Invited Lecture

2026年7月11日(土) 14:20 ~ 14:50 | 第１会場（Conference Hall A）

[IL4] Invited Lecture 4（III-IL4）

Noonan syndrome and related disorders: How to get to less but not too little

Chair:Hiroyuki Yamagishi(Tokyo Metropolitan Children's Medical Center)

[III-IL4-1] Noonan syndrome and related disorders: How to get to less but not too little

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Noonan syndrome (NS) and the related disorders, referred to as the RASopathies, are related genetic traits with overlapping, pleiomorphic characteristics. Cardiovascular involvement is highly prevalent (up to 90% of individuals with NS) and includes congenital heart disease (most prevalently, pulmonary valve stenosis (PVS) and secundum atrial septal defects); atrial arrhythmias, particularly multifocal atrial tachycardia in Costello syndrome; and hypertrophic cardiomyopathy (HCM), which presents in the fetal or infancy periods and can be severe and life threatening. Lymphovascular involvement is also common, starting with increased nuchal translucency in fetuses and later presenting a peripheral lymphedema, pulmonary lymphagiectasia, or central lymphatic conducting anomalies. The first genetic cause of a RASopathy was discovered 25 years ago when *PTPN11* missense alleles were shown to cause approximately 50% of NS. Since then, efforts around the world, including important advances by Yoko Aoki and her colleagues in Sendai, have elaborated nearly 20 genes that cause one or more RASopathies when altered. With the exception of Noonan syndrome with multiple lentigines (NSML), RASopathy alleles engender gain of function in the RAS/mitogen-activated protein kinase (MAPK) signal transduction pathway. In addition to the strong majority of RASopathy genes that have one-to-one relations with specific RASopathy traits (e.g., *HRAS* pathogenic alleles cause only Costello syndrome), there are notable genotype-phenotype relationships within RASopathy traits. Among these are ones relevant for cardiovascular involvement in NS, including *RAF1* and *RIT1* alleles being associated with HCM and *PTPN11* alleles being associated with PVS. Pre-clinical studies of the RASopathies have included modeling of disorders using human induced pluripotent stem cells (iPSCs) and animal models ranging from Drosophila to mice. Due to the activation of RAS/MAPK signaling, a strategy often tested with these various RASopathy models was to use pharmacologic inhibition of that pathway, generally using small molecules developed as cancer therapeutics. Notably, treatment of a *Raf1* knock-in mouse genetic model of NS that recapitulates HCM with the MEK inhibitor (MEKi) mirdametinib resulted in prevention of that cardiac phenotype. In 2017, two critically ill infants with severe HCM due on NS-related *RIT1* pathogenic alleles were treated with the MEKi trametinib on a compassionate-usage basis. Both infants improved dramatically and survived, outcomes unlikely for this disease. Interestingly, both infants had PVS with dysplastic valve leaflets, which also improved during therapy. Subsequently, trametinib has been used more broadly for cardiovascular and lymphovascular issues for patients with RASopathies. A retrospective study of 31 patients with severe RASopathy-associated HCM who were treated with trametinib, half infants and half older children and adolescents, showed significantly better outcomes than similar patients from an earlier era treated with standard of care. Based on case reports, trametinib has also been apparently effective for the treatment of atrial tachyarrhythmias and lymphatic issues. Side effects from MEKi treatment are common but generally mild, with dermatological issues being the most prevalent. To date, no clinical trial of a MEKi for a RASopathy indication has been completed. For this Takao symposium lecture, Dr. Bruce Gelb will review the history and current state of development of therapeutics for cardiovascular

and lymphatic issues in the RASopathies, including insights gained from cell and animal models and the experience to date in treating patients with trametinib.