DIVISION FOR SEX DIFFERENTIATION

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A number of genes are known to play crucial roles during gonadal differentiation. Some of them have been identified as the genes responsible for human diseases, while the functions of the other genes have been elucidated by the phenotypes of gene-disrupted mice. How the genes are regulated by upstream regulators, however, is not yet fully understood. Studies of this aspect of genes are quite important in order to define the molecular mechanisms mediating sex differentiation of the gonad.

Ⅰ. Fetal Leydig enhancer

During development of the testis, fetal and adult Leydig cells arise. The fetal mouse Leydig cells emerge at E12.5 and start to produce the male sex hormone androgen. The number of fetal Leydig cells decreases after birth. The adult Leydig cells start to develop at around postnatal day 10 and thereafter increase in number. The fetal and adult Leydig cells have been revealed to be morphologically and functionally different, and we have discussed whether these two populations originate from two distinct cells. The origins of the two Leydig cells, however, are still unclear.

We have studied the *Ad4BP/SF-1* gene locus by transgenic mouse assays and have recently identified the fetal Leydig cell-specific enhancer. Using the DNA fragment, a mouse line in which the lacZ reporter gene is driven was established. The lacZ expression was first recognized in the testicular interstitium at E12.5. The number of the lacZ-expressing cells increased during the fetal period and declined after birth. In the adult male mice, only a few lacZ-positive interstitial cells were detected. Immunohistochemical analyses revealed that the lacZ colocalized with Leydig cell-specific markers. These results indicated that the enhancer activity is strictly confined to the fetal Leydig cell population.

Ⅱ. Fetal to adult adrenal

As Leydig cells, adrenocortical cells synthesize steroid hormones. Moreover, the tissue is developmentally similar to Leydig cells in terms of the presence of fetal and adult cells. We isolated the fetal adrenal enhancer of the *Ad4BP/SF-1* gene and, using the enhancer, a transgenic mouse to drive Cre-recombinase was established. The mouse was crossed with Rosa 26 mice to trace the cell lineage of the fetal cells. Examination of the adult adrenal gland of the mice demonstrated that the adult adrenocortical cells are derived from the fetal adrenocortical cells. Further examination with another transgenic mouse carrying Cre-ER (a fusion protein of Cre and estrogen receptor, whose recombinase activity is induced in the presence of an estraogen antagonist) demonstrated that the early but not the late stage of the fetal adrenal cortex has the potential to differentiate into adult adrenal cortex.

This division was closed and moved to the Graduate School of Medical Sciences, Kyushu University in July, 2008. All the members of this division wish to thank the members of NIBB for the warm and friendly collaboration we enjoyed here. During the past 10 years at this institute, we recognized the importance of basic research and the responsibilities of the researchers. This experience has formed the backbone of our motivation as basic researchers.

Publication List

〔Original papers〕

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