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Study of planarian hormones may aid in understanding parasitic flatworms

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The new findings should allow researchers to target the reproductive capabilities of other flatworms, called Schistosomes, that parasitize humans and other animals. Credit: David Williams, Illinois State University

A study of peptide hormones in the brain of a seemingly primitive flatworm reveals the surprising complexity of its nervous system and opens up a new approach for combating a major parasitic disease, researchers report.

The study appears in the open-access journal PLoS Biology.

The planarian flatworm, Schmidtea mediterranea, is perhaps best known for its prodigious powers of regeneration. Cut it in half (lengthwise or crosswise) and each fragment will regrow its missing parts, including its brain. The planarian is of interest to those studying reproduction because it exists in sexual and asexual varieties. Asexual planaria reproduce by splitting into two pieces and then regenerating. Sexual planaria are hermaphroditic. Some planaria can even switch between the sexual and asexual forms.

The free-living planarian is also of interest because it is related to several parasitic flatworms. For example, flatworms of the genus Schistosoma parasitize more than 200 million people worldwide. Schistosome larvae can penetrate the skin and spread when a potential host comes into contact with contaminated water. Once inside a host, the worms mature, mate and produce thousands of eggs that damage internal organs.

"Schistosomiasis is one of the major neglected tropical diseases in the world," said University of Illinois cell and developmental biology professor and Howard Hughes Medical Institute investigator Phillip Newmark, who led the new study with post-doctoral fellow James Collins. "And a key to the pathology of the disease is the animal's amazing reproductive output."

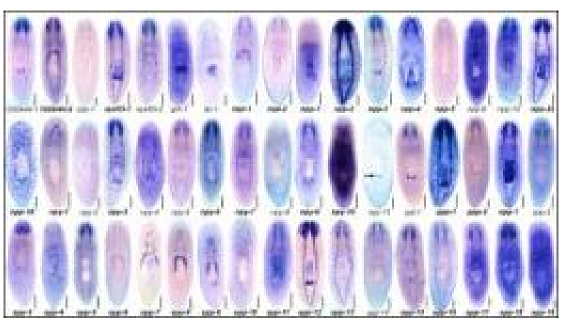
Previous studies suggested that signals from the nervous system play a role in planarian reproduction, but little research had been done to clarify that role.

"We've known for decades that neuropeptides are important for coordinating vertebrate reproduction," Collins said. "But it's not clear whether similar sorts of mechanisms exist for controlling invertebrate reproductive development."

Collins began by disrupting neuropeptide processing in sexually reproducing planaria, and noticed that this caused the animals' reproductive organs to revert to a developmentally primitive stage. This was strong evidence that neuropeptides could influence sexual development in planaria.

Neuropeptides are processed from longer molecules, called prohormones, and often are chemically modified before they become biologically active. Because neuropeptides are made up of only a few (typically between 3 and 40) amino acids, identifying the genes that code for them is a challenging task.

Collins worked with Illinois chemistry professor Jonathan Sweedler, as well as graduate student Xiaowen Hou and post-doctoral associate Elena Romanova, on the painstaking process of identifying prohormone genes in planaria. Using bioinformatics coupled with mass spectroscopy, the researchers identified 51 genes predicted to encode more than 200 peptides. Sweedler's lab worked out the biochemical properties of 142 of these using mass spectroscopy.



The researchers traced expression of 51 prohormone genes in different tissues throughout the planarian body. One of these genes, known as npy-8, appears to promote the development and maintenance of the worm's reproductive organs. Credit: Image courtesy of Jim Collins.

Collins then traced expression of 51 prohormone genes in different tissues throughout the planarian body. This analysis showed a unique pattern of expression for each gene (see image), with some expressed only in specific cells in the brain and other tissues.

"These peptides are showing us that the planarian brain is much more complicated than we had appreciated," Newmark said. "The fact that they can regenerate this brain seems even more amazing now that we know this."

To understand the potential function of the peptides, Collins used RNA interference to block the activity of specific prohormone genes in sexual and asexual planaria.

"We showed that there were different signatures in peptide hormone expression in asexual planarians that reproduce by fissioning, by tearing themselves in half, and by sexually reproducing planarians that are hermaphrodites and mate and lay eggs," Newmark said.

This comparison led to the discovery that one neuropeptide, in particular, profoundly influences the development and maintenance of the animal's reproductive system. When the researchers blocked expression of this neuropeptide, called npy-8, in mature sexual planaria, the worms' testes and other reproductive organs regressed. Blocking npy-8 in juvenile sexual planaria prevented their sexual organs from properly developing.

This last finding may point to a new approach for fighting parasitic flatworm infections, the researchers said. Thwarting the reproductive capabilities of a schistosome, for example, would likely be a very effective treatment.

"The planarian is a relatively innocuous animal that has relevance to a huge human health issue," Sweedler said.

The study also supports the use of planaria as a model organism, the researchers said. Its ability to regenerate, the ease with which it is grown in the lab, and the fact that it exists in sexual and asexual forms always has been of interest, Newmark said. But the newly appreciated complexity of its brain and the fact that it makes use of many of the signaling molecules that are essential in vertebrates also enhances its usefulness to science.

More information: "Genome-Wide Analyses Reveal a Role for Peptide Hormones in Planarian Germline Development," *PLoS Biology* 2010.

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