'Merlin' is a matchmaker, not a magician: The protein 'arranges' other protein interactions to control growth and preven

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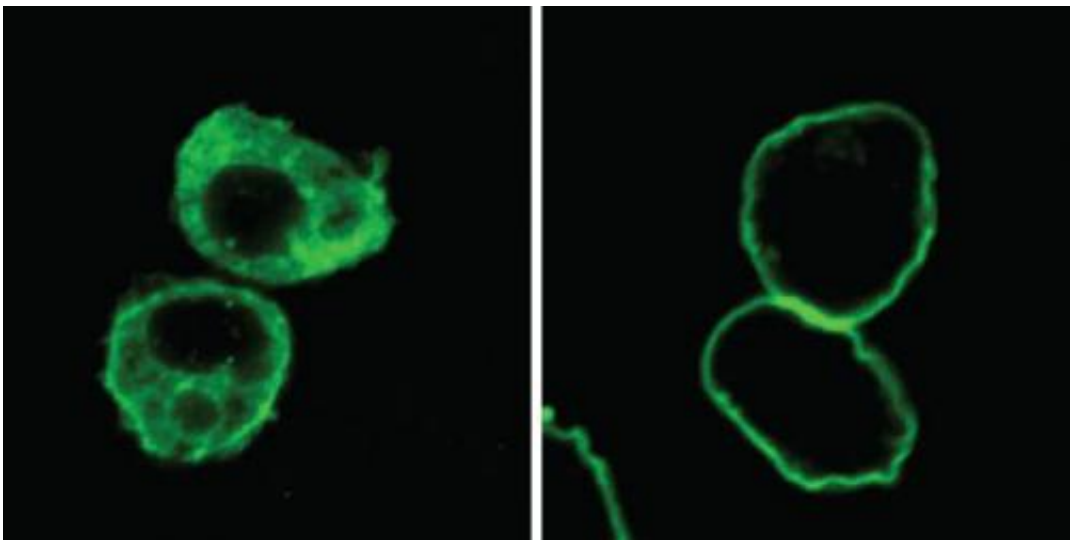

Without Merlin around, Warts (green) is located mostly in the watery interior of the cell (left). When Merlin is there, Warts is localized to the outer envelope of the cell, where Merlin resides (right). Credit: Duojia Pan, courtesy of Cell Press

Johns Hopkins researchers have figured out the specific job of a protein long implicated in tumors of the nervous system. Reporting on a new study described in the Sept. 12 issue of the journal *Cell*, they detail what they call the "matchmaking" activities of a fruit fly protein called Merlin, whose human counterpart, NF2, is a tumor suppressor protein known to cause neurofibromatosis type II when mutated.

Merlin (which stands for Moesin-Ezrin-Radixin-Like Protein) was already known to influence the function of another protein, dubbed Hippo, but the particulars of that relationship were unclear. "Now we've shown how Merlin and Hippo interact to begin a chain of events that controls the growth of many tissues," says Duojia Pan, Ph.D., professor of molecular biology and genetics at the Johns Hopkins University School of Medicine and a Howard Hughes Medical Institute investigator. "This insight is important because not only do malfunctions in that chain of events affect growth and development, they can also lead to cancer and other tumors."

Ten years ago, Pan and his research group discovered Hippo, a gene responsible for keeping body parts proportional to the overall size of the fruit fly. They called it Hippo because the absence of the gene, and the protein it codes for, causes fruit flies to develop unusually large and furrowed organs. Since then, they have been working to understand Hippo and all of the proteins in its network that help control organ size.

Previous work by others suggested that Merlin may be part of the Hippo network, but it was not known how Merlin fits into the network. In the new study, Pan and his team used a combination of genetics, cell biology and biochemistry to demonstrate that Merlin acts as a matchmaker, helping Hippo find its target protein, known as Warts, by keeping Warts in the right part of the cell.

Without Merlin around, inactive copies of Warts would float around in the watery interior of the cell while Hippo waited near the outer envelope of the cell. Merlin, also located near the outer envelope of the cell, arranges their meetings by connecting to Warts so that Warts, too, ends up near the outer envelope, where Hippo then turns it on. Experiments in human cells verified the same relationship between Merlin and Warts' human counterparts.

"The whole goal of Merlin is quite simple but important: It makes sure that Warts is close to Hippo," says Pan. "Without Merlin, Hippo can't find Warts and the flies end up with enlarged organs."

In humans, when Merlin's counterpart NF2 is not working properly, tumors can form, particularly those classified as neurofibromatosis type II. These noncancerous tumors put pressure on nerves in the brain and spinal cord, often resulting in loss of hearing or vision or other functions controlled by the affected nerves.

Because proteins in the Hippo network function similarly in flies and humans, the researchers say their work may lead one day to insights with important implications for human health, not just for those with neurofibromatosis type II but also for those with other types of tumors.

More information: Paper: dx.doi.org/10.1016/j.cell.2013.08.025

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