Motor dysfunction is triggered by miRNA-mediated knockdown of LAMP2A in mouse cerebellar neurons

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Chaperone-mediated autophagy (CMA) mediates the selective lysosomal degradation of cytosolic proteins. CMA activity is regulated by the expression and complex formation of LAMP2A on lysosomal membranes. We have revealed that CMA impairment is commonly observed in cells expressing several types of mutant proteins causing spinocerebellar ataxia (SCA), characterized by the progressive cerebellar ataxia. Therefore, we assumed that the decrease in CMA activity is related to the pathogenesis of SCA. In the present study, we investigated how CMA impairment by LAMP2A knockdown affects motor function of mice. LAMP2A knockdown was conducted by the cerebellar injection of adeno-associated viral vectors, which express GFP and miRNA against LAMP2A in a neuron specific manner, to 4-week old ICR mice. Motor performances of mice was evaluated by beam walking test. LAMP2A knockdown in cerebellar neurons triggered the progressive motor dysfunction. Immunostaining of cerebellar sections revealed that GFP was mainly expressed in interneurons of molecular layer and granule cells. In addition, decrease in Purkinje cells and shrinkage of molecular layer were observed around GFP-positive neurons. These results suggest that CMA impairment in cerebellar neurons causes ataxic phenotype and degeneration of Purkinje cells.