Cell movement provides clues to aggressive breast cancer

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Researchers from the University of Michigan Comprehensive Cancer Center have identified a specific molecule that alters how breast cancer cells move. This affects the cells' ability to spread or metastasize to distant parts of the body, the hallmark of deadly, aggressive cancer.

By looking at cells in the lab, in mice and in human tissue, as well as developing a mathematical model to predict cell movement, researchers found that the p38-gamma molecule controlled how quickly and easily a cancer cell moved. When p38-gamma was inactivated, cells flattened out and changed from fast motion to an ineffective movement.

"Normal motion is commonly seen in aggressive cancers, which is why it's very important to understand what the key switches are for this motion," says lead study author Sofia Merajver, M.D., Ph.D., scientific director of the breast oncology program at the U-M Comprehensive Cancer Center.

Results of the study appear online in Cancer Research.

Merajver's previous work found that the cancer gene RhoC promotes aggressive metastasis. In this research, her team followed the pathway back to see what controls the cells to make them so aggressive. They identified the p38 molecule, which has several different types, and found in particular p38-gamma is highly expressed in aggressive breast cancer.

The researchers modified the cells so that they inhibited p38-gamma in

cell cultures and discovered the changes in shape and motion. Collaborators in the U-M College of Engineering, Ellen M. Arruda, Krishna Garikipati and their team, then developed a mathematical model to show how these changes would impact cell motion. The model predicted exactly what the researchers observed in the cell cultures.

"This gives us a more complete understanding of how aggressive breast cancer cells move and the influence of p38-gamma in particular on modifying this motion," says Merajver, professor of internal medicine at the U-M Medical School. "Cell movement is very difficult to observe, which is why mathematical modeling in oncology is valuable."

Merajver hopes this model, which can be applied to other cancer types, will improve understanding of how cells move, allowing researchers to plan better experiments to look at this function.

Identifying p38-gamma's role in breast cancer provides a strong target for potential new therapies, the researchers say. They believe it will be possible to develop a drug that targets only p38-gamma without affecting other pathways, which would make it more tolerable for patients.

"We do have targeted therapies in the clinic, but the total burden of disease that they ameliorate is still relatively minimal. The reasons may not necessarily be that they are not good drugs, but simply that we don't understand how they work, because we don't understand the biology in sufficient detail. That's why studies like this are so important in advancing drug development," Merajver says.

More information: "p38-gamma Promotes Breast Cancer Cell Motility and Metastasis through Regulation of RhoC GTPase, Cytoskeletal Architecture, and a Novel Leading Edge Behavior", *Cancer Research*, DOI: 10.1158/0008-5472.CAN-11-1291

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