# Oxygen-Sensitive Regulation of Mitochondrial Mass by the von Hippel-Lindau Tumor Suppressor Protein pVHL

Shuijie Li[1], Petra Bullova[1], Wenyu Li[1], Javier Rodriguez[2], Meng Yu[3], Xuepei Zhang[4], Huirong Han[5], Oscar Bedoya Reina[1], Monika Plescher[1], Juan Yuan[7], Johan Holmberg[7], Anna Smed Sörensen[3], Alex von Kriegsheim[2], C. Christofer Juhlin[6], Catharina Larsson[6], **Susanne Schlisio**[1]

[1]Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm, Sweden; [2] Edinburgh Cancer Research Centre, IGMM, University of Edinburgh, Edinburgh, United Kingdom; [3]Department of Medicine, Karolinska University Hospital, Stockholm, Sweden; [4]Department of Medical Biochemistry and Biophysics, Stockholm, Sweden; [5]Department of Anesthesiology, Weifang Medical University, Weifang, Shandong, China; [6]Department of Oncology-Pathology, Cancer Center Karolinska, Stockholm, Sweden ; [7]Department of Cell and Molecular Biology, Karolinska Institutet, Stockholm, Sweden

**Abstract:** The hypoxia inducible transcription factors (HIF) are the key mediators of adaptation to hypoxia. Whereas, the major consumers of oxygen in the cell are mitochondria, mitochondrial transcription and biogenesis has not been reported to be directly regulated by HIF transcription. We identified an oxygen sensitive regulation of mitochondrial transcription Factor TFAM, a key activator of mitochondrial transcription and replication. We found that TFAM is hydroxylated by the oxygen-sensitive hydroxylase EglN3 on proline 53/56 and subsequently bound by the tumor suppressor protein von Hippel Lindau (pVHL). pVHL binding stabilizes TFAM by preventing mitochondrial LON protease recognition and proteolysis. Cells lacking wild-type VHL or in which EglN3 was inactivated genetically or by lack of oxygen have reduced mitochondrial content. All VHL disease mutations tested failed to bind hydroxylated TFAM, regardless of whether they have the ability to bind hydroxylated HIF or not. Tumors of VHL related malignancies such as pheochromoytoma and clear cell renal carcinomas (ccRCC) show low mitochondrial content, implicating that lack of mitochondrial content is related to the malignancies of the VHL syndrome.