Tackling muscle wasting in cancer

K.T. Murphy, Basic and Clinical Myology Laboratory, Department of Physiology, The University of Melbourne, VIC 3010, Australia.

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. The simplest and most effective way to treat cancer cachexia is to cure the cancer. However, this is often not achieved when patients cannot maintain their chemotherapy because of their cachectic state. Even when successful, cancer remission typically occurs after the cachexia has worsened considerably (Murphy & Lynch, 2009).

Current therapies have focused on treating conditions secondary to the cancer, but unfortunately these approaches have proved largely ineffective because they have only targeted one of the mechanisms of this multifactorial condition (Murphy & Lynch, 2012). It is generally accepted that the most efficacious treatment will come from either combined drug therapy or from drugs that can target several of these mechanisms simultaneously (Murphy & Lynch, 2009). Another contributing reason for the lack of progress in the treatment of cancer cachexia has been a lack of consensus regarding standard and appropriate end points for clinical studies. We have recently described standard assessments of whole body and skeletal muscle function that should be employed to maximize the translation of information gained from preclinical studies (Murphy & Lynch, 2012b).

We use non-metastatic and metastatic mouse models of cancer cachexia that have similar functional and metabolic impairments as in humans to maximize the translation of results (Murphy & Lynch, 2012b). Our studies investigate the potential of novel therapies to attenuate the muscle wasting and weakness in cancer.

Based on evidence that activation of the renin-angiotensin system (RAS) causes muscle wasting and weakness, that levels of angiotensin peptides are elevated in patients with cancers associated with cachexia, and that mice lacking the angiotensin type 1A receptor ($AT_{1A}^{-/-}$) have increased whole body and skeletal muscle function compared to wild-type mice (Murphy *et al.*, 2012a), we examined the efficacy of RAS inhibition for enhancing whole body and skeletal muscle function in mice bearing colon-26 (C-26) tumours. Two weeks of RAS inhibition with the ACE inhibitor, perindopril, did not increase muscle mass, but enhanced whole body function and reduced fatigue of isolated diaphragm muscle strips from mildly-cachectic and severely-cachectic C-26 tumour-bearing mice.

The transforming growth factor-β (TGF-β) superfamily member, myostatin, is a potent negative regulator of skeletal muscle mass and is elevated in cancer cachexia. We examined the efficacy of antibody-directed myostatin inhibition for attenuating cachexia in mice bearing Lewis lung carcinoma (LLC) tumours (Murphy *et al.*, 2011). Five weeks of antibody-directed myostatin inhibition increased both muscle mass and function in mildly-cachectic LLC tumour-bearing mice.

Future studies will examine whether combinatorial approaches can provide more efficacious therapies for cancer cachexia.

Murphy KT & Lynch GS. (2009) *Expert Opinion on Emerging Drugs* **14:** 619-632.
Murphy KT & Lynch GS. (2012). *Expert Opinion on Emerging Drugs* **17:** 5-9.
Murphy KT, Chee A, Gleeson BG, Naim T, Swiderski K, Koopman R & Lynch GS. (2011). *American Journal of Physiology Regulatory, Integrative and Comparative Physiology* **301:** R716-R726.
Murphy KT, Allen AM, Chee A, Naim T & Lynch GS. (2012a). *American Journal of Physiology Regulatory, Integrative and Comparative Physiology* **303:** R321-R331.
Murphy KT, Chee A, Trieu J, Naim T & Lynch GS. (2012b). *Disease Models & Mechanisms* **5:** 533-545.

KT Murphy is a Career Development Fellow of the NHMRC. Supported by an early career development grant from the Victorian Cancer Agency (Australia).