



The Hippo effector nuclear membrane proteins: Do they regulate muscle adaptation to hypoxia? Is this important for disease?

MSc thesis with publication potential for up to two Biologists or Molecular Biologists

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Background. The Hippo effector YAP (yes-associated protein, gene symbol *YAP1*) regulates proliferation, stem cell identity, and regeneration in skeletal and cardiac muscle cells (Wackerhage et al., 2014). YAP responds to multiple exercise-associated signals and might be a regulator of the adaptation to resistance and endurance exercise as well as hypoxia (Gabriel et al., 2016).

To study the effect of hypoxia on YAP in muscle cells, our former MSc student Johannes Trefz exposed muscle cells to normoxia or 3% hypoxia, immunoprecipitated YAP and YAP-binding proteins and we then identified the proteins that bind YAP via liquid chromatography and mass spectrometry proteomics. This analysis revealed many proteins that bind YAP. Importantly, we also found several proteins that change their binding to YAP in response to hypoxia.

One of the most striking findings is that hypoxia affects YAP binding to some proteins integral to the nuclear envelope (NE) as well as transcription factors known to interact with these NE proteins. Furthermore there are indications that YAP could be interacting with specific LINC (linker of nucleoskeleton and cytoskeleton) complexes. Strikingly the mentioned proteins are associated with human disease (Meinke et al., 2011; Meinke and Schirmer, 2016) and skeletal muscle function (Meinke et al., 2011; Meinke and Schirmer, 2015; Zhou et al., 2018).

Aim of the project. We now seek up to two motivated and talented biologists or molecular biologists to further characterise this interaction with the aim of moving our discovery towards a scientific publication.

The MSc student(s) will address some of the following research questions:

- 1) Under what conditions (e.g. hypoxia and mechanical stress) does YAP co-localise with nuclear membrane and LINC proteins?
- 2) Do nuclear membrane and LINC proteins regulate the transport of YAP into the nucleus and is this affected by hypoxia?
- 3) Is there a link to YAP-mediated gene expression under normoxia and hypoxia?

Interested?

This project is co-supervised by Peter Meinke (peter.meinke@med.uni-muenchen.de) & Henning Wackerhage (henning.wackerhage@tum.de) and the other authors of this advert are involved and support this project. Please e-mail both of us if you are interested.

References

Gabriel, B.M., Hamilton, D.L., Tremblay, A.M., and Wackerhage, H. (2016). The Hippo signal transduction network for exercise physiologists. *Journal of applied physiology* (Bethesda, Md : 1985) *120*, 1105-1117.

Meinke, P., Nguyen, T.D., and Wehnert, M.S. (2011). The LINC complex and human disease. *Biochemical Society transactions* *39*, 1693-1697.

Meinke, P., and Schirmer, E.C. (2015). LINC'ing form and function at the nuclear envelope. *FEBS Lett* *589*, 2514-2521.

Meinke, P., and Schirmer, E.C. (2016). The increasing relevance of nuclear envelope myopathies. *Curr Opin Neurol* *29*, 651-661.

Wackerhage, H., Del Re, D.P., Judson, R.N., Sudol, M., and Sadoshima, J. (2014). The Hippo signal transduction network in skeletal and cardiac muscle. *Science signaling* *7*, re4.

Zhou, C., Rao, L., Shanahan, C.M., and Zhang, Q. (2018). Nesprin-1/2: roles in nuclear envelope organisation, myogenesis and muscle disease. *Biochemical Society transactions*.