

Bringing Down Cancer's House of Cards

Defining an elaborate yet fragile control pathway offers a new strategy for toppling many cancers.

CANCER CELLS ARE TOUGH, INSIDIOUS SURVIVORS. They deftly use their aberrant genes to subvert normal cellular controls and trigger explosive, often lethal, growth. Given this impressive proficiency, researchers don't expect to discover weaknesses in cancer cells' malignant strategy.

However, HHMI investigator Michael R. Green and his colleagues at the University of Massachusetts Medical School have uncovered just such a weakness—one they hope is fatal for cancer cells. They have found that a major cancer-promoting gene, *ras*, relies on a complex, and gratifyingly vulnerable, “house-of-cards” control pathway to enable tumor cell survival.

This pathway is so precarious that removing just one component could bring cancer cells collapsing down to their death, the scientists have learned. The elaborate pathway depends on more than half a deck of molecular cards—the proteins produced by 28 genes. Thus, it presents cancer researchers many targets for cancer-killing drugs. And because *ras* is involved in about 30 percent of human cancers, discovery of the house-of-cards pathway could lead to treatments for more than one type of cancer.

In experiments published in the October 25, 2007, issue of *Nature*, Green and his colleagues reported their dissection of one of *ras*'s premier talents: its ability to switch off the cell's self-destruct mechanism, called apoptosis. This process rids the body of damaged or unneeded cells.

Specifically, Green wanted to understand how *ras* silences a gene called *Fas*, one of the cell's master kill-switches. *Fas* is a tumor suppressor gene, poised to trigger apoptosis. It is held in check only because its activating region is shrouded in molecules called methyl groups. Such control is called *epigenetic* because it involves modifying the protective packaging that surrounds genes within chromosomes. This modification can regulate whether the genes are switched on or silenced. Epigenetic control is

distinct from *genetic* control, which uses regulatory switches embedded in the DNA sequence of the genes. Specifically, in this case, *ras* silences *Fas* by recruiting other molecules to smother it in methyl groups, a state called “hypermethylation.”

Researchers had advanced two theories about the mechanism by which such silencing takes place: The “random” theory held that addition of methyl groups is random and that the resulting cells have a growth advantage that enables them to proliferate. By contrast, the “instructive” theory held that *ras* uses a specific mechanism to epigenetically silence the tumor suppressor gene.

