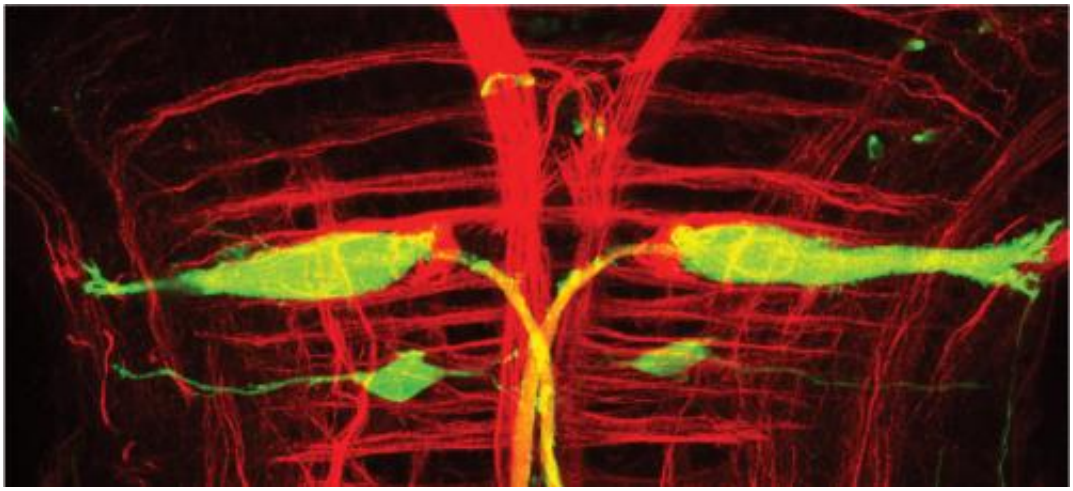
MedicalXpress

Genomewide screen of learning in zebrafish identifies enzyme important in neural circuit

March 23 2015



Zebrafish hindbrain stained with an axonal marker in red and PAPPA-expressing neurons (green). Credit: Michael Granato, PhD lab, Perelman School of Medicine, University of Pennsylvania

Researchers at the Perelman School of Medicine at the University of Pennsylvania describe the first set of genes important in learning in a zebrafish model in the journal *Neuron* this week. "Using an in-depth analysis of one of these genes, we have already revealed an important relevant signaling pathway," says senior author Michael Granato, PhD, a professor of Cell and Developmental Biology. "The proteins in this pathway could provide new insights into the development of novel pharmacological targets."

Over the last 20 years, zebrafish have become great models for studying development and disease. Like humans, zebrafish are vertebrates and over 80 percent of human genes bearing disease descriptions are also present in zebrafish. As such, this animal model has become increasingly popular to study human diseases such as cardiovascular conditions or tumor formation.

Zebrafish have also become an ideal model for studying vertebrate neuroscience and behavior. In fact, Granato developed the first high-throughput behavioral assays that measure learning and memory in fish. "Normal fish startle with changes in noise and light level by bending and swimming away from the annoying stimuli. They do eventually habituate and get used to the alterations in their environment," he explains. "However, fish mutants fail to habituate—they never get used to their surroundings and always flinch at the loud noises."

In nature, this startle response is important for avoiding predators, but is flexible in how the fish use it in different situations, notes first author Marc A. Wolman, PhD, a postdoctoral fellow in the Granato lab who is now an assistant professor at the University of Wisconsin. Past data from the Granato lab indicate that learning and memory defects are reversible with acute pharmacologic treatments and are therefore not hard-wired, as might be expected for a defect in the development of nerves. Habituation represents a fundamental form of learning, yet the underlying molecular genetic mechanisms are not well defined. In humans, deficits in habituation are associated with a variety of neuropsychiatric disorders, including schizophrenia, autism, Tourette's, and obsessive-compulsive disorder.

Years in the Making

To find these genetic needles in the chromosome haystack, the team started four years ago by introducing small, "point" mutations into the

zebrafish DNA. These are changes that affect only one or two DNA building blocks at a time. They then bred mutant fish for three generations to obtain fish whose genomes contain two copies of a mutant gene.

These mutants were then exposed to the startle response test. Using a camera and software to eliminate human observer bias, they recorded how the mutants reacted to a loud noise. Most fish larvae habituated and stopped reacting to the noise stimulus. Some of the mutants, did, however, fail to habituate and continued to respond to the noise.

A genome-wide genetic screen, coupled with whole genome sequencing, identified 14 different mutations in zebrafish that failed to habituate. One of these 14 contained a mutation in the vertebrate-specific gene pregnancy-associated plasma protein-aa (pappaa). This gene encodes an enzyme that cleaves other proteins and works outside the cell. It is known to increase the availability of the hormone IGF at the cell surface, thereby enhancing receptor signaling for the IGF pathway. (A role of the PAPPAA enzyme in or on neurons had not been described; however, IGF is known to be an important molecule in pathways that determine long-term memory.)

"At first we didn't think it was important in learning, but we found that pappaa is expressed by startle-circuit neurons," explains Granato. The team verified the involvement of the IGF pathway by rescuing mutant behavior to normal by adding an activator of downstream molecules that interact with the IGF receptor. Mutants that were treated this way, when put back in the startle test, reacted normally and habituated to the loud noise. Also, when the team used an inhibitor of the IGF receptor in normal zebrafish larvae, these fish showed the same behavior in the startle test as the pappaa mutants. This all indicates that the pappaa gene promotes learning by acutely and locally increasing IGF availability to the cell.

"Our experiments found the first functional gene set for habituation learning in a vertebrate and identify PAPPAA-regulated IGF signaling as a novel mechanism regulating this type of behavior," says Granato. "A mammal pappaa gene exists but its function is as yet unknown. In future studies we hope to capitalize on the identification of pappaa and the other 13 genes we isolated to identify pharmacological treatments that enhance learning and memory."

Provided by University of Pennsylvania School of Medicine

Citation: Genomewide screen of learning in zebrafish identifies enzyme important in neural circuit (2015, March 23) retrieved 3 May 2024 from https://medicalxpress.com/news/2015-03-genomewide-screen-zebrafish-enzyme-important.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.