THE FRAGILE TUMOR

New Insights Into Oncogene Addiction Found

By Ken Garber

A mystery surrounds targeted anticancer drugs like trastuzumab (Herceptin), imatinib (Gleevec), and erlotinib (Tarceva), agents that block the specific signaling pathways thought to drive cancer cell proliferation. For all the molecular sophistication of these new drugs, we know little about why and how they actually work without greatly harming patients. The targets of these drugs are present and active in normal cells as well as tumor cells. So why do targeted drugs kill cancer cells without massive toxic effects?

The answer may lie in the study of oncogene addiction, a relatively new area of cancer research. I. Bernard Weinstein, M.D., of Columbia University, conceived the theory of addiction in 1997, after he observed that only partially blocking cyclin D1 (a protein required for cell division) was enough to arrest the growth of cancer cells overexpressing the protein. “These particular cancer cells needed a very high level of oncogene to survive,” Weinstein recalled. “In that sense they were addicted.”

Oncogene addiction is the dependence of a cancer cell on one overactive gene or pathway for the cell’s survival and growth. Over the last decade, researchers have accumulated evidence for oncogene addiction, and they are now teasing out exactly how such addiction takes place—and how tumors might escape it. The findings may directly affect how targeted therapies will be used to treat human cancers.

Evidence for Addiction

Oncogene addiction remains controversial because cancer cells don’t seem likely candidates to get hooked on one gene. For example, Weinstein’s 1997 cyclin D1—overexpressing esophageal cancer cells stopped growing after a cyclin D1 blockade, despite harboring many other genetic and epigenetic abnormalities. Conventional wisdom holds that so much has gone awry in cancer cells—and so many growth pathways are activated—that hitting only one gene shouldn’t affect it much. But, in these experiments, hitting one oncogene worked.

“It seems to take all these [transforming] events to get a fully malignant tumor,” Weinstein observed. “It is remarkable that in some cases reversing only one of these events can have a strong inhibitory effect.”

Oncogene addiction has also been demonstrated in mice. Beginning in 1999, several labs reported that tumors in transgenic mice were addicted to a range of oncogenes. “That really provided a proof of principle” for oncogene addiction, said Dean Felsher, M.D., Ph.D., of Stanford University in Palo Alto, Calif. “And I think people believe it because of Gleevec [imatinib].” The effectiveness of imatinib, which targets the bcr–abl fusion protein in chronic myelogenous leukemia (CML), implies that leukemia cells are addicted to the abl oncogene.

Stronger evidence for addiction comes from imatinib’s effectiveness targeting the c-kit oncogene in gastrointestinal stromal tumors, which, unlike CML, is a cancer with multiple genetic abnormalities. Yet hitting just c-kit is enough to shrink or eradicate the tumors. Other targeted agents presumably work by exploiting oncogene addiction. These include gefitinib and erlotinib, which target the epidermal growth factor receptor in lung cancer, and sorafenib, which targets B-raf in kidney cancer and melanoma.

Evidence for oncogene addiction in humans remains circumstantial, since directly tracking a tumor’s dependence on individual signaling pathways is difficult. “At one extreme I’ve heard people say that the whole concept is meaningless, because you can’t even define it,” said Harvard University’s William Kaelin, M.D. But Kaelin offers this definition: “If you either introduce an activated oncogene, or you treat the cells with an inhibitor of that oncogene, they’re happy. But if you first come in with the activated oncogene, and then come in with an inhibitor, now the cells die.” Paradoxically, an inhibitor works only when the oncogene is abnormally active. This is the essence of oncogene addiction.

Even short-term inactivation of the oncogene, in transgenic mice, seems enough to stop tumor growth. “Cancers are absolutely, exquisitely dependent on certain oncogenic events,” Felsher said. “When you suddenly remove those events, they’re not able to maintain their cancerous state. So the cancerous state is much, much more fragile than people thought.”

Getting Hooked

Many cancer researchers now accept that oncogene addiction is real, and they are focusing on how it happens. They have proposed several mechanisms for oncogene addiction. One postulates that several signaling pathways are initially driving a cancer cell’s growth, with one activated oncogene dominant. But over time the other pathways are lost, since there’s no selection pressure to maintain them. One problem with this model is the time required for the secondary signaling pathways to wither. “In some [situations] oncogene addiction happens extremely rapidly,” Kaelin noted.

Other models use complexity to explain addiction. Weinstein views the cancer cell as harboring so many genetic changes during the many stages of malignant development that it’s vulnerable to the stress caused by one perturbation. “The circuitry of the cancer cell is screwed up,” he said. Entering that circuit and turning off a critical gene, he said, will therefore have a different effect in cancer cells from that in normal cells. This explanation, however, falls short of explaining exactly what kills the cancer cell.
Felsher and Michael Bishop, M.D., have proposed that an activated oncogene can keep the cancer cell from recognizing its own gross abnormalities. For example, an oncogene might interfere with the cell’s DNA damage response. (Felsher and Bishop showed that this prediction is true for the myc oncogene.) An oncogene “causes a cell to exist in this perverse biologic state,” Felsher explained. “And when you turn off that oncogene, the cell is actually able to recognize that it’s disrupted … that’s part of the reason why it forces itself to arrest and, in some cases, differentiate, and in other cases, die.”

