scientific journals and its impact factor will be released soon. The journal is expanding its authorship, readership, editorial board and enhancing its relevance. Originally devoted to biology, physiology, diagnostic, and the rehabilitation of skeletal muscle tissue, the journal is now moving forward to cover additional fields in myology, thus becoming of a broader medical and clinical interest. We believe that reprinting of specific historical BAM or EJTM papers in the «EJTM Seminal Papers Series» (and publishing of up-dated related reviews) will provide the certain visibility that those papers deserve.

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### Conflict of Interest

The author declares no conflicts of interests.

### Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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