Why the thumb of the right hand is on the left hand side

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It is the concentration of a few signaling molecules that determines the fate of individual cells during the early development of organisms. In the renowned journal *Current Biology*, a team of molecular biologists led by Pia Aanstad of the University of Innsbruck reports that a variety of molecular mechanisms accounts for the interpretation of the concentration of the signaling molecule Hedgehog.

The development of an organism is a complex process to which a dozen or hundreds of signaling molecules contribute. Some of these molecules have dozens of functions in the fruit fly and in humans alike. One of these molecules - Hedgehog - controls the development of, for example, the extremities, the central nervous system, the teeth, eyes, hair, lung and the gastrointestinal tract.

"What is most remarkable: The cells are told what to do not only because the molecule is present but also by the different concentrations of the molecules in the tissue", says group leader Pia Aanstad of the Institute for Molecular Biology of the University of Innsbruck.

"The concentration of Hedgehog makes the thumb of the right hand grow on the left hand side and the thumb of the left hand grow on the right hand side."

Thus, scientists define Hedgehog as a morphogen - a signal that is concentration-dependent and controls the pattern formation of an organism. A mutation in this signaling pathway induces dramatic and

embryonically lethal malformations in the early developmental stage such as the formation of just one central eye. Defects in the Hedgehog signaling pathway in humans are a cause for one of the most common birth defects - holoprosencephaly.

"Hedgehog genes are not new in evolution and the signaling pathway functions in the fly, mouse, fish and in humans similarly", says Pia Aanstad. In her research work she focuses on the zebra danio or zebra fish. Due to the short developmental cycle, the scientists are able to observe the development of the small tropic fish in fast motion. "We want to better understand how the cells process the signals of the signaling molecules and how they react."

Mutants do not react to high concentrations

Already during her time as a post doc in San Francisco, U.S., Pia Aanstad discovered a mutated zebra fish whose Hedgehog signaling pathway was disrupted. The fish showed a genetic alteration at the so-called Smoothened (Smo) protein, which is located at the cell membrane and transfers the Hedgehog signal into the cell. In 2005, Aanstad and her colleagues published a paper in the renowned journal Nature, in which they showed that Smo is concentrated at cilia (cellular projections) and also functions at the cilium.

"By using high-resolution fluorescence microscopy, we have now shown that in the new mutants a small genetic alteration at the extracellular part of this protein inhibits localization in the cilia and that while the cells identify the Hedgehog signals, they interpret the concentration incorrectly", explains Pia Aanstad. "This is evidence for the notion that cells use various molecular mechanisms for interpreting different Hedgehog concentrations."

This fact may also be of importance for the diagnosis and treatment of

certain cancers (basal cell carcinoma), where the constant up-regulation of the Hedgehog signal is responsible for uncontrolled cell growth. Aanstad published the findings together with her colleagues from the University of California, San Francisco in the journal Current Biology.

Source: University of Innsbruck