

Molecular “messenger” of experience during brain circuits formation

【Keywords】

ASD

Mental disorder

Homeoprotein

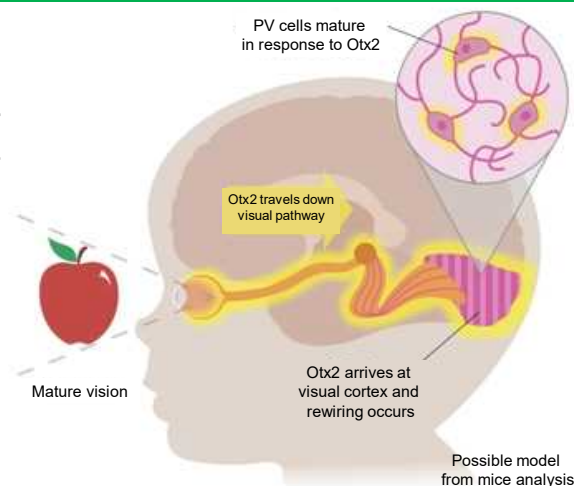
Peptide

Circuit formation

■ Summary

【Aims】 The young brain experiences ‘critical period’ when neuronal circuitry is intensively remodeled based on individual experience. Discovering genes for flexible wiring of neural networks will be useful for the treatment of brain diseases with miswiring and disconnecting networks.

【Results】 Otx2 protein has a unique property of sensing experiences, moving from eyes to brain and promoting the maturation of the target PV cells. By manipulating the amount of Otx2 protein in mice, you can artificially control the critical period. PV cells are required for brain integrity as their abnormality causes mental disorders such as autism.



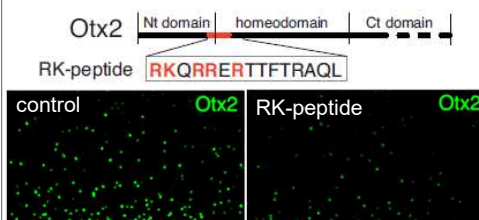
■ Subject Details/Topic

- Neural networks are shaped by experience in the critical period. Imbalanced experience in this period causes unexpected disease for brain function.
- For instance, closing one eye with an eye patch leads to a reduction in visual acuity (amblyopia), that is difficult to improve in adulthood beyond this period.
- Experience-dependent transfer of Otx2 transcription factor acts as “messenger” of experience from peripheral to central nervous system.
- Manipulating the amount of Otx2 protein can activate the critical period in mice.
- Reduction of Otx2 by injecting antibody and RK-peptide* into eyes and brain (the upper panel), reactivates the critical period in adult mice (that can recover amblyopia).
- Risk factors associated with autism and schizophrenia are downstream targets of Otx2 to promote PV-cell function (the middle panel).
- Otx2 mutants in human lead to developmental disorders with disruption of speech, sleep and eating. Indeed, the target genes of Otx2 include risk factors for disease (the lower panel).

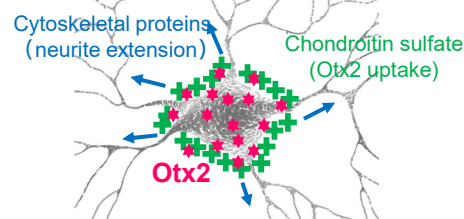
* Patent (WO2010081975,A1)

■ We hope to collaborate with...

RK-peptide inhibits Otx2 uptake to neurons



Otx2 regulates gene expressions for PV-cell maturation



Disease Ontology of Otx2-bound genes

DO Term	Number of genes	p-value
Alzheimer's disease	73	3.36E-22
Schizophrenia	54	5.34E-12
Bipolar disorder	34	6.38E-12
Epilepsy	24	3.41E-09

Pharmaceutical company aiming to develop drugs for mental disorders

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