水谷糖質科学振興財団　第　31 回研究助成　研究報告書

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研究課題：*N*型糖鎖修飾を抑制する内在性機構の意義とがんにおける機能の解明
Grant Title：An intrinsic mechanism to suppress N-glycosylation and its role in Cancer
研究報告：(a) ABSTRACT：

1. Aim: Dolichol-linked oligosaccharides (DLOs) are glycan precursors for *N*-glycosylation in the endoplasmic reticulum (ER). It has long been known that DLO biosynthesis is attenuated during glucose deprivation in mammalian cells, but its biological relevance remains largely unexplored. The aim of this study was to elucidate the role of glucose-dependent regulation of DLO biosynthesis in cancer cell fates in the tumor microenvironment, where glucose availability is often limited due to excessive glucose consumption by cancer cells.

2. Methods: DLO biosynthesis requires three types of nucleotide sugars, all of which can be synthesized through glucose metabolism. We previously reported that during glucose deprivation, decreased GDP-mannose supply is the major cause of DLO biosynthesis attenuation (Harada Y *et al.*, *PNAS* 110:19366, 2013). However, glucose deprivation causes complex metabolic stresses, making it difficult to extract cell fates associated with changes in DLO biosynthesis. To circumvent this problem, we used mannose phosphate isomerase (MPI)-knockout human cancer cells, which require exogeneous mannose for GDP-mannose biosynthesis, allowing us to directly manipulate GDP-mannose supply by controlling extracellular mannose availability.

3. Results: DLO biosynthesis was attenuated by depleting mannose to moderate levels, leading to severe hypoglycosylation while minimally affecting cell survival. We demonstrated that the activation of PERK, which is an ER stress sensor, was required for cell survival during mannose deprivation. We further found that mannose deprivation to minimal levels still maintained cell survival while impairing lysosomal glycocalyx and sensitizing cells to lysosomotropic agents. Our findings suggest that DLO biosynthesis attenuation during glucose deprivation initiates a pro-survival arm of the ER stress response, most likely by causing hypoglycosylation. At the same time, the hypoglycosylation impaired lysosomal integrity, rendering cancer cells vulnerable to lysosomal stress. These findings establish DLO biosynthesis as a mechanism by which cancer cells translate nutrient availability into distinct cell fates by suppressing *N*-glycosylation (Wang Z, *et al.*, *J Biol Chem* 302:111213, 2026).