

CLINICAL HEMATOLOGY/ONCOLOGY NEWSLETTER

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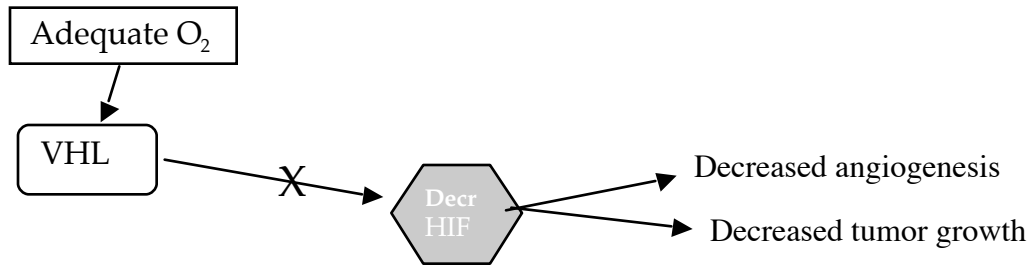
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RE: The Return of von Hippel and Lindau

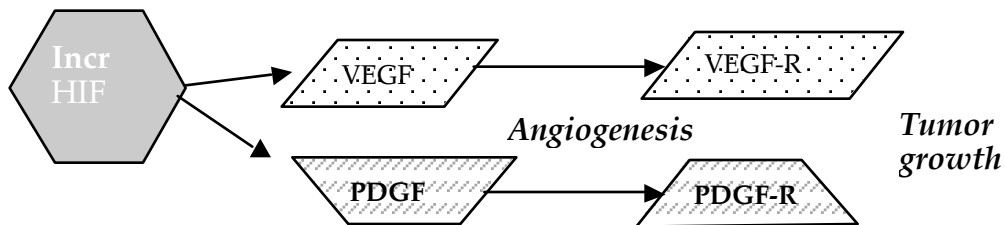
Seems like ages ago that I memorized syndromes, including the one described by von Hippel and Lindau. Soon after I passed my Boards in Internal Medicine, I began forgetting many of them. It seemed acceptable to forget the one by von Hippel and Lindau, an entity that I thought I would never see; an autosomal dominant, neurocutaneous dysplasia characterized by retinal angioma, cerebellar hemangioma, renal and pancreatic cysts, and endolymphatic sac tumors. The penetrance of this disease was high and almost half of the affected subjects manifested some aspect of these growths, however, finding a patient with this disorder appeared remote to me. Now, molecular oncology has placed the syndrome described by von Hippel and Landau at center stage.

In 1904, Eugen von Hippel, a German ophthalmologist, described a rare disease of the retina that he later named "angiomatosis retinae". In 1926, Arvid Lindau, a Swedish pathologist, noted an association between vascular tumors of the retina and other blood vessel tumors of the cerebellum along with other parts of the central nervous system. This disease became known as Von Hippel-Lindau Syndrome (VHL). In the intervening years, other growths have been associated with VHL, some of which include renal carcinoma, pheochromocytoma, islet cell tumors of the pancreas, pancreatic cysts and epididymal cysts. Clear cell carcinoma of the kidney is a cause of death in many patients with VHL. Conversely, many patients with no known VHL syndrome have renal cell carcinoma with mutations of the VHL gene and its products. The VHL gene is a germline mutation that has been well documented and characterized. Furthermore, recent genomic and proteomic investigations of VHL have led to the discoveries of drugs that are the first effective agents in the treatment of renal cell carcinoma. This purpose of this Newsletter is to comment on the interesting biologic information that has been derived from the VHL tumor suppressor gene and its transcription factors.

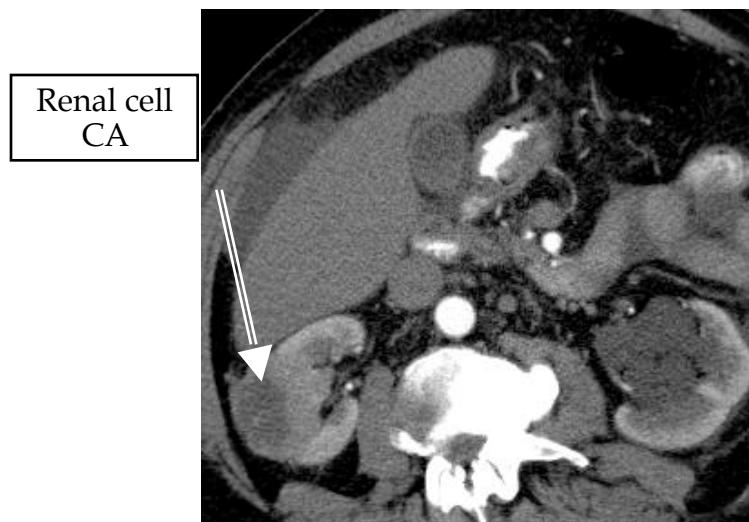
More than half of the patients with clear cell renal carcinomas have an inactivation of the VHL gene. VHL couples alterations in oxygen tension to vital cellular pathways by means of transcription regulators known as the hypoxia-inducible factor (HIF). A terse but very clear review of VHL can be found in a recent editorial[1]. These transcription factors regulate proteins that lead to adaptation to tissue hypoxia. When oxygen is abundant, VHL degrades HIF. Lesser amounts of HIF downregulate angiogenesis and tumor growth.



