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Signaling between protein, growth factor is critical for coordinated cell migration

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The mysterious process that orchestrates cells to move in unison to form human and animal embryos, heal wounds, and even spread cancer depends on interaction between two well-known genetic signaling pathways, two University of Utah medical school researchers have discovered.

The study by Tatjana Piotrowski, Ph.D., assistant professor of neurobiology and anatomy, and doctoral student Andy Aman sheds new light on how the migration of groups of cells is coordinated and is the first to show a functional link between the Wnt and Fgf growth factor signaling pathways in a live animal model (zebrafish). The findings may give clues to how cancer metastasizes or spreads when cancerous cells move to different areas of the body.

Cell migration, though central to the development and maintenance of multicellular organisms, is not well understood, particularly in vivo or in live models. Researchers already knew the Wnt pathway has a role in embryogenesis and cancer by regulating cell-to-cell communication and that the Fgf pathway influences embryogenesis, wound healing, and cell proliferation. But Piotrowski's and Aman's study, published in the Nov. 11 issue of *Developmental Cell*, is the first to demonstrate that interaction between the two pathways is critical for proper collective cell migration.

"We looked at the question of how cells in the tip and the tail of a group of migrating cells communicate so that they move in a coordinated fashion," said Piotrowski, the paper's senior author.

To identify which genes are involved in collective cell migration, Piotrowski and Aman studied a group of migrating cells, called the lateral line primordium. During development the lateral line primordium migrates from the zebrafish head to the tail tip, periodically depositing sensory organs. The lateral line sensory system helps zebrafish and other aquatic vertebrates sense water movement.

Aman and Piotrowski discovered that both Wnt and Fgf pathway genes are activated.
But for proper migration, a cellular division of labor must take place: the Wnt pathway must be restricted to the primordium's tip and the Fgf pathway must be confined to the tail. If the Wnt pathway is not restricted to cells in the tip, a cellular receptor that normally senses guidance cues is turned off and primordium cells stall and tumble randomly instead of migrating directionally, according to the researchers.

To accomplish this division of labor, each pathway stimulates the production of molecular inhibitors that restrict Wnt and Fgf pathway signaling to the tip and tail, respectively. When the Fgf pathway is activated, inhibitors are produced that restrict Wnt pathway signaling to the primordium tip. Conversely, when the Wnt pathway is activated, inhibitors are produced that restrict the Fgf pathway to the tail, the researchers reported.

"Cells use many diverse molecules to communicate with one another and coordinate their behaviors," Piotrowski said. "This work makes a significant contribution to our understanding of how these diverse signaling molecules interact in intact animals and may provide insights into how defects in these interactions might lead to the progression of human disease."

While understanding the signaling between the Wnt and Fgf pathways can inform researchers about cell migration during development or in

the adult, it also has the potential to help them learn more about how some types of cancer spread, according to Piotrowski.

Breast and prostate cancer both invade tissue in groups of cells, for example, and several studies by other researchers indicate groups of cancer cells, like the zebrafish primordium, might be separated into compartments by the Wnt and Fgf pathways. Interestingly, a gene mutation found in 80 percent of colon cancer cases causes Wnt pathway activation in too many cells, raising the question whether defective cell migration is a cause in tumor development.

Thus, by learning more about how cells migrate during normal development, researchers can gain insight into the molecular mechanisms that contribute to metastasis and tumor development of breast and colon cancer.

"The same genes involved in lateral line cell migration can cause aberrant migration in cancer cells," Piotrowski said. "By understanding how lateral line cells migrate, we possibly can understand which genes are not properly regulated when cancer spreads."

Source: University of Utah