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Redefining Intercellular Signaling: Trafficking Mechanism of The Wnt5b-Ror2 Complex in Zebrafish

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The article titled "Cytoneme-mediated transport of active Wnt5b-Ror2 complexes in zebrafish" was written by Steffen Scholpp and other research teams and was published in "Nature" magazine on December 20, 2023. The research team includes a number of biologists and oceanographic experts who are dedicated to uncovering cell signaling mechanisms.This study explores the trafficking mechanism of Wnt5b and Ror2 complexes in zebrafish embryos. Wnt5b is an important ligand in the Wnt signaling pathway, and Ror2 is its receptor. Both of them play a role in cell polarity and migration. The study found that Wnt5b forms a complex with Ror2 in producer cells and is transported from the producer cell to the recipient cell through cell protrusions (called protrusions). Cell protrusions are elongated cell membrane extensions that serve as signaling "highways" to carry signaling molecules from one cell to another.

The research team observed Wnt5b and Ror2 in detail through high-resolution imaging techniques. The results indicate that the Wnt5b-Ror2 complex remains intact during transport and enters the receiving cell via dynein-dependent endocytosis, activating the Wnt-PCP signaling pathway. This mechanism not only enhances the efficiency of signal transmission, but may also influence cell behavior during embryonic development. This study provides new insights into the precise transport of signaling molecules in embryonic development and helps to re-evaluate traditional modes of cell-to-cell communication, which has important applications in aquaculture.

1 A Multi-Technology Approach Using Zebrafish Embryos and CRISPR-Cas9

The study is exquisitely designed and combines a variety of advanced experimental techniques to comprehensively reveal the cell protrusion-mediated transport mechanism of the Wnt5b-Ror2 complex. The research team used high-resolution imaging technology and the application of zebrafish embryos and fibroblast cell models to make the research results have broad biological significance. The use of CRISPR-Cas9 gene editing technology further verified the functions of Wnt5b and Ror2 in the signaling process. This multi-technology, multi-model comprehensive research design ensures the reliability of data and the accuracy of results, and provides a new perspective for revealing intercellular signaling.

2 High-Resolution Imaging Reveals Wnt5b-Ror2 Complex Transport and Signaling in Zebrafish Embryos

This article uses high-resolution imaging technology to analyze the transport process of Wnt5b and Ror2 complexes on cell protrusions. The study showed that Wnt5b and Ror2 co-localized on cell processes of zebrafish fibroblasts and ectodermal cells, and their presence was confirmed by fluorescent labeling and antibody staining. Live-cell imaging showed that the Wnt5b-Ror2 complex remained intact during transport, entering the receiving cell via dynein-dependent endocytosis. FLIM-FRET and FCCS analyzes further confirmed the stability of the interaction between Wnt5b and Ror2 during transport, measuring the distance and interaction force between them. Experimental results also show that cell protrusion-mediated Wnt5b-Ror2 transmission activates the Wnt-PCP signaling pathway in zebrafish embryos, affecting cell migration and tissue polarity during embryonic development.

Figure 1 shows the process of Wnt5b-Ror2 complex transport from producer cells to recipient cells through cytonemes, and analyzes this transport mechanism in detail. Figures 1a and 1b show that Wnt5a/b is mainly localized on the cell processes of zebrafish fibroblasts (PAC2 cells), and the cell processes with Wnt5a/b are significantly longer. This result shows that the presence of Wnt5a/b in cell protrusions is directly related to the length of these protrusions, suggesting its important role in the signal transmission process. Figures 1c to 1e further demonstrate the colocalization of Ror2 and Wnt5b on cell protrusions, and staining with anti-Ror2 and anti-Wnt5a/b antibodies confirmed the co-localization of Ror2 and Wnt5a/b on these protrusions. The experiments in Figures 1h to 1k demonstrate the colocalization of Wnt5b-GFP and Ror2-GFP on cell protrusions and their endocytosis in the receiving cell by fluorescent labeling and treatment with a dynasore (Dyn) inhibitor. These results illustrate that the Wnt5b-Ror2 complex remains intact during transport through cell protrusions and that endocytosis is dependent on dynein. This illustration provides an intuitive model of how the Wnt5b and Ror2 complexes carry out cell-to-cell transmission and signaling through cell protrusions.

