LABORATORY OF BIOLOGICAL DIVERSITY

KOMINE Group

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We have been interested in the developmental and evolutional aspects of the structure of mammalian brains. In a comprehensive analysis of homeobox genes expressed in the developing mouse neocortex, we isolated a novel gene *Zfhx2*, which encodes a transcription factor containing three homeobox domains and 18 Zn-finger motifs. *Zfhx2* is highly expressed in the developing mouse brain, particularly in differentiating neurons, and continues to be expressed throughout adulthood at a low level. Two other phylogenically related genes, *Zfhx3* and *Zfhx4*, have been identified. The former was reported to be expressed in a manner dependent on neural differentiation, and the latter is a candidate gene causing congenital bilateral isolated ptosis. Although these three genes are expressed in substantially similar patterns in the developing brain, common functional features have not been clarified. Currently we have been focusing on *Zfhx2* to reveal its function and mechanisms of expression control in the developing brain.

I. Expression of *Zfhx2* is negatively regulated by its own antisense RNA

We found that the antisense strand of *Zfhx2* is also expressed in the mouse brain in a manner complementary to the expression of *Zfhx2* mRNA (Figure 1). Although most neurons express *Zfhx2* mRNA immediately after their final mitosis, several types of neuron (e.g., granule cells in the olfactory bulb and pyramidal and granule cells in the hippocampus) express antisense RNA prior to *Zfhx2* mRNA during the early phase of their differentiation. By generating a gene-targeting mouse line in which *Zfhx2* sense RNA is expressed but not antisense RNA, we showed that this antisense RNA has a negative regulatory role in the expression of *Zfhx2* mRNA. These observations suggest that the ZFHX2 protein might have a role in a particular step of neuronal differentiation, and in some types of neuron, this step might be delayed by the expression of antisense RNA.

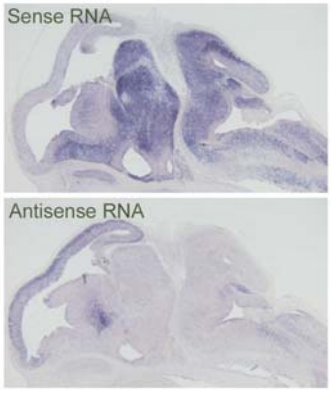

Figure 1. Expression of *Zfhx2* sense RNA (mRNA) and antisense RNA in the embryonic mouse brain. The antisense RNA was expressed where mRNA was not.

II. ZFHX2 might play roles in controlling emotional aspects

To elucidate the function of ZFHX2, we have also generated a *Zfhx2*-deficient mouse line. Although the production of the ZFHX2 protein is completely abolished in the homozygous mutant mice, the mice appear grossly normal and healthy. No anatomical abnormality has been observed in the mutant mouse brains so far examined. We hence subjected the *Zfhx2*-deficient mice to a comprehensive battery of behavioral tests to explore the physiological function of ZFHX2 in the nervous system. The homozygous *Zfhx2* deficient mice showed several behavioral abnormalities, namely, hyperactivity, enhanced depression-like behaviors, and an aberrantly altered anxiety-like phenotype. These behavioral phenotypes suggest that ZFHX2 might play roles in controlling emotional aspects through the function of monoaminergic neurons where ZFHX2 is expressed.

III. *ZFHX2* works also in pain perception process in human and mice

Recently, Cox's group in University College London found that a point mutation in the human *ZFHX2* gene segregates with the pain insensitivity found in a family with an inherited pain insensitive phenotype. Through the collaboration of several groups, including us, it has been shown that *ZFHX2* works as a critical gene for pain perception in humans and mice. Further work will resolve how the mutated *ZFHX2* gene contributes to the hypoalgesic phenotype and may help development of new analgesic drugs.

Publication List:

〔Original paper (E-publication ahead of print)〕

● Habib, A.M., Matsuyama, A., Okorokov, A.L., Santana, S., Bras, J.T., Aloisi, A.M., Emery, E.C., Bogdanov, Y., Follenfant, M., Gossage, S.J., Gras, M., Humphrey, J., Kolesnikov, A., Le Cann, K., Li, S., Minett, M., Pereira, V., Ponsolles, C., Sikandar, S., Torres, J.M., Yamaoka, K., Zhao, J., Komine, Y., Yamamori, T., Maniatis, N., Panov, K.I., Houlden, H., Ramirez, J.D., Bennett, D.L.H., Marsili, L., Bachiocco, V., Wood, J.N., and Cox, J.J. A novel human pain insensitivity disorder caused by a point mutation in *ZFHX2*. Brain 2017 Dec 14.