Postdoc Program between the Freie Universität Berlin (FUB) and the China Scholarship Council (CSC)

Open Postdoc position for CSC scholarship candidates 2015

The postdoc position is only offered to Chinese who graduated with a PhD degree from a Chinese university.

Department/Institute: FB Biology, Chemistry, Pharmacy; Institute of Chemistry; Division of Biochemistry

Subject area: Biochemistry, Neuroscience

Professor / Research Group: Volker Haucke

Number of open positions: 1

Project title: Phosphoinositide-based switches in endocytotic membrane traffic and signaling

Project description:

Phosphoinositides (PIPs) regulate nearly all aspects of cell physiology ranging from modulation of the cytoskeleton to membrane traffic and cell signaling[1-3]. A hallmark of PIP function is rapid interconversion by PIP kinases and phosphatases, which underlies PIP-based functional switches in membrane traffic and cell signaling[1,2]. How such PIP switches operate in space and time in most cases is unknown, due to the lack of specific tools to acutely manipulate select PIP species in living cells.

Recently, we have identified phosphatidylinositol 3,4-bisphosphate [$PI(3,4)P_2$] as a novel key lipid that spatiotemporally regulates clathrin-mediated endocytosis from the cell surface *en route* to endosomes[4,5]. $PI(3,4)P_2$ synthesis is mediated by the class II phosphatidylinositol 3-kinase type C2α, an enzyme recruited to the plasma membrane and stimulated by clathrin. $PI(3,4)P_2$ synthesis is counterbalanced by regulated $PI(3,4)P_2$ turnover involving INPP4A/B 4-phosphatases resulting in generation of endosomal PI(3)P[6]. Conversely, endosomal PI(3)P hydrolysis by the 3-phosphatase MTM1, an enzyme mutated in inherited myotubular myopathy, is a prerequisite for phosphatidylinositol (4)-phosphate [PI(4)P]-dependent endosomal fusion with the plasma membrane during recycling (unpublished; see related ref[7] in 3.4). Further unpublished work from the Haucke lab shows that cellular depletion of class II phosphatidylinositol 3-kinase type C2β, another $PI(3,4)P_2$-synthesizing enzyme, is crucial for the switch between active mTORC1 signaling and autophagic/ lysosomal protein turnover during nutrient depletion. These data suggest that $PI(3,4)P_2$- and PI(3)P-based switches regulate endocytosis and endosomal sorting at steady state and play crucial roles during nutrient signaling. How these switches operate in time and space and are linked to cell signaling is largely unknown.

The proposed project fills this gap by providing elaborate chemical tools and molecular biological approaches that enable the dissection of PIP-based switches in living cells. To this aim we will use and where necessary develop rapidly photoactivatable membrane-permeant PIP derivatives, chemical dimerizer-based as well as optogenetic tools to

locally and acutely manipulate PIP levels within cells and study their effect on endocytotic and endosomal membrane traffic and on growth factor and nutrient signaling. Photo-crosslinkable PIP derivatives will enable us to capture and identify protein-lipid conjugates that modulate cellular responses to PIP based switches. We anticipate that our studies will provide new insights into the mechanisms underlying PIP-based functional switches in eukaryotic cells and how dysfunction of such switches may contribute to diseases ranging from cancer to neurodegeneration and muscle disease.

References:

1. Balla, T. Phosphoinositides: tiny lipids with giant impact on cell regulation. *Physiol Rev* **93**, 1019-137 (2013).
2. Di Paolo, G. & De Camilli, P. Phosphoinositides in cell regulation and membrane dynamics. *Nature* **443**, 651-7 (2006).
3. Posor, Y., Eichhorn-Grunig, M. & Haucke, V. Phosphoinositides in endocytosis. *Biochim Biophys Acta* (2014).
4. Daumke, O., Roux, A. & Haucke, V. BAR domain scaffolds in dynamin-mediated membrane fission. *Cell* **156**, 882-92 (2014).
5. Posor, Y. et al. Spatiotemporal control of endocytosis by phosphatidylinositol-3,4-bisphosphate. *Nature* **499**, 233-7 (2013).
6. Franco, I. et al. PI3K class II alpha controls spatially restricted endosomal PtdIns3P and Rab11 activation to promote primary cilium function. *Dev Cell* **28**, 647-58 (2014).

Academic requirements:

PhD in genetics, molecular biology, or neuroscience; publications in international peer-reviewed journals; good command of the English language

Link to professor/contact and further information:

http://www.fmp-berlin.info/research/molecular-physiology-and-cell-biology/research-groups/haucke/department.html

Please note:
In a first step the complete application should submit to the Beijing Office for evaluation by November 21, 2014. Please don't contact the professor before. He will get in contact with you after having received the complete application.