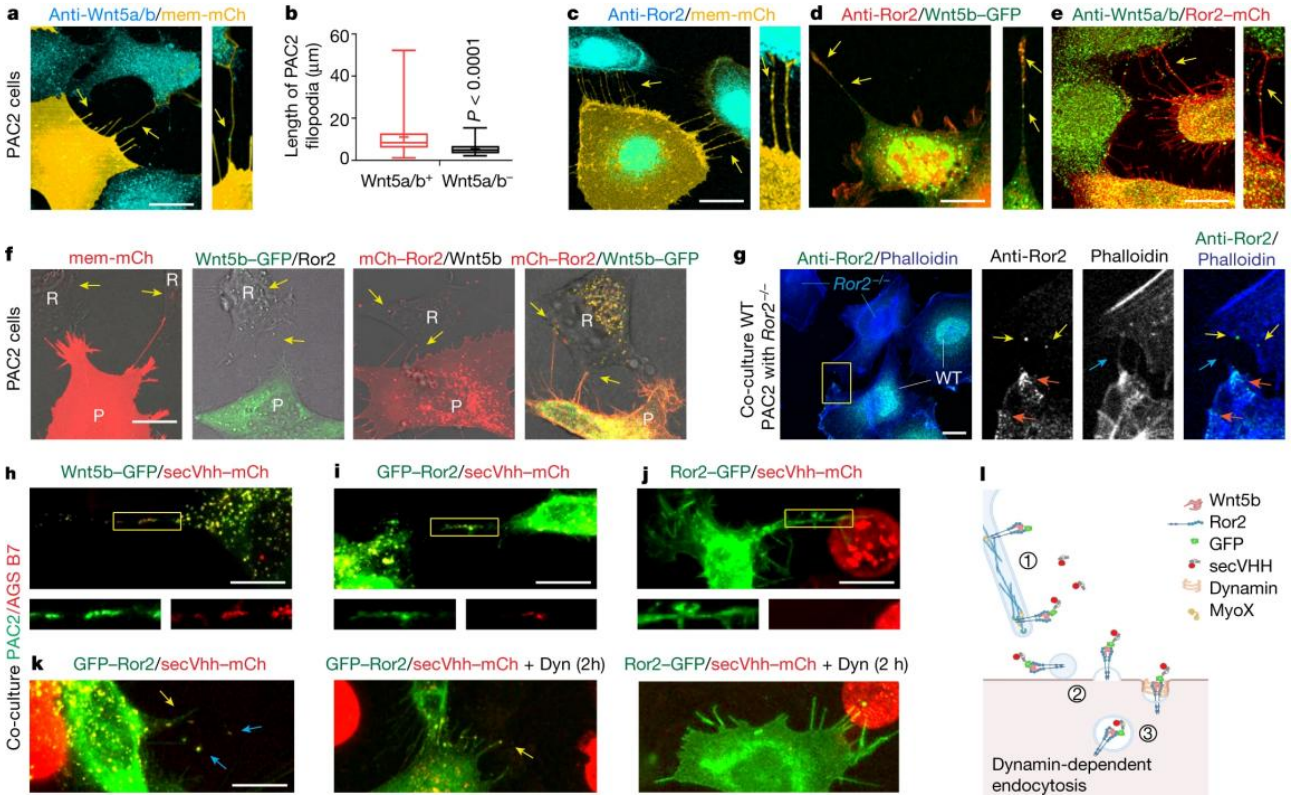

Figure 1 Wnt5b-Ror2 complexes are transported from the producing cells to the receiving cells via cytonemes

Figure 4 demonstrates the paracrine signaling mechanism mediated by the Wnt5b-Ror2 complex through cell processes through experimental data, revealing the key role of this process in JNK signal activation. Figure 4a shows that in wild-type zebrafish embryos, clones expressing Wnt5b-Ror2 were able to significantly activate JNK signaling, demonstrating the effectiveness of the Wnt5b-Ror2 complex. Figure 4b quantifies the relative intensity of JNK signaling activated by different doses of Wnt5b-Ror2 clones within five cell rows, and the results show that the activation of JNK signaling is significantly enhanced as the Wnt5b-Ror2 dose increases. Figures 4c and 4d demonstrate the effect of IRSp534K mutant on JNK signaling activation. IRSp534K is a mutant that inhibits cell protrusion formation. These experimental results indicate that cell protrusions are not only a key channel for Wnt5b-Ror2 complex transmission, but also play an important role in the regulation of signal intensity.