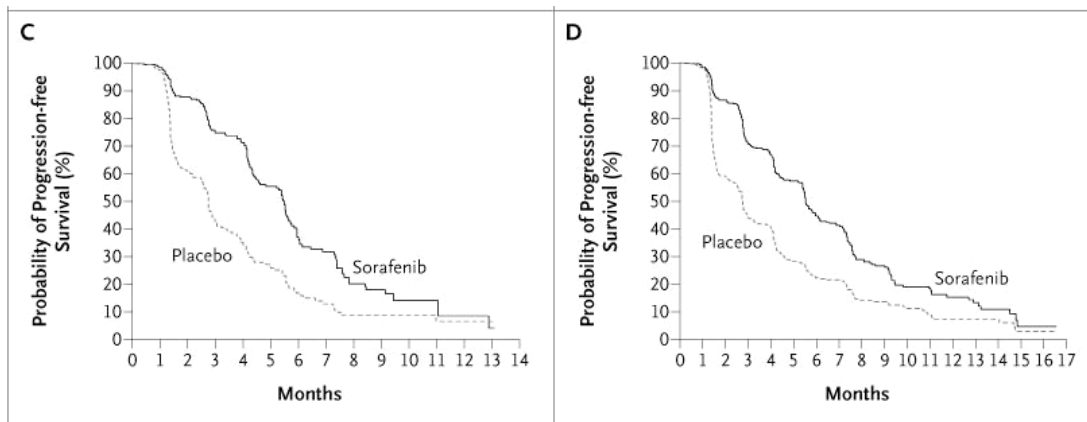
Malignant cells that lack VHL inappropriately cause an accumulation of HIF, despite normal oxygen tensions. In these VHL tumors, the malignant cells participate in angiogenesis pathways that perpetuate tumor growth. The inactivation of VHL causes a greater expression of angiogenesis factors; vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor (TGF).



Radiologists have always recognized the vascular nature of clear cell renal carcinoma. This tumor has hypervascularity that is characteristic by angiographic criteria such that the need for a diagnostic biopsy is almost unnecessary. When biopsies are performed, radiologists anticipate that blood will exit from the needle, once the obturator is removed, in a manner similar to cannulation of a blood vessel.



Sorafenib binds to the same receptors and similarly affects tyrosine kinase expression. The graphs below are taken from the recent report wherein sorafenib was compared to placebo[3].



Both molecular drugs provide new opportunities for patients with renal cell carcinoma. Unfortunately, a reasonable degree of toxicity accompanies these drugs, primarily with fatigue and diarrhea. In addition, tumor resistance to these agents is already being seen. However, other molecular drugs that affect the VHL-HIF-angiogenesis pathway are already on the testing platforms. It is hoped that some of them will have an improved therapeutic ratio.

Certainly, having a new treatment modality for renal carcinoma is exciting. However, more importantly, can this concept be used in other hypervascular tumors? – inflammatory breast carcinoma? – angiosarcoma? – Kaposi sarcoma? – etc.? The von Hippel Lindau syndrome describes vascular tumors (benign and malignant); perhaps, there are acquired abnormalities of the VHL and HIF that are present in other malignancies such that the same principles of treatment can be applied? Regardless, an important conclusion of the recent reports of sunitinib and sorafenib in renal cell carcinoma is the documentation that genetically derived (VHL) abnormalities is responsible for angiogenesis and tumor growth and that they can be downregulated. This is an important proof of theory that explain the original observations made by von Hippel and Lindau on vascular growths.

Yes, VHL has reappeared on the scene – at least it has reappeared for me!

Keywords: *VHL, von Hippel Lindau, VEGF, VEGFR, PDGF, PDGFR, renal cell carcinoma, angiogenesis, sunitinib, sorafenib, immunotherapy, molecular therapy, tyrosine kinase.*

References:

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