Researchers describe how digits grow

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Researchers at the University of Wisconsin School of Medicine and Public Health (SMPH) are wagging a finger at currently held notions about the way digits are formed.

Studying the embryonic chick foot, the developmental biologists have come up with a model that explains how digits grow and why each digit is different from the others.

As reported in the *Proceedings of the National Academy of Sciences Online Early Edition* the week of March 10-14, 2008, the scientists found that the development and fate of each digit depends on a surprisingly dynamic process in unanticipated locations and involving unexpected players.

The UW-Madison team showed that growth begins in a portion of the developing digit they have named the phalanx-forming region (PFR). They illustrated that phalanges, structures that later become finger or toe bones, arise not from cartilage cells but from mesenchymal cells. And they discovered that a complex array of signals from a variety of genes at different times combine to form each phalanx.

Though the research was done on chick digits, it may have implications for humans born with a genetic condition known as bradydactyly, or stubby fingers and toes.

The work was undertaken in the laboratory of John Fallon, the Harland Winfield Mossman Professor of Anatomy at the SMPH, who for years

has sought to understand how cell fate is determined and patterning-of digits, teeth and feathers-is achieved during embryonic development.

In birds and mammals, digits arise in the mitten-shaped autopod, or developing foot, which consists of two alternating regions. The digital rays, made up of cartilage and mesenchyme, become the phalanges in the adult chicken's toes. These alternate with the interdigits, also consisting of mesenchymal tissue, which fill the space between the digit rays and eventually regress.

Scientists know that the gene Sonic Hedgehog (SHH) plays an important role in determining the form and number of digits, and many believe that other secondary signaling centers downstream of SHH also are involved in establishing a particular digit's identity.

In a 2000 paper published in Science, Fallon and graduate student Randall Dahn showed that the interdigit tissue was more important than previously thought. It was not just a spacer between developing digits; experimental manipulations showed that it controlled how the neighboring digit would develop. The team proposed that different signal levels in each interdigit resulted in specific digit identities.

"We thought that bone morphogenic protein (BMP) signals from interdigit cells were sent to the digit primordium, a rod of cartilage, in the neighboring digit ray, breaking up the cartilage into phalanges," Fallon says.

Sean Hasso, Fallon's current graduate student, wanted to know precisely which cells in the digital ray give rise to phalanges and which molecular events determine the number, size and shape of each phalanx. Performing microsurgery and cell marking studies on the embryonic chick autopod, Hasso showed that the cells that eventually form phalanges arise from the growth of mesenchyme at the tip of the digital

ray.

"This finding is absolutely contrary to what we and other scientists had been thinking-which was that growth and phalanx formation occurred in the cartilaginous rods in the digit primordia," says Fallon. "These observations were the foundation for further studies."

In the next set of experiments, Takayuki Suzuki, a post-doctoral fellow in the Fallon lab, conducted an in-depth examination of several aspects of genetic expression in the PFR. He observed that the up-regulation of a gene called Sox9 indicated that the cells of the PFR commit to becoming cartilage.

The scientists were most interested to see that these cells also up-regulated a BMP receptor. Suzuki devised an assay to quantitate BMP receptor signaling in the PFR cells. The assay showed that the signaling activity through the BMP receptor correlated with the digit that forms either normally or after experimental manipulation of the interdigit.

"Our studies showed that a specific region of mesenchymal cells in the digital ray receive the interdigital signal, and that BMP receptor signaling in this region plays a central role in the process," notes Fallon. "Changes in the levels of signaling lead to different developmental outcomes."

The research explains how improper signaling through specific BMP receptors may lead to malformations of phalanges, such as those seen in certain types of bradydactyly in humans.

"The molecular mechanisms controlling the formation of chicken and mammalian limbs, including those of humans, are similar," says Fallon. "We can learn a great deal about the causes of human malformations from studying these mechanisms in the developing chick."

Source: University of Wisconsin