Splicing-mediated regulation of Sec16-directed COPII scaffold assembly

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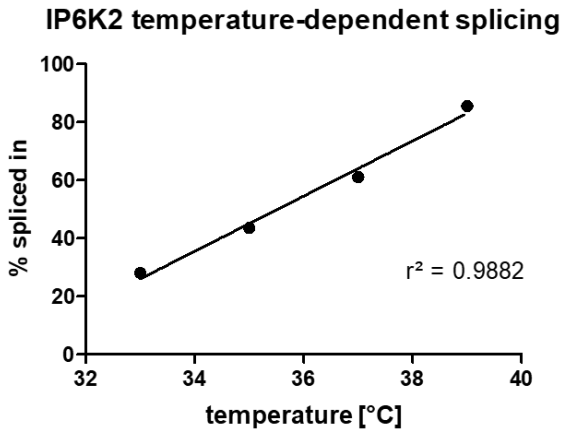

Abstract:

In the current funding period, we demonstrated the tight regulation of the early secretory pathway by a splicing switch in Sec16. Upon T cell stimulation, inclusion of Sec16 exon 29 is increased and this switch sets up the cell for an upregulation of cargo flux between the endoplasmic reticulum (ER) and the Golgi apparatus [1]. Apart from a more detailed investigation of this specific event (with Markus Wahl, project A06), we also employed a genome-wide approach to identify additional splicing switches that regulate protein secretion in the early as well as later secretory pathway. We indeed determined that a network of RNA binding proteins controls numerous splicing events that modulate protein secretion efficiency (manuscript in preparation).
We also recently described that body temperature changes lead to alternative splicing of many mammalian target exons [2]. These temperature changes happen in a circadian manner and result in rhythmic alternative splicing. Interestingly, we found that alternative splicing one of our top secretion regulators, inositol hexakisphosphate kinase 2 (IP6K2), is also highly sensitive to temperature changes (see figure above). The splicing change we observe likely reduces kinase activity at higher temperatures due to the production of a non-functional protein. We speculate that by adjusting inositol phosphate levels, IP6K2 might regulate intracellular trafficking in a temperature-dependent manner. We propose to further elucidate the connection between body temperature, circadian splicing and protein secretion efficiency in a tissue-specific manner. A collaboration partner could be Volker Haucke (A01/A07, IP signaling).

Publication/s:

[1] I. Wilhelmi, R. Kanski, A. Neumann, O. Herdt, F. Hoff, R. Jacob, M. Preußner, and F. Heyd, “Sec16 alternative splicing dynamically controls COPII transport efficiency,” *Nat. Commun.*, vol. 7, p. 12347, 2016.

[2] M. Preußner, G. Goldammer, A. Neumann, T. Haltenhof, P. Rautenstrauch, M. Müller-McNicoll, and F. Heyd, “Body Temperature Cycles Control Rhythmic Alternative Splicing in Mammals,” *Mol. Cell*, pp. 1–14, 2017.