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Researchers explore link between human birth defect syndrome, cancer metastasis

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Some cells are natural rule-breakers. Neural crest cells for example, not only migrate throughout the body during development (most cells are more selective in their wandering), they are also more developmentally flexible than their predecessors (a no-no for nearly all cell types). Now researchers at the Stanford University School of Medicine have shown that a protein that controls DNA accessibility is responsible for the cells' unruly ways.

The finding not only offers a better understanding of the molecular basis of a spontaneous genetic disease in humans called CHARGE syndrome, it may also be important in understanding how cancer cells gain the ability to migrate, or metastasize.

"Most cells lose developmental potential as they differentiate," said Joanna Wysocka, PhD, assistant professor of developmental biology and of chemical and systems biology. "But neural crest cells are a spectacular example of migratory cells that are capable of becoming over 100 different cell types, including neurons, the bone and cartilage of the face, jaw and teeth, pigment cells and certain heart structures." Wysocka is the senior author of the research, which will be published online Feb. 3 in *Nature*.

Wysocka, who studies how chromatin modification affects development, became interested in the cells when it became apparent that mutations in a protein called CHD7 were responsible for CHARGE syndrome. The condition's name is an acronym for a constellation of associated birth

defects that affect about one in 10,000 children. Children with the disorder have a combination of craniofacial malformations; eye, ear and heart defects; and other abnormalities. The unusual combination of this wide array of symptoms led physicians and researchers to speculate that the problem arose early in development in the neural crest cells.

Most DNA in a cell is tightly wrapped around proteins and compacted into what is called chromatin. CHD7 belongs to a class of proteins called ATP-dependent chromatin remodelers, which orchestrate the movement of the DNA packing proteins to provide or restrict access to particular genes. Choosing which portions of DNA to expose and which to keep tightly bundled can control cell fate.

"This was fascinating to me because next to nothing is known about chromatin regulation in neural crest cells, which are multipotent by nature," said Wysocka, who is also a member of Stanford's Cancer Center. "And yet, CHD7's involvement in CHARGE indicated that this chromatin remodeler is a critical component of the proper migration and specialization of the neural crest."

The neural crest forms early in development (in humans, at three to five weeks of gestation) when a portion of the cells that will become the embryo folds inward into a tube that will become the brain and the spinal cord. Neural crest cells form at the seam of this tube and rapidly migrate throughout the body to form the bones and cartilage of the face; the neurons and glia of the peripheral nervous system; heart structures; a portion of the gut; and many other important components of the developing organism.

Ruchi Bajpai, PhD, a postdoctoral scholar in Wysocka's lab and first author of the study, coaxed human embryonic stem cells to become what resembles functional neural crest cells in a laboratory dish. These cells could become neurons and many other cell types derived from the neural

crest. When the researchers suppressed CHD7 expression, they saw that fewer neural crest cells formed and migrated across the surface of the dish.

For obvious ethical reasons, the researchers couldn't study the effect of tweaking CHD7 levels in human embryos. Because the problems occur so early in development, Wysocka and her colleagues turned to frog embryos to test how CHD7's activity affected neural crest cells in a living animal. Unlike mice, frog embryos develop outside of the body and can be easily monitored. Researchers found that blocking CHD7 expression or its activity in frog embryos interfered with the ability of the neural crest cells to migrate during development. What's more, the resultant tadpoles also exhibited many of the major clinical features of human CHARGE syndrome.

"This gave us confidence that we were on the right track," said Wysocka. "It's apparent that CHD7 is required for the reprogramming and migration of the neural crest cells, which is when one would predict major changes in chromatin organization would be taking place."

Further research showed that CHD7 works with another protein called PBAF to bind areas of DNA associated with, but far from, genes involved in neural crest cell specialization and migration. These so-called distal DNA elements control the expression of faraway genes. "It's a long-distance relationship," said Wysocka.

The finding may not only lead to a new understanding of CHD7's role in CHARGE syndrome, it also suggests that CHD7 and PBAF may be involved in the reprogramming and migration of other types of cells, such as cancer cells. Two genes controlled by CHD7 and PBAF — called Twist and Slug — have been implicated in metastasis in many human cancers.

"If we can cause a CHARGE syndrome in tadpoles simply by reducing CHD7 levels by twofold," said Wysocka, "it's possible that increases in CHD7 levels in cancer may significantly enhance the metastasis program. Interestingly, CHD7 duplications have been recently associated with small-cell lung cancer, one of the most highly metastatic and aggressive types of cancer. "

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