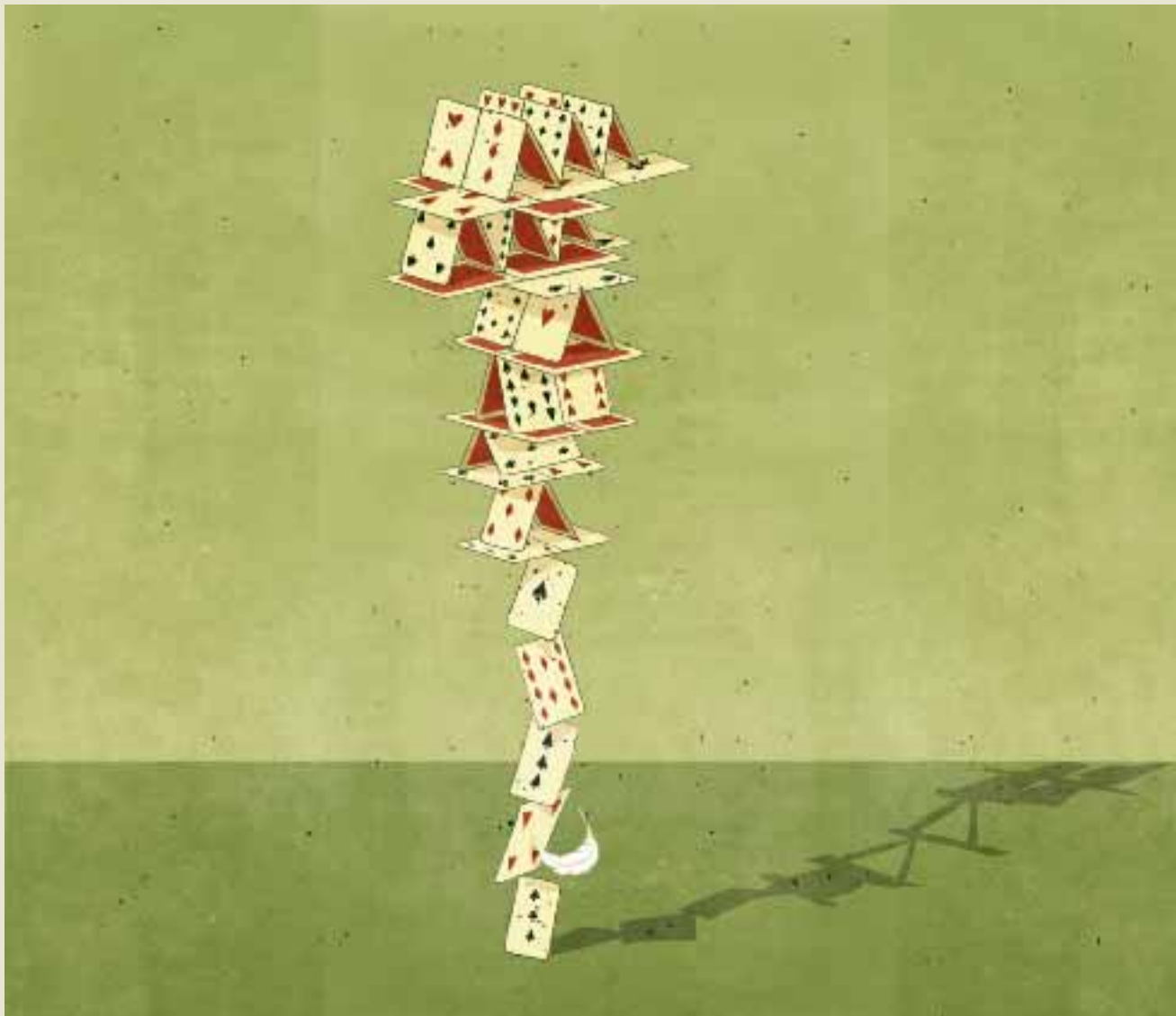
“The existing literature was equally compatible with either of those two models,” says Green. “So, we decided to do an unbiased test to determine which of these two models was correct.”

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MICHAEL GREEN

That test consisted of a mass screening using mouse cells engineered to have a mutated *ras* that was abnormally activated to silence *Fas*. One by one, the researchers switched off each of 28,000 genes in the mutant mouse cells. They were looking for any genes that, when switched off, blocked *ras*'s silencing mechanism, freeing *Fas* to do its work. The screening identified 28 genes that were necessary for *ras* to silence *Fas*. The proteins encoded by these genes compose a pathway responsible for regulating a chain of events, beginning at the cell surface, where *ras* works, and leading into the nucleus, where *Fas* is silenced.

“The most surprising thing was the complexity of this pathway and its apparent nonredundancy,” says Green. “I might have predicted that an instructive pathway such as this



would consist of a handful of genes, but certainly not twenty-eight components.”

Besides studying *Fas* silencing, the researchers also tested whether *ras* used the same house-of-cards pathway to silence other genes known to be suppressed in cancer cells. They found that most of the 28 genes were critical for *ras* to silence each of the five other genes tested. This broad dependence on the house-of-cards pathway means that drugs that target the pathway might well cut a wide, lethal swath through the aberrant machinery of *ras*-driven cancers.

Having found that the pathway was integral for *ras*'s ability to silence genes, the researchers then asked whether any of the components were also required for *ras* to cause cancer.

The team found that removing any one of several components abolished the ability of *ras* to induce tumor growth in mice. These results demonstrated that taking out a single participant in the house-of-cards pathway could bring down *ras*'s ability to cause cancer. The findings have important therapeutic implications.

“We are not very good at curing cancer,” Green says. “Chemotherapeutic drugs currently in use are toxic to all dividing cells, which means that they have very broad side effects. Inhibitors of *ras*-mediated epigenetic silencing—which cause changes only within cancer cells—could represent important progress toward targeted therapies.” ■

—DENNIS MEREDITH