The Mouse Embryo Autonomously Acquires Anterior-Posterior Polarity at Implantation.

TAKAOKA Katsuyoshi and HAMADA Hiroshi
(Graduate School of Frontier Biosciences)

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The earliest recognizable sign of patterning of the mouse embryo along the antero-posterior (A-P) axis is the migration of the distal visceral endoderm (DVE) toward the future anterior side. We report a molecular asymmetry in the mouse embryo that precedes the onset of DVE migration. The gene for Lefty1, a Nodal antagonist that influences the direction of DVE migration, was found to be asymmetrically expressed in the primitive endoderm of the implanting blastocyst. *Lefty1* is initially randomly localized in the inner cell mass (ICM), but is regionalized to one side of the tilted ICM shortly after implantation. Asymmetric expression of *Lefty1* can be established by *in vitro* culture, indicating that it does not require interaction with the uterus. The asymmetric *Lefty1* expression is induced by Nodal signaling, although *Nodal* and genes for its effectors are expressed symmetrically. This asymmetry in molecular patterning of the mouse embryo pushes back the origin of the A-P body axis to the peri-implantation stage.

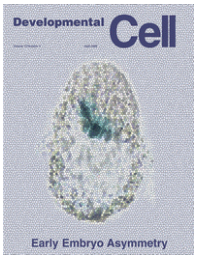

Fig. 1 Asymmetric expression of *Lefty1* transgenes in peri-implantation mouse embryos.

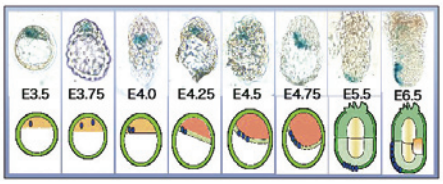

Fig. 2 Mouse embryos harboring the *Lefty1-9.5 lacZ* transgene were recovered at the indicated stages and stained with X-gal.

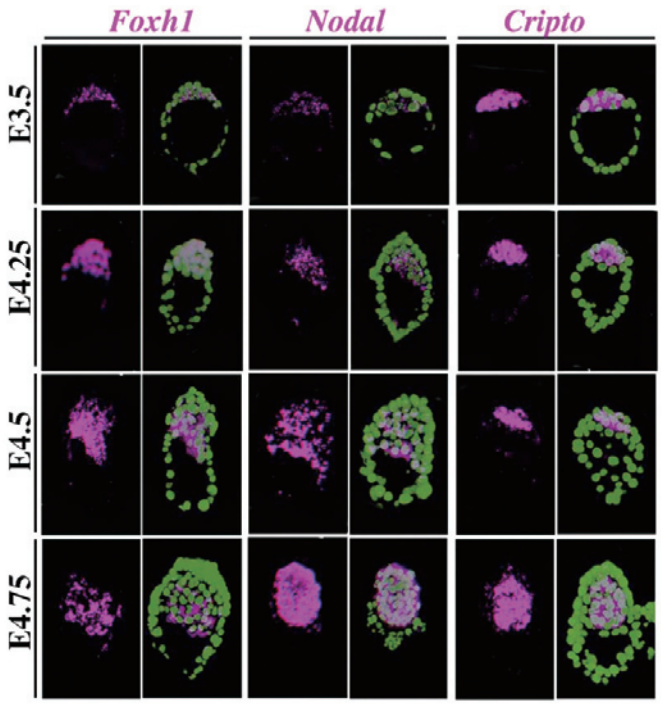

Fig. 3 Lack of asymmetry in the expression of *Nodal, Foxh1, and Cripto* in mouse embryos between E3.5 and E4.7

Triggering Neural Differentiation of ES Cells by Subtype Switching of Importin-α

YASUHARA Noriko and YONEDA Yoshihiro
(Graduate School of Frontier Biosciences)

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Eukaryotic cell nucleus is separated from cytoplasm, by lipid bi-layer of nuclear envelope. A cell must respond to various cellular events with regulated signal exchanges between cytoplasm and nucleus. Nuclear-cytoplasmic transport of functional proteins is a selective transport mediated by specific transport systems through the nuclear pore. In this paper, we report that a transport receptor family plays a significant role in neural differentiation of ES cells. This is the first study to propose that nuclear transport factors should be considered as major players of cell-fate determination.

Importin-α, a receptor of cargo proteins imported into the nucleus, is classified into three subtypes, importin-α1, -α3 and -α5, which are differentially expressed in tissues, suggesting a possible role in the tissue-specific regulation of cellular processes. Although there was an indication that various types of importin-α proteins contribute to embryonic development and cell differentiation in *Drosophila melanogaster* and *Caenorhabditis elegans*, little has been known about how the mammalian importin-α subtypes are involved in the regulation of cell differentiation. This paper shows that the expression of importin-α subtypes is modulated during neural differentiation of mouse ES cells induced by retinoic acid; whereas undifferentiated ES cells are characterized by high importin-α1 and low importin-α5 expression, the induction of neural differentiation causes an increase of importin-α5 expression with a concomitant decrease of importin-α1 expression. Reproducing this pattern of importin-α expression, by inhibiting importin-α1 expression with RNAi and exogenously overexpressing importin-α5, induced neuronal differentiation in LIF-containing medium without retinoic acid. This neuronal differentiation triggered by the switch in importin-α1subtype was accompanied by modulation in expression of transcription factors such as Oct3/4, Brn2 and SOX2, which play important roles in ES cell-fate determination. In addition, we demonstrated that these transcription factors are differentially imported into the nucleus by importin-α subtypes.

Regulation of transcription factor activity has been regarded as the major process that controls cell differentiation. However, our study demonstrates that the switching of importin-α subtypes is interdependently critical to the cell differentiation process, underscoring the importance of the coordinated regulation of importin-α and their transcription-factor cargoes.

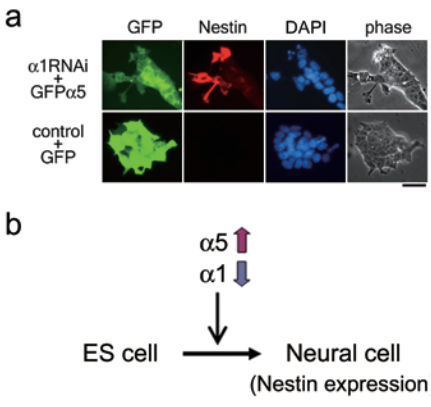

Fig. 1 Downregulation of importin-α1 expression and upregulation of importin-α5 expression induced neural differentiation of ES cells cultured in LIF+ medium.

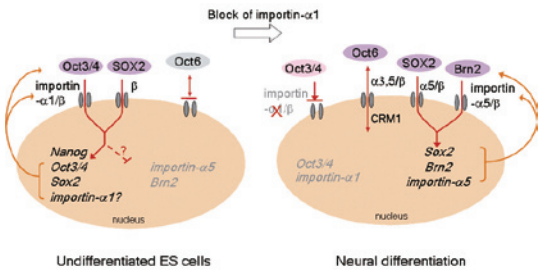

Fig. 2 A model for cell fate determination by the interdependent regulation of nuclear transport machineries and transcription factors.