Spatiotemporal Control of *Hox* genes by microRNA

by **Chung-Jung Li & Jun-An Chen**
Institute of Molecular Biology, Academia Sinica

Hox genes have been extensively studied for more than 30 years. Although it is well-known that *Hox* genes are essential to the specification of spinal motor neuron subtype identities along the rostrocaudal axis, it remains unclear how the *Hox* genes are precisely regulated to achieve their collinear spatiotemporal expression. In collaboration with Prof. Qing Nie from the Mathematics Department of UC Irvine, Dr. Jun-An Chen from IMB Academia Sinica has uncovered a novel microRNA/*Hox* gene expression network that contributes to the dynamic control of *Hox* gene expression, thereby ensuring proper motor neuron subtype identities during development. This model was established by *in silico* mathematical simulations and was examined further using embryonic stem cell differentiation systems and investigations of mouse and chicken embryos. Their work was published in *Nature Communications* on 24 March 2017, under the title *"MicroRNA Filters Hox Temporal Transcription Noise to Confer Boundary Formation in the Spinal Cord".*

Fig. 1. A novel microRNA/Hox gene expression network is uncovered by in silico mathematical simulations and further examined by using embryonic stem cell differentiation systems and investigations by mouse and chicken embryos.

Hox genes are expressed in a specific spatial and temporal pattern during motor neuron development. These specific patterns then dictate the specification of particular subtypes of motor neurons, which in turn affects the innervation pattern of their respective muscle targets. Previous studies reported a delay in translation of Hox proteins from messenger RNA; whereas the messenger RNAs of *Hox* genes are detected at progenitor stages of motor neurons, Hox proteins are not translated until the later postmitotic stage.

MicroRNAs belong to a class of non-coding RNAs (ncRNAs) that regulate cell function by repressing the translation of target messenger RNAs after transcription. Dr. Chen and his collaborators hypothesized that microRNAs might mediate the delayed Hox protein translation. Indeed, when the microRNA-generating *Dicer* gene was deleted from motor neuron progenitor cells, they started to immediately translate *Hoxa5* messenger RNA into proteins, i.e. before the postmitotic stage. The result of this early expression is a fuzzy distribution of Hoxa5 proteins that disrupts a particular Hox5-Hox8 boundary in postmitotic motor neurons. This boundary is essential for defining different motor neuron subtypes. The network of *Hox* genes and microRNAs were then explored *in silico* and two feed-forward Hox-microRNA loops were identified that accounted for the observed phenotypes. Finally, gain- and loss-of-function studies, both *in vitro* and *in vivo*, revealed a specific microRNA (*mir-27*) to be a major regulator of the temporal delay and spatial collinearity of Hox protein expression. It is notable that the *mir-27*-dependent phenotype established through the study of mice can be reproduced in chicken embryos, indicating that this novel Hox-microRNA genetic circuitry is essential and evolutionarily well-preserved.

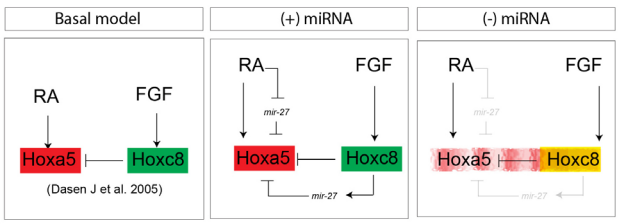

Fig. 2. Model of the role of mir-27 in the control of Hoxa5 noise and the Hox boundary. Previous studies suggest that RA induces Hoxa5, whereas FGF activates Hoxc8. We reveal that Hoxa5 transcription in progenitor cells fluctuates, and translation of fluctuating transcripts at this time propagates noise, leading to strong stochastic variability. We further underscore two critical, coherent forward loops involving mir-27 that are capable of preventing precocious Hoxa5 protein expression and can maintain the critically sharp boundary between Hoxa5 and Hoxc8 protein expression in embryonic spinal cords.

This study was supported by Academia Sinica, MoST and NHRI.

Website: http://www.nature.com/articles/ncomms14685

Contact:
Dr. Jun-An Chen (Assistant research fellow, IMB, Academia Sinica)
jachen@imb.sinica.edu.tw
(Tel) +886-2-2788-0460
http://www.imb.sinica.edu.tw/~jachen/