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Targeting oncogenes

Laurie Goodman

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News

Cancers are formed through a whole series of genetic alterations. It is for this reason that the results of recent studies were unexpected (1– 3). These reports showed that a single change to the myriad alterations in a tumor, inactivating the Myc oncogene, resulted not only in inhibition of tumor growth but also in tumor regression. Dean Felsher, assistant professor at Stanford University, and colleagues have carried out much of this work. They have generated transgenic mice that conditionally express the Myc oncogene in a cell-specific manner. In addition, Myc expression can be blocked when mice are treated with doxycycline. When Myc is expressed, tumors form in the specific tissue or organ that the researchers have targeted for their investigation, e.g., epithelial tissue, connective tissue, liver, or lymphocytes. Felsher told the JCI, “We purposely targeted all the different tumor types — epithelial, sarcomas, and hematopoietic — because we thought the rules would be different in each type. And they are.” A recent publication by Felsher and colleagues (4) shows that inactivation of Myc can cause regression of hepatocellular cancers in mice. While Felsher had hoped to see such […]

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Dean Felsher, assistant professor at Stanford University, and colleagues have carried out much of this work. They have generated transgenic mice that conditionally express the *Myc* oncogene in a cell-specific manner. In addition, *Myc* expression can be blocked when mice are treated with doxycycline. When *Myc* is expressed, tumors form in the specific tissue or organ that the researchers have targeted for their investigation, e.g., epithelial tissue, connective tissue, liver, or lymphocytes. Felsher told the *JCI*, "We purposely targeted all the different tumor types — epithelial, sarcomas, and hematopoietic — because we thought the rules would be different in each type. And they are."

A recent publication by Felsher and colleagues (4) shows that inactivation of *Myc* can cause regression of hepatocellular cancers in mice. While Felsher had hoped to see such regression, he stated, "I think of all the results we have, the liver results are the most spectacular in terms of them being most surprising."

Hepatocellular cancer is very refractory to treatment, making it one of the most deadly forms of cancer. Ultimately, patients with such cancers rely on liver transplantation for survival.

While Felsher and colleagues saw regression of the hepatocellular tumors when they blocked *Myc* expression, they also noted that these tumors differed in their frequency of relapse from other tumor types they had tested. Mice with lymphomas or sarcomas that were treated with doxycycline ultimately showed a relatively high percentage of tumor relapse. Liver cancers had an extremely low level of relapse. "We have had these mice on doxycycline for over a year," Felsher said, "and they have been fine. And this is with mice with really big tumor burdens, much bigger than the lymphomas, and we have only seen a couple of relapses. It is not at all what I have expected."

Felsher added that he and his colleagues see many differences in the way these distinct tumor types respond to *Myc* inactivation. "They all regress initially but a sign of their biological differences is how they regress. Of the three tumors, hematopoietic tumors have the quickest response, but the strongest relapse. In the liver, everything happens more slowly; the tumor mass takes days to weeks to regress, whereas in the lymphoma it's bang — it's gone."

Felsher told the *JCI* that the variations in response to *Myc* inactivation reflect the way the same tumors in humans respond to treatment. In hematopoietic tumors, "you treat a patient, and the tumor responds very quickly, but the relapse rate is high. With sarcomas, you can put people into remission for years after treatment."

Dean Felsher: "The fact that we saw regression in liver cancer is amazing."

Felsher does point out, however, that simply dividing tumors along cell type in terms of expected response to oncogene inactivation is, unfortunately, not quite so simple. Liver cancers are epithelial-based tumors as are breast cancers and, Felsher noted, "Lou Chodash has looked [at] breast cancer [tumors] and those relapse (5)."

While all of the tumors that Felsher and colleagues have tested so far regress upon *Myc* inactivation, they likewise all regrow once *Myc* expression resumes, which indicates that these cells are in a state of dormancy. Felsher and colleagues found that in the regressed hepatocellular cancers, the remaining tumor cells differentiated into hepatocytes and biliary cells that formed bile ducts. Yet these differentiated cells remained capable of regenerating tumors.

Felsher believes the cells that regenerate the tumors are likely to be the least differentiated of the original tumor cells. He explains that when he and his coworkers turn *Myc* off, "some [tumor cells] differentiate into hepatocytes, and some differentiate into hepatocyte stem cells. We think [the stem cells] are the ones that regenerate the tumor, but we have not proven that. We have to isolate the cells." Felsher and colleagues have been trying to do this, but it has proven extremely difficult. The hypothesis is well worth testing since a fair amount of recent work in other systems and laboratories likewise suggests that the stem cells that serve to regenerate different tissues may be the cells that develop into tumors.

In addition to carrying out further examination of the underlying mechanisms for the regrowth of tumors from their dormant state, at the 3rd Mouse Models of Hematopoietic Malignancies Workshop on Oct. 11–13, Felsher updated the attendees on the progress he and his colleagues have made in their studies of lymphoma in mice. He presented their latest molecular data along with information regarding some intriguing studies in which Felsher and his colleagues have begun testing the use of exogenous agents to inactivate the *Myc* oncogene, which appears to result in tumor regression. This work moves the field another step closer to making oncogenes a viable therapeutic target.

Felsher does note, however, that while the work is very promising, there remains a great deal more to do. In addition to more work being needed in order to understand the mechanisms of tumor relapse, he points out that "for treatment in humans, [researchers] will have to use a much more robust method to inhibit *Myc*. Tumor burden [in humans] is higher and human tumors tend to be more genetically complicated."

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