Learning from Whales: Identifying key genes in genetic pathway responses to low oxygen

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Energy & Environment

Background

- Oxygen levels are declining in warming oceans, posing challenges for marine life
- Marine mammals tolerate oxygen scarcity (hypoxia) during their dives, making them a great model to understand the low oxygen response
- Responses to hypoxic conditions in early eukaryotes include physically moving away (cell motility) or reducing metabolic rate
- The stress response may also play a role in affecting the hypoxia response

How do cell motility, stress, and metabolism interact with the hypoxia response?

Methods

Data sourcing:

- Gene sets of hypoxia and glucocorticoid pulled from the Molecular Signature Database (MSigDB)

Analysis:

- Gene regulatory networks created using the Cytoscape framework with GeneMANIA application (Shannon et al., 2003)

RNA-sequencing:

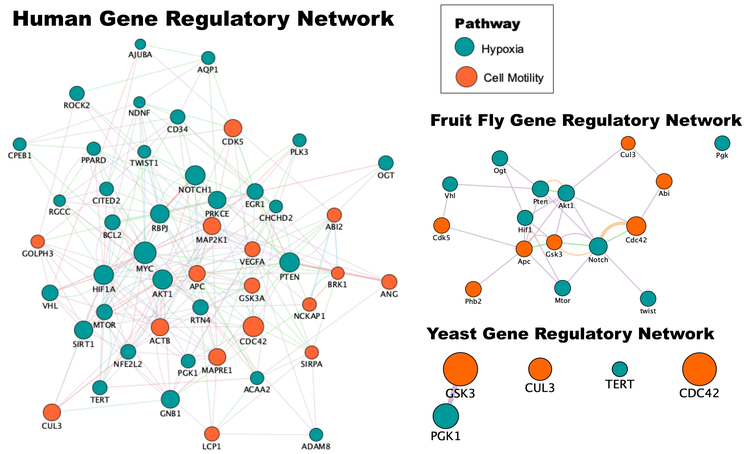
- Human, dolphin, pilot whale, humpback whale, sperm whale, and beaked whale cells exposed to +/- hypoxia/cortisol
- Gene expression quantified with RNAseq

Results *Do these three genetic responses help tolerate low-oxygen conditions?*

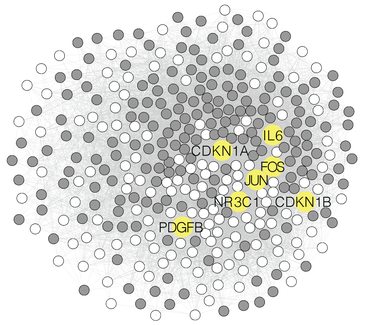
Cell Motility

Evidence for coupling of the hypoxia and cell motility pathways in early eukaryotic evolution

- PGK1 and GSK3 are co-expressed even in non-motile yeast



Stress Hormones

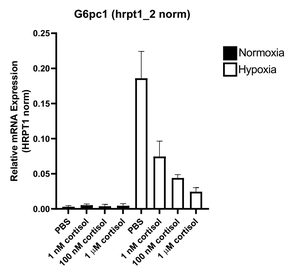


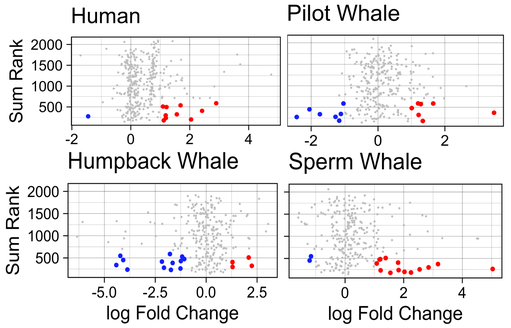
Hypoxia and GR pathways are highly interconnected

- GR: glucocorticoid – the molecular stress response
- NR4A2, ADM, and LOX are key genes mediating hypoxia GR interaction that were found only in the marine mammal species

Adding cortisol to beaked whale cell cultures suppressed the hypoxia response

- Tested in Pck1, G6pc, Per1, SGK1, and Igfbp1 (known GR downstream targets)

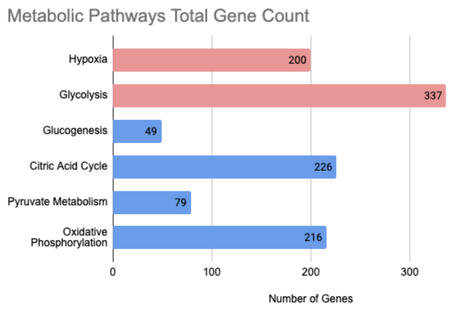




Metabolism

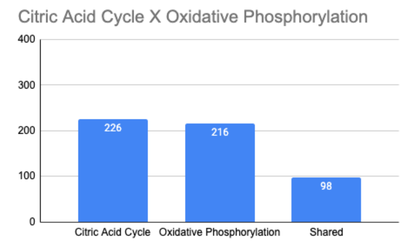
The most genes present are used for anaerobic respiration

- Glycolysis is overrepresented, with 337 genes in the genome



However, an abundance of shared genes were found between aerobic metabolism pathways

- Oxidative Phosphorylation and the Citric Acid Cycle share 98 genes



Takeaways and Applications

Marine Mammal Conservation

- Knowing how stress reduces low oxygen response in marine mammals can guide policy regulating anthropogenic stressors

Applications to human health

- Could provide insight into ways humans cope with low oxygen conditions in medicine, such as strokes or cardiac arrest

References:

Shannon, P., Markiel, A., Ozier, O., Baliga, N. S., Wang, J. T., Ramage, D., Amin, N., Schwikowski, B., & Ideker, T. (2003). Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome research, 13(11), 2498–2504. https://doi.org/10.1101/gr.1239303

Acknowledgements:

We would like to thank the advisors and other student members of the Learning from Whales team for guiding and supporting our work. Thank you to the Duke Bass Connections program for funding this project.