Two recent reports offer models that more deeply explore the mechanism of oncogene addiction. In the November issue of Cancer Cell, Jeffrey Settleman, Ph.D., of Harvard University, proposed that the different rates of decay of proliferative and death signals emanating from the same oncogene lead to the cell’s death when the oncogene is blocked. Many earlier studies had shown that a variety of oncogenes, paradoxically, send out signals for death as well as for growth. Settleman showed, in a variety of cell lines, that the death signal appears to last longer than the proliferative signal when the oncogene is inhibited, thus providing a “time window” in which the balance between survival and death in the cell shifts toward death.

“The prosurvival signal decays very rapidly, whereas the proapoptotic [prodeath] signals can linger for a longer period,” Settleman explained. “That leads to an imbalance in signaling.” Settleman calls his model “oncogenic shock” because signals from the oncogene itself, rather than some passive process, lead to cell death.

Normal cells don’t die from oncogenic shock, possibly because their oncogenes aren’t turned on at a high level. So they “just do not put out that much apoptotic signaling,” Settleman speculated. “You do not get that acute burst of activity when you disrupt survival signaling in those cells. So it could be just as simple as that.”

**Addicted Environment**

None of these models include the altered environment that provides a tumor with blood supply, growth factors, and tissue remodeling factors, allowing it to spread. Oncogene addiction models should take this into account, Felsher said. “There are probably two major [addiction] processes: things that happen within the tumor cell and things that happen in response to the environment.”

In an October 21 Proceedings of the National Academy of Sciences report, Felsher and Judah Folkman, M.D., of Harvard, argued that angiogenesis—creating new blood vessels—is an essential component of oncogene addiction. Together with Harvard colleague Sandra Ryeom, Ph.D., they showed that tumors in transgenic mice regressed when the myc oncogene was turned off, and this regression involved the collapse of surrounding blood vessels caused by release of a potent antiangiogenic factor. But when the p53 tumor suppressor gene (involved in inducing the antiangiogenic factor) was lost, the tumors thrived.

Oncogene addiction, Felsher concluded, depends on events both inside and outside the cell. When it’s blocked, “… it’s not just that the tumor cells say, ‘We don’t belong; we were misbehaving; we’re reformed citizens; we should kill ourselves,’” he said. “But they also send a signal to the environment: ‘We don’t belong.’”

None of the models yet proposed prove addiction, because demonstrating what happens when you treat a human tumor with a drug is hard. Several of them may be valid. “It’s unlikely there will be one explanation,” Felsher said. “The gene you’re talking about will influence the explanation. The type of tumor will influence the explanation.”

**Treating the Addiction**

The biggest knock against the addiction hypothesis is clinical reality. No patient with a metastatic epithelial tumor is cured with one drug. Two factors probably contribute to this failure: oncogenic escape and tumor heterogeneity. Oncogenic escape is the theoretical ability of tumors to mutate around their addiction. “A potential limitation of exploiting oncogene addiction is genomic instability, the likelihood that tumors can evolve to a new state of circuitry that no longer requires the oncogene in question,” Weinstein said. He added that combination drug therapy will be necessary to eliminate most tumors. Several labs are actively investigating the mechanism of oncogene escape.

One hopeful sign is that CML cells, when treated with imatinib, do not seem to shift their dependence to a new signaling pathway to avoid the drug but instead mutate the abl oncogene to keep the drug from binding. The tumor remains addicted to abl and is still vulnerable to drugs that hit the target differently. This finding suggests that cancer cells often can’t easily shake their addiction. “The leukemia cells had a chance to develop a variant in which another pathway could take over, but they didn’t,” Weinstein said. “They were locked in.”

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Another potential pitfall is tumor heterogeneity—the possibility that each person’s tumor is addicted to a different oncogene or pathway. This obstacle would make treatment decisions difficult—if not impossible—since drugs do not yet exist targeting each of the more than 100 known oncogenes. In the October 13 issue of *Science*, researchers at Johns Hopkins University reported unexpectedly large genetic differences between individual colorectal and breast cancer tumors. Although the researchers estimated that an average of 14 mutant genes contribute to colorectal cancer, no cancer had more than six mutant genes in common with any other. “Each cancer specimen of a given tumor type carried its own distinct [cancer] gene mutational signature,” the researchers reported.

If every individual’s cancer harbors a different addiction, treatment becomes a nightmare. “You almost have to have designer drugs, because any given breast cancer is going to be driven by very different mutations,” Kaelin said. This supposition isn’t yet known, because the Hopkins study did not identify the active tumor growth pathways. “I hope, at the end of the day, that we have for every common tumor a short list of oncogenes that are frequently altered, frequently enough that there are … drugs available to inhibit them,” Kaelin said.

Oncogene addiction so far is mostly a laboratory phenomenon. Whether most human tumors are oncogene addicts remains unknown, despite the isolated successes of targeted therapies. “Molecular targeting relies on the assumption that amidst all the chaos in the tumor, there [are] one or a few molecular targets that are very critical,” Weinstein said. For most tumors, this assumption remains unproven, because oncogene addiction may be present only in a minority. Are the animal models too simple, and will the complexity of most human tumors foil strategies to target addiction? “I don’t know,” said Felsher. “We’re really eager to try to understand the answer to that question.”