Novel therapies for reducing muscle wasting in cancer

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Cancer cachexia describes the progressive skeletal muscle wasting and weakness associated with many cancers. Cachexia reduces mobility and quality of life, impairs the response to anti-cancer therapies and accounts for 20-30% of all cancer-related deaths. Cachectic patients admitted to hospital stay for twice as long and have higher inpatient mortality compared with non-cachectic patients (Arthur *et al.*, 2014). The simplest and most effective way to treat cancer cachexia is to cure the cancer but this is not usually achieved because patients cannot sustain their treatments. Even when successful, cancer remission typically occurs after the cachexia has worsened considerably (Murphy & Lynch 2009).

One of the bottlenecks limiting development of effective treatments for cancer cachexia has been a lack of consensus regarding primary endpoint measures for the assessment of muscle function in preclinical models (Murphy & Lynch, 2009). Cachectic patients exhibit functional impairments, including reductions in whole body strength, mobility and physical activity levels. They also experience severe fatigue. Loss of muscle function impairs functional independence and loss of diaphragm function is implicated in respiratory fatigue. We have described a battery of tests to be used in preclinical studies that comprehensively assess the same functional impairments experienced by cachectic patients (Murphy *et al.*, 2012). Adoption of these standard assessments will facilitate accurate comparisons of data generated by different laboratories and assist development of effective preclinical treatments for translation to the clinic.

Cancer cachexia can develop in stages from pre-cachexia to cachexia to refractory cachexia (Fearon *et al.*, 2011). Not all patients experience the entire spectrum and patients can present at any of the stages when diagnosed. Since the mechanisms underlying the pathogenesis may differ at the varying stages of the disease, it is essential that preclinical studies employ models at each of these stages. We have developed non-metastatic and metastatic mouse models of cancer cachexia that represent different stages of the cachexia continuum. The pathogenesis and treatment approaches for cachexia will depend on the specific cancer and so we utilize mouse models of colorectal cancer, lung cancer and pancreatic cancer with similar functional impairments as humans so as to maximize the translation of our findings.

The pathogenesis of cancer cachexia is multifactorial and includes anorexia, inflammation, and enhanced proteolysis leading to muscle protein breakdown. Our studies investigate the potential of novel therapies targeting each of these events. Our recent studies include tackling the anorexia component of cancer cachexia by administering novel peptide leptin antagonists. We have also modulated the renin-angiotensin system in an attempt to reduce muscle breakdown. We have found that severely cachectic mice have a reduced response to chemotherapy and are investigating the possible mechanisms underlying this response. Current studies aim to treat the cardiac wasting and dysfunction associated with cancer and to enable patients to better cope with the rigors of chemotherapy. Future studies will also examine whether combination approaches are more efficacious for cancer cachexia.

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