Metabolic Effects of VHL Deficiency

Fulvio Della Ragione

Professor, Department of Precision Medicine, University of Campania, Naples, Italy

Mutations in *VHL*, which encodes von Hippel–Lindau tumor suppressor (VHL), are associated with various different diseases. These include not only the VHL syndrome, a hereditary condition associated with tumors arising in multiple organs (including brain, retina, kidney, pancreatic NET, pheochromocytoma, and reproductive tract) but also a congenital form of polycythemia (ECTY2). Although the syndrome has been identified in the first decades of the last century, several basic questions are still unexplained. Particularly, the reason(s) for which specific tissue/cell phenotypes are target to malignant transformation. Recently, we have characterized a patient showing about 80% VHL reduction. The decreased protein levels are due to the presence of a novel *VHL* gene synonymous mutation that alters the VHL transcript splicing, giving rise to not-functional mature mRNA. The strong protein decrease results in the early onset of a complex syndrome clearly different from VHL disease and ECTY2. It is indeed associated with a strongly reduced growth rate, persistent hypoglycemia, and limited exercise capacity. In my talk, I will describe how the reduction of VHL might result in important gene expression changes able to reprogram carbohydrate and lipid metabolism, impairing muscle mitochondrial respiratory function, and uncoupling oxygen consumption from ATP production. Particularly, I will focus on the effects of VHL on specific key enzymatic activities that modulate fatty acids and cholesterol biosynthesis (mainly, INSIG2/SREBP1c mechanism). Intriguingly, these effects have not been previously demonstrated in VHL-dependent familiar erythocytosis. Putative consequences of these changes on the elasticity and function of cell membrane will be also discussed. The mechanisms by which changes in gene transcription might impair muscle mitochondrial network will be also highlighted. I will describe the identification of unusual intermitochondrial connecting ducts. In conclusion, novel pieces of knowledge will be added on the importance of the VHL–hypoxia-inducible factor (HIF) axis to human phenotypes (physiology).