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TEMASEK LIFESCIENCES LABORATORY

*Scan for address

14 Mar 2023 (Tues), 4pm
The Auditorium (Level 1)

Hosted by: Dr YU Fengwei

Convergent Insulin and TGF-β signalling drive cancer cachexia by promoting aberrant ECM accumulation and muscle atrophy in a *Drosophila* tumour model

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A/Prof Louise Cheng is an ARC Future fellow and is jointly appointed as a group leader at the Peter MacCallum Cancer Center and the Department of Anatomy and Physiology, University of Melbourne. Louise started her own lab at the Peter MacCallum Cancer Institute in 2012. Her lab uses the fruit fly Drosophila to address fundamental questions such as how differentiation is maintained in post-mitotic neurons, and inter-organ communication in the context of cancer cachexia.

Cancer cachexia is a wasting disease suffered by advanced stage cancer patients and ultimately causes ~30% of cancer mortalities. Tissue wasting is caused by multiple tumour-secreted signals. However, how these signals converge on downstream signalling in the target tissues remains largely unknown. In this study, using a larval *Drosophila* cachexia model, we explored how two tumour secreted proteins, ImpL2 (an insulin antagonist) and Gbb (a TGF-β ligand), crosstalk and drive tissue wasting via the activation of intracellular signalling pathways in the adipose tissue (called fatbody) and muscle. We showed that these proteins converge to activate TGF-β signalling in the fatbody, with ImpL2 mediated regulation of insulin controlling TGF-β signalling by regulating expression of the BMP antagonist *short gastrulation* (*sog*). This in turn caused aberrant ECM accumulation in the fatbody, which contributes towards muscle detachment by preventing ECM secretion and subsequently depleting muscles of fatbody-secreted ECM proteins. In the muscle, tumour secreted ImpL2 mainly impinged on insulin signalling to affect protein translation and muscle atrophy. Strikingly, the activation of insulin signalling in the muscle or fatbody, or the inhibition of TGF-β signalling in the fatbody, was sufficient to over-ride tumour secreted factors, and was able to rescue tissue wasting in the presence of tumour. Thus, this study highlights the importance of peripheral tissues signalling in facilitating cancer cachexia and identifies new potential targets for disease diagnosis and treatment.

Recent Publications:

1. Lodge W, Zavortink M, Golenkina S, Froldi F, Dark C, Cheung S, Parker BL, Blazev R, Bakopoulos D, Christie EL, Wimmer VC, Duckworth BC, Richardson HE, **Cheng LY** (2021) Tumor-derived MMPs regulate cachexia in a Drosophila cancer model. Dev Cell 2021 Aug 31;S1534-5807(21)00638-9. doi: 10.1016/j.devcel.2021.08.008.
2. Dong Q, Zavortink M, Froldi F, Golenkina S, Lam T, **Cheng LY** (2021). Glial Hedgehog signalling and lipid metabolism regulate neural stem cell proliferation in Drosophila. EMBO Rep. 2021 May 5;22(5): Epub 2021 Mar 10. PMID: 33751817, https://pubmed.ncbi.nlm.nih.gov/33751817
3. Froldi F, Pachnis P, Szuperak M, Costas O, Fernando T, Gould AP, **Cheng LY** (2019). Histidine is selectively required for the growth of Myc-dependent dedifferentiation tumours in the Drosophila CNS. EMBO J. Apr 1;38(7)