Invited Lecture

2026年7月11日(土) 10:55 ~ 11:20 | 第１会場（Conference Hall A）

[IL2] Invited Lecture 2（III-IL2）

From Discovery of Csx/NKX2-5 to Genome Editing Therapy for Congenital Heart Disease

Chair:Makoto Nakazawa(Former Chairperson, JSPCCS)
Chair:Hiroyuki Yamagishi(Tokyo Metropolitan Children's Medical Center)

[III-IL2-1] From Discovery of Csx/NKX2-5 to Genome Editing Therapy for Congenital Heart Disease

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キーワード：Transcription factor、congenital heart disease、genome editing

In 1993, we identified a novel cardiac-specific homeobox gene, Csx, later renamed NKX2-5, as one of the earliest transcription factors expressed in the developing heart. This discovery provided one of the first molecular frameworks for understanding cardiogenesis and congenital heart disease (CHD). Subsequent studies demonstrated that homozygous deletion of Nkx2-5 in mice causes severe defects in heart development and embryonic lethality. Multiple groups, including ours, showed that heterozygous mutations in human NKX2-5 cause a broad spectrum of congenital heart diseases, including atrial septal defects, tetralogy of Fallot, and atrioventricular conduction disturbances. These studies established the concept that mutations in cardiac transcription factors can directly cause structural heart disease.

Using a murine model harboring the Nkx2-5 R52G mutation, which develops atrial septal defects resembling human disease, we applied prime editing during embryonic development. Successful correction of the mutation was confirmed by sequencing analysis, and embryos with repaired Nkx2-5 no longer developed atrial septal defects. This study represents the first successful demonstration that a congenital heart disease phenotype caused by a cardiac transcription factor mutation can be rescued through precise genome editing in vivo.

The trajectory from the discovery of Csx/NKX2-5 to successful genetic correction of Nkx2-5-associated congenital heart disease illustrates how fundamental discoveries in developmental biology can ultimately lead to transformative therapeutic strategies. Future integration of developmental biology, cardiovascular genetics, and genome engineering may open a new era of precision medicine for congenital heart disease.