Novel mechanisms associated with cachexia during chemotherapy

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Cancer cachexia describes the progressive skeletal muscle wasting and weakness associated with many cancers. Cachexia decreases mobility and enhances fatigue leading to reduced quality of life (Murphy & Lynch, 2009). It also increases mortality resulting from respiratory and/or cardiac failure, and accounts for 20-30% of all cancer-related deaths. A contributing factor to the mortality with cancer cachexia is thought to be a diminished response to anti-cancer treatments, with failure-free and overall survival following chemotherapy being reduced in patients with continuing weight loss (cachexia) compared with those whose weight stabilised or increased (Kimura *et al.,* 2015; Andreyev *et al.,* 1998). Although these studies found associations between cachexia and response to treatment, the causative role of cachexia in chemotherapeutic efficacy has yet to be demonstrated clearly. Given that more than 80% of patients with gastrointestinal (GI) or pancreatic cancer and more than 40% of patients with colorectal or lung cancer exhibit cachexia upon diagnosis and initiation of treatment (Dewys *et al.,* 1980), it is essential to establish whether existing cachexia impairs the response to chemotherapy and if so, to identify potential mechanisms and treatment approaches to enhance the effectiveness of treatments in cachectic patients.

To investigate this, we utilised Colon-26 (C-26) cancer cells from different sources that induced no cachexia or cachexia, respectively. Since 5-Fluorouracil (5-FU) based therapy is used commonly to treat GI, pancreatic and colorectal cancer patients, we investigated the response to 5-FU treatment in C-26 tumour-bearing mice with existing cachexia or no cachexia. The tumour response to chemotherapy in cachectic mice was only ~50% of that in non-cachectic mice. Analysis of the potential mechanisms revealed skeletal muscle derived IL-6 as a likely initiating factor driving upregulation of proteins involved in drug efflux and reduced 5-FU metabolism in cancer cachexia. These findings highlight the clinical potential of IL-6 inhibitors as adjunct therapy to 5-FU based treatments in cachectic patients.

It is well known that many chemotherapeutics induce skeletal muscle wasting and weakness, demonstrated clinically by reduced lumbar skeletal muscle index, a slower chair-rise time and reduced hand-grip strength. Our study also revealed that existing cachexia exacerbated chemotherapy-induced muscle wasting; an effect associated with a microRNA (miR) dependent reduction in ERK1/2 signalling. These results add to the mounting evidence implicating miRs in the regulation of muscle size and support the potential of targeting specific miRs for treating muscle wasting.

Our findings demonstrate that cachexia impairs the efficacy of chemotherapeutics and exacerbates chemotherapy-induced wasting in tumour-bearing mice. We have identified mechanisms involved in each of these effects and future studies will investigate the therapeutic potential of targeting these mechanisms to improve the effectiveness of chemotherapeutics.

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