Researchers Isolate Protein Domain Linked to Tumor Progression

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(PhysOrg.com) -- When a promising cancer drug reached clinical trials in the 1990s, researchers were disappointed by the debilitating side effects that limited the trials. The drug inhibited a family of enzymes known as matrix metalloproteinases (MMPs). Now, researchers at Rensselaer Polytechnic Institute have shown that creating drugs that inactivate a different part of the MMP enzyme could have the capacity to target the tumor without the damaging side effects. Their findings, which hold promise for improved cancer therapies, were published Feb. 5 in the online Early Edition of the *Proceedings of the National Academy of Sciences (PNAS).*

“The failure of the clinical trials suggest that the proteinases were not only involved in the pathology of the disease, but also in maintaining the normal health of the patient,” said Andrea Page-McCaw, assistant professor of biology at Rensselaer and the corresponding author of the study. Page-McCaw and her colleagues, including senior research specialist Bernadette M. Glasheen and undergraduate biology student Aasish Kabra, set out to determine the functions of different parts of an MMP enzyme. These parts, known as domains, usually correlate to a specific protein function. Inactivating one domain within a protein can often have significant and unknown consequences.

To determine MMP domain function, the researchers used a simple model organism, the common fruit fly. Unlike mouse and other mammal models that have 24 or more different and semi-redundant MMPs, the fly model has only two. This substantially simplifies the problem of

understanding function of each domain, as there aren't so many other closely related proteins that can fill in if a domain on one is broken.

The researchers found that a domain known as the hemopexin domain was important for tissue invasion events. During tissue invasion, cells from one tissue invade into and usually move through another tissue, sometimes ending up in a completely different part of the body from where the tissue was formed. This pathway is similar to metastasis, where cancer cells spread from the original tumor to other sites in the body. Fly larvae missing the hemopexin domain of Mmp1 had highly distorted or absent head and wings. The growth of such body parts requires tissue invasion to move the cells to the right place in the animal. These abnormalities indicate that a hemopexin domain is needed for tissue invasion in fly development, and possibly in cancer metastasis, according to Page-McCaw.

The other primary domain in MMPs, the catalytic domain, is considered the business part of the enzyme, as it is where MMPs break up or destroy other proteins. The catalytic domain was extensively targeted by pharmaceutical companies in efforts to block MMP function in cancer. The researchers found that in flies, like in patients, blocking or removing the catalytic domain caused many different kinds of problems, beyond simply failures of tissue invasion. When the catalytic domain was removed, the larvae could not grow normally because they were unable to make necessary and basic developmental changes in their exoskeletons. The findings shed light on why inhibiting the catalytic domain in the drug trials would have both the favorable impact of stopping tissue invasion and unfavorable impact of significant side effects. In the future, inhibiting only the hemopexin domain could be a method to inhibit tissue invasion without inhibiting all other necessary MMP functions, Page-McCaw said.

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