Tumor suppressor protein also helps establish body patterns in developing embryos

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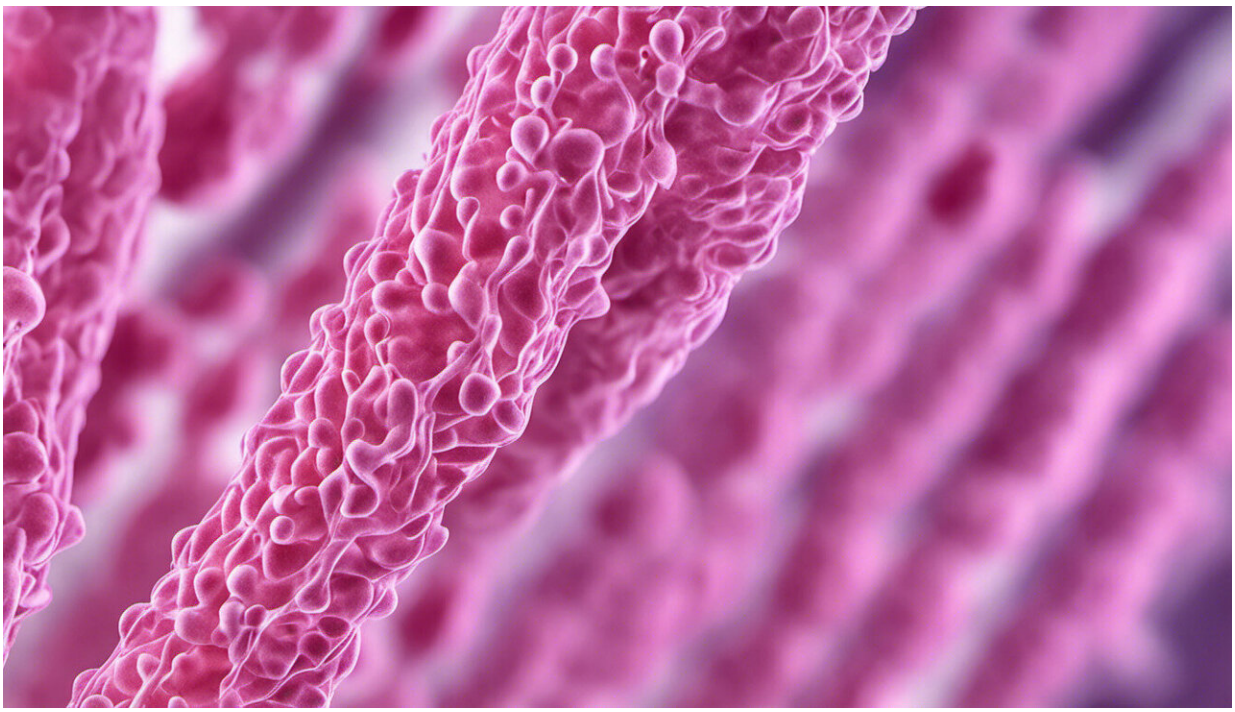

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Scientists first identified a gene called 'mutated in colorectal cancer' (Mcc) back in 1991, and yet many questions still remain about the gene's function in both cancer formation and normal tissue development. Using zebrafish as a model laboratory system, researchers from A*STAR have

now discovered that Mcc plays a critical role in the cellular alignment of the early embryo.

"Our work revealed how Mcc participates in the complex cellular movements that establish the vertebrate body plan in the zebrafish embryo," says Ray Dunn, a cell and developmental biologist at the A*STAR Institute of Medical Biology in Singapore who led the research.

The zebrafish (Danio rerio) is a powerful model system for the study of vertebrate development. The tropical freshwater minnow has small, transparent embryos that allow scientists to watch molecular processes in the laboratory in exquisite detail—all in real time.

Dunn and his colleagues thus decided to isolate and study the zebrafish version of the Mcc gene to better evaluate its expression and functions. Using a combination of bioinformatic and genetic techniques, they pinpointed the zebrafish Mcc gene near the end of chromosome 5. (Zebrafish have 25 chromosomes, two more than humans.) The researchers silenced the Mcc gene in developing zebrafish and observed multiple morphological defects in the embryos.

Several complex cellular rearrangements shape the primordial body plan during the gastrulation phase of development in all vertebrates, including humans. One crucial step involves the polarization of cells, which is coordinated by members of the Wnt signaling pathway. Through a series of detailed laboratory experiments, Dunn's team showed that, in the zebrafish embryos, the protein encoded by the Mcc gene acts downstream of various Wnt proteins to regulate the developmental process that narrows the fish body and elongates it from head to tail.

In one such experiment, for example, the researchers demonstrated that overexpression of the Mcc protein can reverse the developmental ills

caused by depletion of two Wnt proteins, Wnt5b and Vangl2. Furthermore, increased Mcc activity can overturn problems caused by the ablation of a Wnt5b receptor protein called Ror2. Biochemical studies also revealed a direct physical interaction between Mcc and a specific part of the Vangl2 protein. Dunn and his colleagues repeated many of the same experiments in the African clawed frog (Xenopus laevis) and observed similar expression patterns and molecular interactions.

"Our identification of Mcc as an intracellular component of non-canonical Wnt signaling is entirely novel and unexpected," Dunn says. The team's next step will be establishing a better understanding of Mcc's role in colorectal cancer and in hepatocellular carcinoma, a common form of liver cancer.

More information: Young, T., Poobalan, Y., Tan, E. K., Tao, S., Ong, S. et al. "The PDZ domain protein Mcc is a novel effector of non-canonical Wnt signaling during convergence and extension in zebrafish." *Development* 141, 3505–3516 (2014). dx.doi.org/10.1242/dev.114033

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