Roles of monosomy 7 and *SAMD9/SAMD9L* mutations in myeloid leukemogenesis

Hirotaka Matsui

Kumamoto University, Japan

Pediatric myelodysplastic syndrome (MDS) is a rare hematological disorder which account for less than 5% of hematological malignancies in children. *GATA2* and *SAMD9/SAMD9L* genes, the latter of which locates on the long arm of chromosome 7, have been recently shown to be mutated in the disease with or without preceding clinical manifestations. In addition, *GATA2* mutation in pediatric MDS is often accompanied by monosomy 7, thus functional analysis of candidate responsible genes on chromosome 7 including *SAMD9/SAMD9L* is underway in many laboratories.

More than 15 years ago, we undertook isolation of responsible genes from 21.7 Mb region within 7q21.2–7q31.1. Array CGH was performed on Juvenile Myelomonocytic Leukemia specimens that show no apparent deletion on chromosome 7 by conventional chromosome analysis, and we identified around 200Kb common micro deletionin 7q21.3. There are three genes in this region, namely *SAMD9*, *SAMD9L* and *MIKI(HEPACAM2)*,whose function had not been extensively investigated.

Among which, *SAMD9* and *SAMD9L* are derived from a common ancestral gene and encode proteins with 60% similarity. Both *SAMD9L* heterozygote and homozygote mice naturally developed MDS at advanced age. *SAMD9L* protein is localized in early endosomes, and mechanistically, the downregulation of the protein inhibits the fusion of early endosomes, which gives rise to sustained cytokine signals due to the delayed disassembly of cytokine receptors incorporated into the endosomal fraction. Based on these observations, we concluded *SAMD9/SAMD9L* as promising myeloid tumor suppressor genes.

SAMD9 was recently identified as the responsible gene for MIRAGE syndrome, which exhibitsvarious symptoms including myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy. *SAMD9L* missense mutation was also reported to cause Ataxia Pancytopenia syndrome, a disease showing ataxia due to the atrophy of cerebellum and pancytopenia that sometimes progress into MDS. The mutations in these syndromes are supposed to be gain-of-function mutations, in which expression of mutant protein suppresses growth of hematopoietic cells, and this is consistent with our view that *SAMD9/SAMD9L* are tumor suppressor genes. It is noteworthy that the loss of chromosome 7 occurs always in mutant-containing allele when cells acquire growth advantage to evolve into malignant clones.

In this presentation, I would like to discuss the recent findings on how monosomy 7 contributes to the development of myeloid malignancies.