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New protein promotes embryonic brain formation

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Figure 1: Staining reveals the specific expression of the Jiraiya gene within the neuroectoderm of a developing Xenopus embryo. Credit: 2010 Yoshiki Sasai

The various bone morphogenetic protein (BMP) signaling factors play an important role in early neural development in the vertebrate embryo. However, maturation of these tissues ultimately depends on the coordinated activity of factors that suppress BMP activity within the neuroectoderm, a cell population that ultimately gives rise to the nervous system.

Yoshiki Sasai and colleagues at the RIKEN Center for Developmental

Biology in Kobe have now revealed a novel regulator of BMP signaling, *Jiraiya*, which they originally identified in a screen for genes activated by the BMP inhibitor Chordin in the African clawed frog, Xenopus laevis. “Jiraiya was intriguing as it encoded a novel membrane protein that had no homology to known proteins, and its expression was neural-specific,” says Sasai.

Unexpectedly, his team determined that the Jiraiya protein acts as a specific inhibitor of BMPRII, one of two core subunits of the BMP receptor, within the neuroectoderm (Fig. 1). BMPRII chemically modifies BMPRI in response to BMP binding; BMPRI subsequently activates downstream components of the signaling cascade. Initial experiments showed that Jiraiya specifically interferes with signaling at a point between ligand binding and BMPRI activation.

When overexpressed in cultured embryonic frog cells, Jiraiya depleted BMPRII from the plasma membrane by sequestering it within complexes in the cytoplasm. Evidence suggests that this protein physically interferes with the delivery of newly synthesized receptor molecules to the cell surface.

BMPRII is part of a larger family of receptor proteins that are relatively similar to one another, but features a distinctive ‘C-terminal tail domain’ (TD) that contains within it the specific Jiraiya-binding motif. This enigmatic ‘EVNNNG’ sequence appears to be a unique feature of BMPRII, although it is closely conserved in receptor homologues from other species. Transplantation of the motif onto a different receptor, ActRIIA, was sufficient to make that protein susceptible to similar Jiraiya-mediated inhibition. “The most intriguing part is that it acts only on the type II subunit of BMPR via this tail-domain whose role in dynamic signaling modulation had not been known,” says Sasai.

He and his colleagues conclude that Jiraiya appears to represent an

important mechanism for the cell-specific inactivation of BMP-responsive pathways, and thereby helps define the boundaries of neural tissue development. The Jiraiya gene is found in a broad range of vertebrate species, although expression in the mouse embryo does not seem to follow the same neural-specific pattern of localization seen in frog embryos. Sasai hopes to further clarify its role in mammalian development in future studies.

More information:

-- Aramaki, T., et al. Jiraiya attenuates BMP signaling by interfering with Type II BMP receptors in neuroectodermal patterning. *Developmental Cell* 19, 547–561 (2010).
-- Sasai, N., et al. Requirement of FoxD3-class signaling for neural crest determination in Xenopus. *Development* 128, 2525–2536 (2001).

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