INVESTIGATION OF PEROXISOMAL DISEASE ENTITIES

Y.Mizuno[1], I.Kurochkin[2], C.Schönbach[3],[4*], Y.Okzaki[1]

[1]Division of Functional Genomics and Systems Medicine, Research Center for Genomic Medicine, Saitama Medical University, Hidaka-shi, Japan; [2]Bioinformatics Institute, A*STAR Biomedical Sciences Institutes, Singapore; [3]Department of Biology, School of Science and Technology, Nazarbayev University, Astana, Kazakhstan; *christian.schoenbach@nu.edu.kz; [4]Department of Bioscience and Bioinformatics, Biomedical Informatics R&D Center, Kyushu Institute of Technology, Fukuoka, Japan

INTRODUCTION.

Peroxisomes are single-membrane subcellular organelles whose oxidative functions play important roles in lipid and energy metabolism of almost all eukaryotic cells. In human and mammalian model organisms approximately 120 genes encode peroxisome-targeted proteins. About 30 of these genes have been firmly associated with human peroxisome biogenesis disorders or single-enzyme deficiencies that affect mostly metabolic and developmental processes but sometimes also innate antiviral response, Alzheimer's and ageing. Dysfunctions involve either improper localization of the enzymes and/or peroxisomal biogenesis. Known peroxisomal pathways do not fully account for the processing, degradation of imported proteins and regulation of peroxisome activity. Thus a number of peroxisome-associated pathologies are expected to fall outside the current clinical classifications.

MATERIALS AND METHODS.

We applied a sequence- and motif-based, multi-step knowledge discovery strategy to identify novel peroxisome-targeted protein candidates in mouse and human in addition to *in vitro* and *in vivo* analyses of mouse regulatory circuits associated with lipid metabolism conditions.

RESULTS AND DISCUSSION.

One of the hypothetical protein candidates turned out to be a long-sought protease, called trypsin domain containing 1 (Tysnd1). Tysnd1 is involved in the β-oxidation of very long-chain fatty acids, plasmalogen synthesis. Tysnd1 deficiency in mice interferes with the peroxisomal localization of PTS2 enzymes, causing lipid metabolic abnormalities and male infertility. Sperms of male knock-out mice show acrosomal deformation which is thought to be the effect of altered plasmalogen compositions [1].

CONCLUSIONS.

The results are likely to be of relevance for some patients with Zellweger Syndrome Spectrum disorders. Detailed structure-function relationships of Tysnd1 with regard to substrate interactions and processing and activation await the determination of its 3D structure.

ACKNOWLEDGMENTS.

This work was supported in part by grants from MEXT (YO, CS), Genome Network Project, Innovative Cell Biology by Innovative Technology and Support Project (YO); Strategic Research Center in Private Universities from the MEXT to Saitama Medical University, Ono Medical Research Foundation (YO); Ministry of Education Singapore (CS), and Nanyang Technological University(CS).

REFERENCES.

1. Mizuno Y, *et al.* (2013). Tysnd1 deficiency in mice interferes with the peroxisomal localization of PTS2 enzymes, causing lipid metabolic abnormalities and male infertility. PLoS Genet. 9(2):e1003286.