Mehboob and Lang *Cell Death and Disease* (2021)12:71
https://doi.org/10.1038/s41419-020-03314-y

Cell Death & Disease

REVIEW ARTICLE Open Access

Structure, function, and pathology of protein *O*-glucosyltransferases

Muhammad Zubair Mehboob[1] and Minglin Lang[1,2]

Abstract

Protein *O*-glucosylation is a crucial form of *O*-glycosylation, which involves glucose (Glc) addition to a serine residue within a consensus sequence of epidermal growth factor epidermal growth factor (EGF)-like repeats found in several proteins, including Notch. Glc provides stability to EGF-like repeats, is required for S2 cleavage of Notch, and serves to regulate the trafficking of Notch, crumbs2, and Eyes shut proteins to the cell surface. Genetic and biochemical studies have shown a link between aberrant protein *O*-glucosylation and human diseases. The main players of protein *O*-glucosylation, protein *O*-glucosyltransferases (POGLUTs), use uridine diphosphate (UDP)-Glc as a substrate to modify EGF repeats and reside in the endoplasmic reticulum via C-terminal KDEL-like signals. In addition to *O*-glucosylation activity, POGLUTs can also perform protein *O*-xylosylation function, i.e., adding xylose (Xyl) from UDP-Xyl; however, both activities rely on residues of EGF repeats, active-site conformations of POGLUTs and sugar substrate concentrations in the ER. Impaired expression of POGLUTs has been associated with initiation and progression of human diseases such as limb-girdle muscular dystrophy, Dowling–Degos disease 4, acute myeloid leukemia, and hepatocytes and pancreatic dysfunction. POGLUTs have been found to alter the expression of cyclin-dependent kinase inhibitors (CDKIs), by affecting Notch or transforming growth factor-β1 signaling, and cause cell proliferation inhibition or induction depending on the particular cell types, which characterizes POGLUT's cell-dependent dual role. Except for a few downstream elements, the precise mechanisms whereby aberrant protein *O*-glucosylation causes diseases are largely unknown, leaving behind many questions that need to be addressed. This systemic review comprehensively covers literature to understand the *O*-glucosyltransferases with a focus on POGLUT1 structure and function, and their role in health and diseases. Moreover, this study also raises unanswered issues for future research in cancer biology, cell communications, muscular diseases, etc.

Facts

- *POGLUTs*, similar to their *Drosophila* homolog *rumi*, add *O*-Glc to serine residues within the consensus sequences of EGF-like repeats found in several proteins and these repeats are essential for regulating many cellular functions.
- POGLUTs have a CAP10 catalytic domain involved in transferring Glc from UDP-Glc and a KDEL-like terminal signal, necessary for their binding to the KDEL receptors and recycling to the endoplasmic reticulum.
- Despite the glucosyltransferase activity, POGLUTs can also act as xylosyltransferases, i.e., adding Xyl from UDP-Xyl onto a serine residue.
- POGLUTs use both Notch and TGF-β1 pathway to manipulate the expression of CDKIs and, in turn, function in a cell type-dependent manner. Their overexpression increases cell proliferation in some cells, while inhibiting cell growth in other cells.

Correspondence: Minglin Lang (langml@ucas.ac.cn)
[1]CAS Center for Excellence in Biotic Interactions, College of Life Science, University of Chinese Academy of Sciences, Beijing 100049, China
[2]College of Life Science, Hebei Agricultural University, Baoding 071001, China
Edited by F. Pentimalli

© The Author(s) 2021
Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

SPRINGER NATURE
CDDpress