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In journey from maggot to fruit fly, a clue about cancer metastasis

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Scientists trying to understand how cancer cells invade healthy tissue have used the fruit fly's metamorphosis from maggot to flying insect as a guide to identify a key molecular signal that may be involved in both processes.

The research by a team at the University of Rochester Medical Center, published as the cover article in the January issue of the journal *Developmental Cell*, identifies a molecule that is key for determining how cells invade and create new tissues. That process, which is what makes cancer so deadly, has proven very difficult for scientists to understand in enough depth to interrupt to stop the spread of cancer.

At a glance, the change from crawling maggot to flittering fruit fly seems a long way from the search for new treatments or cures for human health. But there are good reasons scientists study the fruit fly. Many processes in fruit flies are very similar to those in people, only simpler and thus much more approachable to the probing eyes of scientists. In the case of cancer, the action in fruit flies allows scientists to take a close look at molecular signals that may be involved in both development and disease.

"The principles that govern how organs are made in a fruit fly and in a person are more similar than most people ever believed," said Dirk Bohmann, Ph.D., professor of Biomedical Genetics and the leader of the team. "Many of the same signals that control the growth and organization of fruit fly organs control similar processes in people. If we can

understand such signaling in fruit flies, it will help us understand what is happening in people, to try to prevent or stop diseases like cancer in which such signaling process go astray.

"It's surprising, but fruit flies - which in nature actually never get cancer themselves - have taught us more about that disease than many other animals that do," added Bohmann, who is also a scientist at the James P. Wilmot Cancer Center.

The first author of the current work is graduate student Qiong Wang. Also contributing to the research was former post-doctoral associate Mirka Uhlirova, Ph.D., who is now a faculty member at the University of Cologne in Germany.

In the current work, the team looked at the development of the air sac in a fruit fly. The air sac is a crucial organ that connects the flight muscles to an air supply, allowing the wings to operate and the insect to fly. The air sac arises late in development, at the same time when the wings and the flight muscle are added to an organism that did not need such structures during its life as a maggot. That's why the growing air sac has to burrow its way through already-existing tissues, a process that requires a good amount of cellular choreography and exactly the kind of molecular trickery that cancer cells need themselves.

During metamorphosis from maggot to fruit fly, complex molecular signals govern the change from rudimentary structures in the maggot to the air sac in the fruit fly.

For scientists like Bohmann who study cancer, understanding how a maggot develops the air sac is an exploration into how some cells develop, dominate, and push out of the way existing tissue while creating a whole new structure. That's what happens in cancer, where cells from a tumor of the prostate, breast, lung or other organ push their way through

tissue and spread to other organs. The spread or metastasis of a tumor, not the first tumor itself, is usually what kills a patient.

"A maggot, of course, looks very different from a fruit fly. Generally when it becomes an adult, a maggot pretty much melts down all its material and starts over, building new cells and tissues. But not completely. A maggot has a rudimentary tubular structure that supplies oxygen, and that structure forms the basis for the air sac," said Bohmann.

"The formation of the air sac in a fruit fly is a great example of careful, planned invasive cell movement," added Bohmann. "It resembles, in many ways, the invasive growth carried out by a tumor in the body of a person with aggressive cancer. That's why we think that it's possible that cancer cells spread into healthy tissue by hijacking similar normal mechanisms of tissue growth."

Scientists have known that fibroblast growth factor or FGF plays an important role in directing tissues to migrate and grow through other tissues. FGF has a part in creating the air sac as well as other processes involving growth and spread of tissue.

Now Bohmann's team has identified a molecule that controls FGF. That important task falls to a protein known as a matrix metalloprotease or MMP. Scientists had known that this class of proteins has an important role directly clearing a path for one type of tissue to grow through another. MMPs play a role in a myriad of processes involved in tissue rearrangement, including the growth of lung, breast and kidney tissue.

Bohmann's team found that in the fruit fly, MMP2 controls FGF. While Bohmann says the involvement of an MMP in some aspects of invasive tissue growth has already been known, Bohmann's team found that the protein works by controlling FGF signaling, which is a surprise. If a

similar mechanism is at work in humans, scientists might be able to exploit it as a new way to knock out FGF, which contributes to many types of cancer.

Provided by University of Rochester