NAIST® Research Highlights

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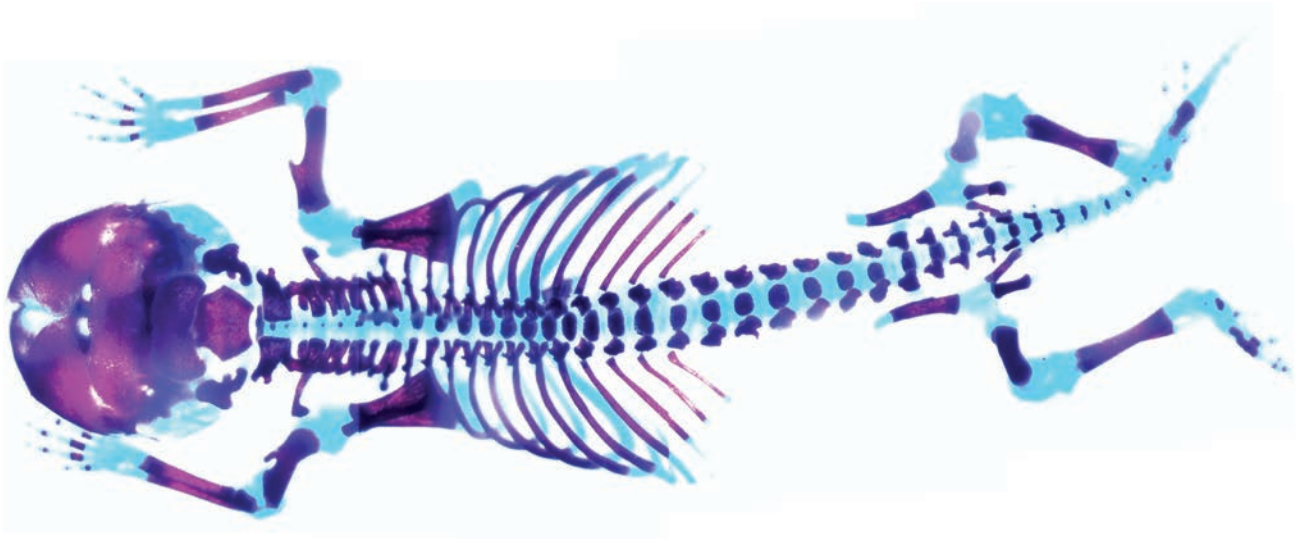

The axial skeleton of a newborn mouse.

Embryology

Signal loop sets vertebrae numbers

A signalling feedback loop regulates the molecular clock that controls the number of vertebrae in backbones

Researchers at NAIST are unravelling the regulatory mechanism determining the number of vertebrae formed in the embryo, a critical process in the development of back-boned animals.

Embryonic development in animals includes a carefully choreographed interaction between a moving chemical gradient and a ticking molecular clock to measure out segments (called somites) along the body's length. The segmentation clock involves oscillations in gene activity that regulate a principal cell-to-cell communication mechanism, known as the Notch signalling pathway, as well as Notch intracellular domain (NICD). By tuning these oscillations, each species develops a specific number of somites, determining how many vertebrae it has.

> **"I feel that the Nara Institute has an atmosphere in which we can wrestle with fundamental questions."**

To better understand this process, a team of researchers at NAIST and other institutes investigated the role of a negative Notch regulator, Nrarp. Since Notch controls the expression of Nrarp, the two form a feedback loop regulating NICD levels. The researchers studied mice lacking Nrarp to discover how this feedback loop regulates somite formation.

"Nrarp knock-out mice are almost normal, but they have small anomalies in their axial skeletons," says Yasumasa Bessho, from NAIST's Graduate School of Biological Sciences. In addition to these defects, the mutant mice have fewer vertebrae than normal. Measuring the segmentation clock showed that it ran slightly slower in the mutant mice, a decrease that was linked to higher Notch levels.

When the team used a drug to reduce Notch levels, the segmentation clock ran faster and more somites were formed. Based on their findings, the researchers speculate that the Notch-Nrarp feedback loop provides robustness to the segmentation clock.

During somite formation, "most of the cells are synchronized with the gene oscillations, but some of them are out of phase because of perturbations from the environment, such as chemical agents or temperature changes, or intrinsic perturbations, such as cell division," explains Bessho. Since the out-of-phase cells don't disrupt development, something must resynchronize them with their neighbours. Bessho and his colleagues suspect that Nrarp plays an important role in this resynchronization mechanism.

The team is now testing this hypothesis by checking whether Nrarp knock-out mice are more sensitive to a drug that causes embryonic abnormalities. So far, the results suggest that Nrarp is necessary for robust somite development, but research is still ongoing.

"Nowadays, this kind of basic research may be neglected," says Bessho. "However, I feel that the Nara Institute has an atmosphere in which we can wrestle with fundamental questions."

Reference

1. Kim, W., Matsui, T., Yamao, M., Ishibashi, M., Tamada, K., Takumi, K. *et al.* The period of the somite segmentation clock is sensitive to Notch activity. *Molecular Biology of the Cell* **22,** 3541-3549. (2011) doi: 10.1091/mbc.E11-02-0139

More information about the group's research can be found at the Gene Regulation Research Laboratory webpage:
http://bsw3.naist.jp/eng/courses/courses308.html