Mass spectrometry-based ribonucleoproteomic approach reveals a novel metabolic pathway for snRNP biogenesis driven by Survival Motor Neuron Protein

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Spinal muscular atrophy (SMA) is characterized by the loss of lower motor neurons and atrophy of muscle, and is an incurable autosomal recessive disease caused by a genetic defect in the SMN1 gene, which codes survival motor neuron 1 protein (SMN1). Despite almost all cells produce SMN1; its reduced levels cause specifically the damage of the lower motor neurons in SMA. Many other neurogenetic disorders, including amyotrophic lateral sclerosis, Huntington’s disease, etc. are also caused by mutations in ubiquitously expressed genes. Thus, understanding the mechanism by which deficiency of SMN1 causes SMA may lead to understanding the pathogenesis of the other neurological diseases as well. SMN1 is involved in the biogenesis of small nuclear ribonucleoprotein (snRNP) complexes, building blocks of splicing machinery (spliceosome), and in the biogenesis of mRNA transport complexes. Therefore, abnormal RNA metabolisms specific to motor neurons are suspected to be the cause of SMA. Although many researchers have been looking for neuron specific mRNAs by using large-scale nucleotide sequencing technologies, none of those has identified such mRNAs related to the cause of SMA yet. In this study, we apply ribonucleoproteomic technologies based on mass spectrometry to the detailed re-examination of snRNPs associated with SMN1 (SMN complexes). These analyses reveal the presence of a short form of U1 snRNA (short U1) as a novel component of SMN complexes. Short U1 lacks Sm protein-binding region and stem loop 4 and has the mono-methylated cap structure at the 5’-end of the U1 snRNA molecule with an irregular posttranscriptional modification. In this presentation, we also show evidence that short U1 is formed dependently on transcription of the U1 snRNA genes, and is eliminated with SMN complexes from the regular pathway of U1 snRNP biogenesis through P bodies, in which RNA surveillance and decay take place. We will discuss a possibility that the deficiency of SMN1 causes aberrant metabolism of short U1 in SMA.

Keywords: neurological disorder, ribonucleoproteomics, RNA-protein complex