UKE Paper of the Month September 2012

Brain, Sep 2012 (PMID: 22961545)

Lysosomal dysfunction causes neurodegeneration in mucolipidosis II 'knock-in' mice

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ABSTRACT: Mucolipidosis II is a neurometabolic lysosomal trafficking disorder of infancy caused by loss of mannose 6-phosphate targeting signals on lysosomal proteins, leading to lysosomal dysfunction and accumulation of non-degraded material. However, the identity of storage material and mechanisms of neurodegeneration in mucolipidosis II are unknown. We have generated 'knock-in' mice with a common mucolipidosis II patient mutation that show growth retardation, progressive brain atrophy, skeletal abnormalities, elevated lysosomal enzyme activities in serum, lysosomal storage in fibroblasts and brain and premature death, closely mimicking the mucolipidosis II disease in humans. The examination of affected mouse brains at different ages by immunohistochemistry, ultrastructural analysis, immunoblotting and mass spectrometric analyses of glycans and anionic lipids revealed that the expression and proteolytic processing of distinct lysosomal proteins such as α-L-fucosidase, β-hexosaminidase, α-mannosidase or Niemann-Pick C2 protein are more significantly impacted by the loss of mannose 6-phosphate residues than enzymes reaching lysosomes independently of this targeting mechanism. As a consequence, fucosylated N-glycans, GM2 and GM3 gangliosides, cholesterol and bis(monoacylglycero)phosphate accumulate progressively in the brain of mucolipidosis II mice. Prominent astrogliosis and the accumulation of organelles and storage material in focally swollen axons were observed in the cerebellum and were accompanied by a loss of Purkinje cells. Moreover, an increased neuronal level of the microtubule-associated protein 1 light chain 3 and the formation of p62-positive neuronal aggregates indicate an impairment of constitutive autophagy in the mucolipidosis II brain. Our findings demonstrate the essential role of mannose 6-phosphate for selected lysosomal proteins to maintain the capability for degradation of sequestered components in lysosomes and autophagolysosomes and prevent neurodegeneration. These lysosomal proteins might be a potential target for a valid therapeutic approach for mucolipidosis II disease.

STATEMENT: "*This paper reports on the generation of a knock-in mouse which shows all symptoms of the human lysosomal storage disorder mucolipidosis II. This comprehensive and interdisciplinary study allowed i) to follow the progression and region-specific neurodegeneration in the disease, ii) the characterization of impaired constitutive autophagy as pathogenic mechanism for neuronal cell death, iii) the identification of storage material using lipidomics and glycomics, and iv) to define subpopulations of lysosomal enzymes that are more susceptible to the loss of mannose 6-phosphate residues than others and therefore more crucial for lysosome functions in the brain. These enzymes represent potential targets for specific enzyme replacement or alternative therapies. Finally, the data provide insight into sequential degradative processes which may be applicable to other lysosomal disorders*."

BACKGROUND: This work was performed at the Department of Biochemistry at the Children's Hospital in the group of Thomas Braulke in collaboration with Michaela Schweizer and Irm Hermans-Borgmeyer of the Center for Molecular Neurobiology. The study was supervised by Dr. Katrin Kollmann and comprises parts of the PhD thesis of Sandra Markmann (MSc) and MD thesis of Anna Katharina Röchert, associated and graduated members of the DFG-funded Research Training Group "Sorting and Interactions between Proteins of Subcellular compartments" (GRK1459). The Braulke group is interested in inherited metabolic and neurodegenerative diseases, and in the biogenesis and functions of the lysosomal compartment.