UKE Paper of the Month March 2015

J Cell Biol (2015) 208(2):171-1

Mannose 6 phosphorylation of lysosomal enzymes controls B cell functions

Takanobu Otomo, Michaela Schweizer, Katrin Kollmann, Valéa Schumacher, Nicole Muschol, Eva Tolosa, Hans-Willi Mittrücker, Thomas Braulke

Abstract: Antigen processing and presentation and cytotoxic targeting depend on the activities of several lysosomal enzymes which require mannose 6-phosphate (M6P) sorting signals for efficient intracellular transport and localization. In this paper, we show that mice deficient in the formation of M6P residues exhibit significant loss of cathepsin proteases in B cells, leading to lysosomal dysfunction with accumulation of storage material, impaired antigen processing and presentation, and subsequent defects in B cell maturation and antibody production. The targeting of lysosomal and granular enzymes lacking M6P residues is less affected in dendritic cells and T cells and sufficient for maintenance of degradative and lytic functions. M6P deficiency also impairs serum immunoglobulin levels and antibody responses to vaccination in patients. Our data demonstrate the critical role of M6P-dependent transport routes for B cell functions *in vivo* and humoral immunity in mice and human.

Statement: *Mucolipidosis II (MLII) is a severe inherited lysosomal storage disorder in children affecting several organs. The disease is caused by the incapability to modify 60 lysosomal enzymes with mannose 6-phosphate (M6P) residues which subsequently leads to missorting and hypersecretion of multiple enzymes associated with lysosomal dysfunction and accumulation of nondegraded storage material. However, depending on the cell type the targeting efficiency varies for selected lysosomal enzymes. In the present study, we demonstrated for the first time that in B cells of an MLII mouse model, lysosomal cathepsin proteases were severely decreased and impair proliferation, differentiation, proteolytic antigen processing and interactions with T helper cells, resulting in reduced antibody response. In contrast, the functions of other immune cells were only moderately affected. Importantly, defective humoral immunity was also observed in MLII patients suggesting that the functionally impaired immune system contributes to the high predisposition to infections in MLII patients.*

Background:

This work was performed as an interdisciplinary project at the Dept. of Immunology and Dept. of Biochemistry, Children´s Hospital in the group of Hans-Willi Mittrücker and Thomas Braulke, respectively, in collaboration with Michaela Schweizer of the Center for Molecular Neurobiology. Takanobu Otomo received a 2-yrs Postdoctoral Fellowship by the Japan Society for the Promotion of Science. This study was supported by the DFG (FOR885, MI 476/3, SFB841 and KFO228), and the Thyssen Foundation. Thomas Braulke's group is interested in the biogenesis and function of lysosomes, and inherited lysosomal storage diseases.