CDB SEMINAR

Jun K. Takeuchi

Cardiovascular Research, The Hospital for Sick Children

Wednesday, July 19

16:00~17:00 C1F CDB Auditorium

From a Nucleus to an Organ: Combinatorial Regulation between T-box and Spalt genes, and the Chromatin Remodeling Complexes in heart development

Summary

Congenital heart defects (CHDs) are the most common and most devastating birth defects in human, occurring about ~2% of births, and resulting in significant mortality and mobility. However, we currently have very little understanding of the processes that cause CHDs. Transcription factors expressed in heart regulate many aspects of embryonic development, and mutations such as the T-box genes *TBX5* and *TBX1*, the homeodomain gene *NKX2-5*, and the zinc-finger gene *GATA4* can cause CHDs in human. Thus understanding the roles of transcription factors playing in heart development is critical for understanding of normal heart development and for the elucidation of CHDs.

Tbx20, another T-box gene expressed in heart, is expressed from very early cardiac crescent stage, and to address the function of *Tbx20*, I used *in vivo* RNA interference (RNAi) methods. This method is very useful for gene analysis since we can obtain embryos directly from ES cells. *Tbx20* si-knockdown experiments showed that *Tbx20* functions in right ventricle formation cooperatively with Islet1 and *Nkx2-5*. To understand molecular mechanism of heart development, we need to clear combinatorial gene functions. *Sall4* is a zinc-finger type *Spalt-like* transcription factor will be one of good candidates for this purpose, and mutations in *SALL4* cause CHDS whose phenotype is identical to *TBX5* mutations. We found Sall4 functions synergistically with *Tbx5* and they function more specifically in limb and heart formation. These results indicate that individual transcription factors specify intricate organ patterning cooperatively with other transcription factors.

The function of transcription factors is intimately related to and regulated by the status of chromatin at their target binding sites; chromatin structure would affect the accessibility and activity of transcription factors. From these hypotheses, we have investigated cardiac chromatin remodeling factors. One of SWI/SNF type chromatin remodeling factors, *Baf60c*, is essential for cardiac development through interaction with specific transcription factors. Furthermore I will show deletion experiments of *Brg1*, a core factor of SWI/SNF complex suggest that SWI/SNF factors functions on the same pathway as *Tbx5* in cardiogenesis. Thus chromatin-remodeling complexes not only modulate chromatin assembly, but also have specific function with tissue specific factors.

At this seminar, I would like to talk about combinatorial gene functions to generate intricate organs.

Host:
Shinichi Aizawa
Vertebrate
Body Plan, CDB
saizawa@cdb.riken.jp
Tel:078-306-3149
(ext:4301)