

CONTENTS

Taking a Closer Look

BY KAREN PATTERSON

Just as one push can cause a row of dominoes to topple, mutation of a single gene—the von Hippel-Lindau, or VHL, gene—can launch a series of biochemical interactions that lead to the development of clear-cell renal cell carcinomas.

Understanding these interactions has allowed researchers to develop medicines that target the process at specific points, slowing or stopping cancer's growth much in the way that moving one domino in a series can affect how the rest will fall.

VHL gene mutations are responsible for a hereditary syndrome known as von Hippel-Lindau syndrome, which occurs in about one in 36,000 births and greatly raises risk for kidney cancer as well as a variety of cysts or other tumors, including blood vessel tumors of the brain, spinal cord, and retina. (Genetic testing is warranted for people who develop more than one of the hallmark VHL tumors or cysts, and/or have VHL syndrome in the family.)

But VHL mutations don't need to be inherited to cause kidney cancer. They can arise spontaneously—and in total account for between 50 and 70 percent of patients with clear-cell renal cancers, notes Michael Atkins, MD, of Beth Israel Deaconess Medical Center.

“Mutations in the VHL gene create a situation where the tumor feels like it's hypoxic—it doesn't have enough oxygen—even when it's not hypoxic,” he says. Levels of a specific form of a protein known as hypoxia-inducible factor 1 alpha (HIF-1 alpha) rise, a situation that has biological and potential therapeutic consequences—that is, other dominoes that can be targeted.

Among those dominoes regulated by HIF-1 alpha are the vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) genes. The VEGF gene, for instance, orchestrates production of proteins whose interactions on the cell surface appear to play a role in angiogenesis—the development of blood vessels that supply a tumor with oxygen and nutrients. Interfering with VEGF or PDGF “puts those tumors under stress and forces them to die, or to come up with another way of surviving,” Atkins says.

Researchers have found two ways to target VEGF. One, the antibody Avastin (bevacizumab), binds to VEGF on the cell surface. Another strategy uses drugs such as Nexavar (sorafenib) and Sutent (sunitinib) to block the action of proteins called tyrosine kinases, which are receptors for VEGF and PDGF on the cell surface that mediate their actions.

Beyond VEGF are other dominoes, including a biochemical process called the

mTOR pathway. Medicines impacting mTOR appear to work in two ways. One involves targeting cancer cells, slowing the growth of tumors otherwise apt to progress rapidly. Another might involve a domino early in the series—HIF—with mTOR inhibitors such as Torisel (temsirolimus) apparently affecting formation of tumor blood vessels, especially yielding benefits among patients who have poor prognosis features. However, research is still sorting out exactly which patients are most likely to benefit from these drugs, Atkins says.