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Flip the switch

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A molecular switch determines whether neural progenitor cells differentiate into motor or serotonergic neurons.

When making a major life decision, many people make pro and con lists. During development, the same hindbrain progenitor cells sequentially develop into both visceral motor neurons (VMN), which innervate cranial muscles, and serotonergic neurons. How do these neural progenitors decide which type of neuron to become? Jacob *et al*. report a transcription factor that induces one fate and represses the other in a recent article in *Nature Neuroscience*.

The developing hindbrain is divided into 8 anterior-posterior segments called rhombomeres (r). In r2-3 and r5-8, a progenitor population localized to a region called p3 produces VMNs from mouse embryonic days 9-10.5 (E9-E10.5) and serotonergic neurons from E10.5-E12. However, VMNs never develop in r1, which produces approximately half of all serotonergic neurons, and serotonergic neurons are never produced in r4.

Several transcription factors regulate VMN and serotonergic neuron production. For example, Nkx2.2 is required to differentiate both VMNs and serotonergic neurons, and Phox2b is necessary for VMN differentiation but blocks serotonergic differentiation. Does a similar factor induce serotonergic and block VMN differentiation?

The forkhead transcription factor Foxa2 regulates the differentiation of midbrain dopaminergic neurons. In the hindbrain, the authors localized Foxa2 to the floorplate on E9.5. After E10.5, Foxa2 localization expanded into p3. In contrast, Phox2b localized to p3 on E9.5 and moved dorsally on E10.5. On E11.5, Pet1, an early marker of serotonergic neurons, localized laterally to Foxa2-positive neurons in p3. In r4, Foxa2 never moved beyond the floor plate, suggesting that the localization of Foxa2 correlates with sites of serotonergic neuron production.

Researchers previously showed that *Phox2b* knockout embryos lack VMNs. In the current study, the authors found expanded expression of Foxa2 in *Phox2b*-deficient embryos. Conversely, *Foxa2*-deficient embryos showed ectopic Phox2b expression in r1. Relative to untreated chicks, chicks treated *in ovo* with wild-type and dominant-negative *Foxa2* showed reduced and prolonged Phox2b expression, respectively, suggesting that Foxa2 and Phox2b reciprocally repress each other.

Foxa2 blocks VMN differentiation. *Foxa2*-deficient embryos showed ectopic expression of the VMN markers Isl1 and T-box 20 in r1. In contrast, chick embryos unilaterally electroporated with *Foxa2* had fewer VMNs on the ipsilateral side of the brain.

Foxa2 is necessary for the differentiation of serotonergic neurons. Chicks treated with wild-type and dominant-negative *Foxa2* showed premature Pet1 expression and reduced serotonergic neuron production, respectively. In the mouse, deletion of *Foxa2* after the completion of VMN differentiation reduced the number of serotonergic neurons, suggesting that the roles for Foxa2 in the differentiation of serotonergic neurons and repression of Phox2b are independent.

Therefore, Foxa2 and Phox2b comprise the molecular switch between VMN and serotonergic neurons. How does the switch know when it is time to be flipped? The authors note that the timer's identity is currently unknown but suggest that reciprocal transcriptional repression may be involved in the differentiation of other neurons from common progenitors.

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1. Jacob, J. *et al.* Transcriptional repression coordinates the temporal switch from motor to serotonergic neurogenesis. *Nature Neuroscience* **10**, 1433–1439 (2007). | Article | PubMed | ChemPort |