Several FDA-approved anti-cancer drugs induce stem cell tumors, perhaps thwarting therapy

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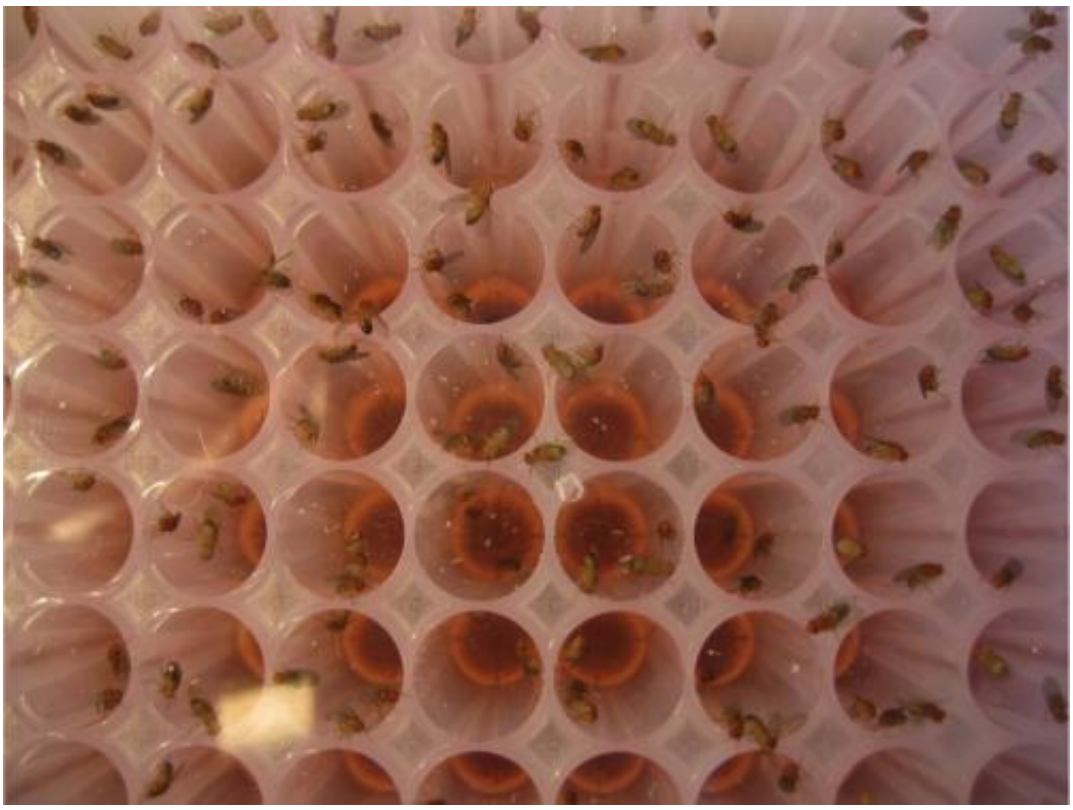

Drosophila intestines provide 'ready-made stem cell microenvironments' that are 'difficult-to-impossible' to create in petri dishes, offering an unconventional screen that allows researchers to test drugs in vivo. Credit: University of Massachusetts Amherst

Using a new approach to systematically test chemotherapy drugs in an unusual animal model, a research team led by University of Massachusetts Amherst molecular biologist Michele Markstein, with Norbert Perrimon at Harvard Medical School, report that several have a serious side effect: Inducing hyper proliferation in stem cells that could lead to tumor recurrence.

Markstein says, "We discovered that several chemotherapeutics that stop fast growing tumors have the opposite effect on stem cells in the same animal, causing them to divide too rapidly. This was a surprise, because it showed that the same drug could have opposite actions on cells in the same animal: Suppressing tumor growth on one cell population while initiating growth in another. Not only is the finding of clinical interest, but with this study we used an emerging new non-traditional tool for assessing drugs using stem cells in the fruit fly gut."

She adds, "We did these experiments in the fly because *Drosophila* stem cells, in the intestine, are very much like the stem cells in our intestine, and it's a lot easier to do experiments in flies than humans or even mice."

Further, Markstein explains, "When it comes to stem cells, it is important to conduct studies in living animals because stem cells are acutely attuned to the other cells in their microenvironment. Indeed the side effect that we observed is caused by damage that the chemotherapy drugs to cells in the stem cell microenvironment. The stem cells respond to this damage by hyper proliferating."

Markstein and Samantha Dettorre at UMass, with Perrimon and colleagues at Harvard Medical School, pioneered large-scale chemical screening in adult fruit flies that they feel will be useful for testing other chemicals. Conventional in vitro cell screens can identify drugs that act directly on stem cells, the authors note, but they cannot test and identify drugs that act on the all-important microenvironment, which provides

cues for stem cell division, differentiation, and death.

The flies provide "ready-made stem cell microenvironments" that are "difficult-to-impossible" to create in petri dishes, Markstein notes. Specifically, she and her colleagues inserted a human cancer-causing gene in the fly genome, turned on that gene in its intestinal stem cells, and found that it did form fast-growing tumors.

To take full advantage of *Drosophila*'s ready-made microenvironments, they developed new technology to determine the size of tumors inside each fly gut. The previous standard in the field was to dissect flies to visualize tumors, which are typically labeled green with green fluorescent protein. In the new method, the researchers decided to use a different label, an enzyme from fireflies called luciferase. This allows them to measure tumor size simply by crushing the flies en masse, rather than dissecting them one-by-one.

They asked the National Cancer Institute for chemotherapy drug samples and received a library of 88 currently in clinical use. After demonstrating that flies are sensitive to human chemotherapy drugs, they obtained a library of over 6,000 small molecules from the Harvard Institute of Chemistry and Cellular Biology, to screen for novel drugs. The screen identified new compounds, three of which are from Chinese medicinal extracts that can inhibit tumors without causing the side effect.

Markstein recalls, "We systematically fed the FDA-approved drugs to the flies and found that 14 suppressed tumor growth in the intestine. This was a great result, validating the relevance of flies as a clinical model. It was also very interesting, however, that we found that half these tumor-suppressing drugs had the opposite effect on the non-tumor stem cells, causing them to over-proliferate. This resulted in small growths or 'tumors,' that with the right genetic background could potentially become

cancerous."

These results in the fly may seem surprising. But recent work by others reported a similar effect of the drug doxorubicin in mice, Markstein points out. In mice, doxorubicin induced cells to overgrow by triggering the TNF-alpha pathway, but in flies several chemotherapy drugs including doxorubicin triggered a different pathway called JAK-STAT which has been conserved through evolution in both flies and humans. Both pathways trigger the inflammatory response, which is generally associated with cancer.

Overall, the authors conclude that screening in whole animals such as flies pays off, and is necessary to detect effects that involve more than one cell type. Indeed, Markstein argues that the impact of a chemotherapy drug on the stem cell microenvironment is just as important as its impact on the stem cell itself.

More information: Systematic screen of chemotherapeutics in Drosophila stem cell tumors, www.pnas.org/cgi/doi/10.1073/pnas.1401160111

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