The role of isomerized protein repair enzyme, PIMT, in cellular functions

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Proteins are susceptible to various spontaneous modifications that could disrupt their biological activities. The formation of L-isoaspartyl (or D-aspartyl) residues, through either the deamidation of asparagines or dehydration of aspartates, is among the most frequently occurring type of deterioration under physiological conditions, and these isomerized residues are able to destroy local conformation of the protein structure and affect the biological activities. Protein L-isoaspartate/D-aspartate *o*-methyltransferase (PIMT) is a conserved and ubiquitous enzyme, which is involved in the repair of various isomerized proteins. PIMT specifically recognizes L-isoaspartyl (or D-aspartyl) residues and catalyzes the transfer of the methyl group of S-adenosyl-L-methionine onto the α-carboxyl group of these residues, which initiates the conversion of the abnormal residues to L-aspartyl residues. PIMT-deficient mice have been shown to die at a mean age of 42 days from progressive epileptic seizures with grand mal and myoclonus. The brains of PIMT-deficient mice start to enlarge at approximately 28 days of age when the apical dendrites of the pyramidal neurons in the cerebral cortices show aberrant arborizations with disorganized microtubules. However, mechanisms leading to progressive epilepsy in PIMT-deficient mice are still obscure. PIMT-deficiency causes the accumulation of isomerized proteins, which might lead to disruption of cellular functions. To clarify the biological role of PIMT, we isolated PIMT knockdown cells from HEK293 cells that were stably transfected with PIMT small interfering RNA expression vector, and analyzed the features of these cells, especially focusing on cell signaling cascade.