3 Breakthrough in Intercellular Signaling: Cell Protrusions Drive Wnt5b-Ror2 Transport in Zebrafish Embryos

By revealing the cell protrusion-mediated transport mechanism of the Wnt5b-Ror2 complex in zebrafish embryos, this study makes a significant contribution to the field of intercellular signaling and challenges the traditional

diffusion model of signaling molecules. This study demonstrates the critical role of cell protrusions in the precise delivery of signaling molecules, highlighting the mechanism by which producer cells deliver active ligand-receptor complexes directly to receiving cells via cell protrusions.

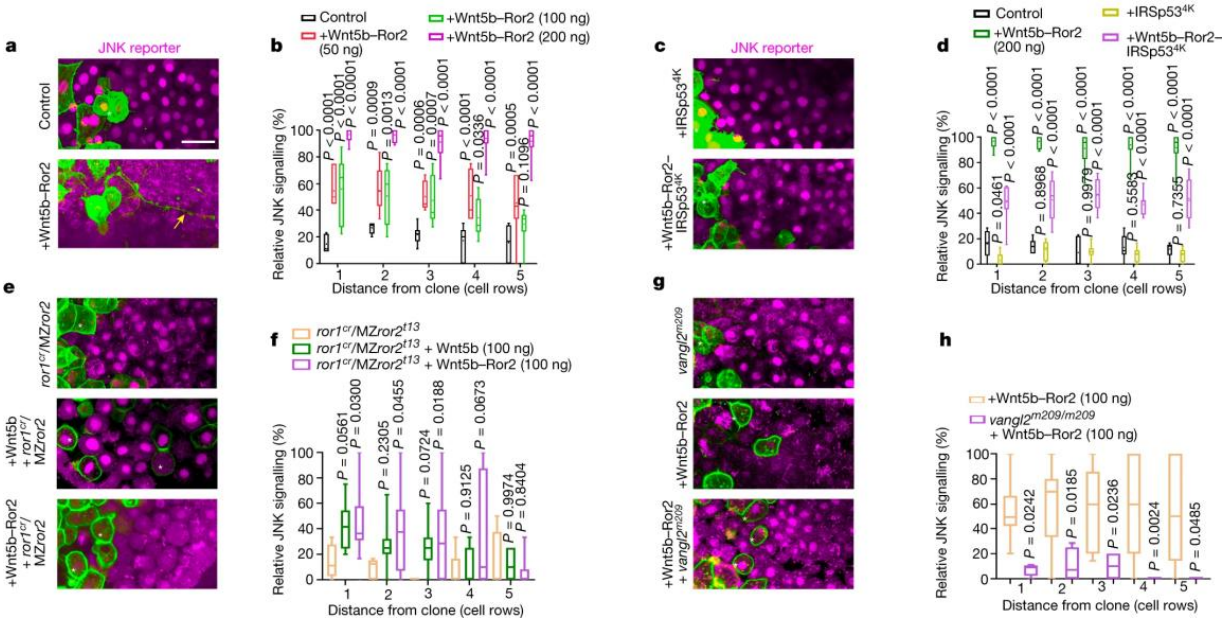

Figure 4 Wnt5b-Ror2-expressing clones activate paracrine JNK signalling

4 Unveiling Wnt5b-Ror2 Cytoneme Transport：A Paradigm Shift in Embryonic Development and Aquaculture Efficiency

The important finding of this study is the efficient transport of Wnt5b and Ror2 complexes from producer cells to recipient cells via cytonemes. In aquaculture, understanding the mechanisms of embryonic development and intercellular signaling can optimize the culture environment and improve culture efficiency. This mechanism breaks the traditional concept of paracrine signaling and shows that signaling molecules can be precisely delivered through cell protrusions to activate the Wnt-PCP signaling pathway in target cells, even if the receiving cells lack functional Ror2 receptors. This finding reveals a critical role for Wnt5b-Ror2 in embryonic development, particularly in cell migration and tissue polarity, provides new insights into understanding the trafficking of signaling molecules in complex tissues, and may have implications for reassessing intercellular communication mechanisms. of great significance.

5 Original Text Reading

Scholpp S., Zhang C.T., Brunt L., Ono Y., and Rogers S., 2023, Cytoneme-mediated transport of active Wnt5b-Ror2 complexes in zebrafish, Nature, 625: 126-133 (2024), https://doi.org/10.1038/s41586-023-06850-7

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