

RIMD–IPR Joint Seminar

“Insight into the functions of the CRK gene family from a view of DiGeorge Syndrome”

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DiGeorge syndrome, also known as *del22q11* syndrome, is the most prevalent deletion syndrome, as microdeletions are localized most frequently to 22q11. Patients affected by this syndrome exhibit a broad spectrum of congenital malformation frequently in anterior tissues including craniofacial tissues, heart, and pharyngeal tissues such as thymus and parathyroid, often associated with growth retardation and neurological/psychiatric disorders. In addition, approximately 30% of the patients are known to extend a range of malformation into more posterior tissues in the genitourinary (GU) system. While most patients have a 3Mb deletion referred to Typically Deleted Region (TDR) or Common Deletion, a small but significant number of individuals have smaller deletions that do not overlap with a 1.5 Mb so-called “critical” region nested proximally within the TDR. We originally identified *CRKL* (*CRK-like*) as a DiGeorge candidate gene localized distally to the critical region, based on a set of anterior malformations in mice lacking the mouse homolog of this gene. Our recent multicenter study has identified nonsense or missense point mutations within the *CRKL* protein coding sequence among a large cohort of patients with genitourinary defects without a microdeletion. Furthermore, we have shown that mouse ortholog is essential for normal genitourinary development. Previous reports identified the essential role of *TBX1*, a gene encoding a transcription factor, in the 22q11 critical region. We showed that compound heterozygosity of mouse *Crkl* and *Tbx1* was sufficient to produce a synergistic synthesis of a stable syndromic phenotype. However, mouse embryos deficient for *Tbx1* alone do not show GU defects. Therefore, these results supply a definitive piece of evidence that DiGeorge syndrome is a true contiguous gene syndrome in which *CRKL* and *TBX1* are involved in most patients, while heterozygosity of *TBX1* or *CRKL* alone with point mutations or in small nonoverlapping deletions may affect syndromic patients possibly with other modifiers. Interestingly, we have also found that *Tbx1* heterozygosity can also synergize with heterozygosity of *Crk*, the paralog of *Crkl*, to produce DiGeorge-like anomaly in mice. As the *CRK* gene family encode adapter proteins consisting of SH2 and SH3 domains, we suggest that the genetic or signaling network affected in this syndrome is sensitive to function shared in the *CRK* gene family. I will also discuss recent unpublished results to shed light onto shared functions identified by omics approach.

日時：2017年3月28日(火) 16:00～ 15:00～

Date : Tuesday, March 28th 2017, 16:00～ 15:00～

会場：微生物病研究所本館1階 微研ホール

Venue : BIKEN Hall ,RIMD

※講演は英語で行われます This seminar will be held in English

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