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Learning from skeletal muscle to treat metastatic cancer

Alastair A.E Saunders[1], Rachel E Thomson[1], Robin L Anderson[2], Paul Gregorevic[1]

[1]*Centre for Muscle Research, Department of Anatomy and Physiology, The University of Melbourne, VIC, 3010, Australia*

[2]*Metastasis Research Laboratory, Olivia Newton-John Cancer Research Institute, Heidelberg, VIC, 3084, Australia.*

Cancer is one of the leading causes of death worldwide. These deaths are most commonly caused by complications arising from the secondary, metastatic tumours, rather than the primary tumour alone. Not all organs are affected equally by metastatic cancer. Skeletal muscles, for example, are very rarely the site of secondary tumours, in contrast to organs such as the lung, liver and bone (Willis, 1952). This is despite muscles making up 30-40% of body mass whilst also receiving a rich blood supply.

This research aims to understand why muscles are infrequently affected by metastatic cancers, in order to exploit these findings for the purposes of potential novel therapeutics. Based on previous studies that have identified the TGF-β family as a regulator of cancer cell dissemination and colonisation (Padua et al., 2008), and our own research into the role of the opposing BMP family of proteins in muscle growth and homeostasis, we hypothesised that the TGF-β superfamily of proteins would play a role in protecting muscle from metastatic cancer. We therefore employed recombinant adeno-associated viral vectors (rAAV) to manipulate elements of the TGF-β family within muscles of mice bearing metastatic breast cancer to investigate the susceptibility of skeletal muscle to metastasis.

All experiments were approved by the Animal Ethics Committee of The University of Melbourne and conducted in accordance with the Australian code of practice for the care and use of animals for scientific purposes (NHMRC). Female Balb/c mice were anaesthetised under 3-5% isoflurane and received either an intramammary fat pad injection of mCherry labelled 4T1.2 breast cancer cells, or phosphate buffered saline (PBS; control), and intramuscular injections of rAAV expressing elements of the TGF-β network. Once mice developed signs of metastatic cancer they were humanely killed with sodium pentobarbitone (60mg/kg). Histological analysis and qPCR identified mCherry positive tumour cells in the muscles receiving AAV:TGF-β1 and not in the muscles receiving control AAV. Unexpectedly, muscles injected with TGF-β1 were 49.5% smaller in tumour-bearing mice ($p<0.05$), whilst there was no mass difference observed in tumour-free controls. Injection of another TGF-β family member, Activin A, or a BMP inhibitor Noggin, did not result in colonisation of metastatic cells within muscles.

Here we have demonstrated that TGF-β1 can promote colonisation of growth of cancer cells within an environment that is otherwise inhospitable to tumour growth. Successfully defining the unique factors within muscles that deter the propagation of metastatic cancers may identify potential anti-metastatic agents that could prevent metastatic cancer growth in other vulnerable organs.

Padua, D., Zhang, X. H.-F., Wang, Q., Nadal, C., Gerald, W. L., Gomis, R. R. & Massagué, J. 2008. TGFβ primes breast tumors for lung metastasis seeding through angiopoietin-like 4. *Cell,* 133**,** 66-77.

Willis, R. 1952. The Spread of Tumors in the Human Body. London, Butterworth & Co Ltd.