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.