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The VHL gene, which is mutated in the Von Hippel-Lindau syndrome and also in most kidney cancers, is key to the normal function of the cell. This gene allows the cells to sense and adapt to the amount of oxygen that is available, which in turn determines a host of other cell functions and characteristics. Deciphering the many different functions of VHL and other oxygen-sensing genes is integral to understanding how cells work, why VHL mutation has such a profound impact on the behaviour of the cell, and how to counteract VHL mutation and design therapeutic strategies.

One of the strongest testaments to the importance of studying this process was perhaps this year's announcement of the Nobel Prize in Physiology or Medicine, which was awarded to William Kaelin, Peter Ratcliffe, and Gregg Semenza for their discovery of the oxygen-sensing pathway and the role of the VHL gene. I am proud to be among McGill researchers who are studying this process, which has tremendously benefited from the generosity of the Canadian VHL Alliance. The CVHLA/Cancer Research Society funding has allowed my group to make significant progress in our efforts to understand new aspects of the function of the VHL gene and the oxygen adaptation pathway.

This project started with our discovery that a gene called MBNL2 mediates part of the effect of the loss of VHL gene in kidney tumours. We aim to comprehensively identify other genes and pathways that are involved in the oxygen-sensing pathway and play a part in kidney tumour development and metastasis. Among highlights of our progress so far are two main discoveries: First, we have found that VHL-deficient tumours are made of various previously unknown cell types with different characteristics. Particularly, in one cell type, the oxygen sensing pathway (also known as the hypoxia signaling pathway) is significantly more active than in other cells. Given that all tumour cells lack VHL, this observation can lead us to other factors that work in parallel to VHL to regulate oxygen sensing.
Secondly, we have re-introduced the VHL gene in kidney cancer cells. Using a technology called RNA-sequencing, we have identified tens of previously unknown genes that are affected by the reintroduction of VHL in these cells. Many of these genes appear to respond to the amount of oxygen available to the cell, but there are also oxygen-independent genes. This observation points us to other VHL functions that go beyond oxygen adaptation.

We are continuing this research on several fronts, supported by the funding provided by CVHLA and the Cancer Research Society. Together, these analyses will help us figure out which genes are required for the malignant behaviour of VHL-deficient cells. These discoveries will bring us closer to the identification of new targets for development of treatments against kidney cancer cells and other VHL-deficient tumours.