



Title	Mannose metabolic pathway senses glucose supply and regulates cell fate decisions
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論文内容の要旨
Synopsis of Thesis

氏 名 Name	WANG Ziwei
論文題名 Title	Mannose metabolic pathway senses glucose supply and regulates cell fate decisions (マンノース代謝経路はグルコースの供給を感知し、細胞の運命決定を制御する)
論文内容の要旨 〔目 的(Objective)〕 Glucose deprivation is a hallmark of the tumor microenvironment and induces adaptive responses that enable cancer cells to survive and acquire malignant properties during tumor progression. Elucidating the molecular mechanisms underlying these adaptive responses is essential for the development of effective cancer therapies. One of the consequences caused by glucose deprivation is the suppression of asparagine-linked glycosylation (<i>N</i>-glycosylation), a fundamental post-translational modification of proteins synthesized in the endoplasmic reticulum (ER). <i>N</i>-Glycosylation is initiated by the assembly of dolichol-linked oligosaccharides (DLOs), which consist of three glucose, nine mannose, and two <i>N</i>-acetylglucosamine (GlcNAc) residues linked to pyrophosphate-dolichol (Glc₃Man₉GlcNAc₂-PP-dolichol). The biosynthesis of DLOs requires three nucleotide sugars, UDP-GlcNAc, GDP-mannose, and UDP-glucose, which are derived from glucose metabolism. We previously reported that owing to depletion of GDP-mannose, glucose deprivation causes biosynthetic arrest and degradation of DLOs in the ER, thereby causing <i>N</i>-glycosylation defects. However, because glucose deprivation simultaneously perturbs multiple metabolic pathways, it was difficult to investigate the specific role of <i>N</i>-glycosylation defects in cell fate decisions. In this study, we aimed to overcome this limitation and elucidate the specific role of <i>N</i>-glycosylation suppression under glucose deprivation by using a metabolic compartmentalization strategy that selectively shuts down GDP-mannose biosynthesis independently of glucose deprivation. 〔方法ならびに成績(Methods/Results)〕 Metabolic compartmentalization approach involved knockout (KO) of the <i>MPI</i> gene, which encodes mannose phosphate isomerase that interconnects glycolysis and the GDP-mannose biosynthesis. In <i>MPI</i>-KO cells, GDP-mannose is synthesized solely from mannose that is supplemented in the culture medium. In contrast, mannose deprivation depletes GDP-mannose in <i>MPI</i>-KO cells, leading to <i>N</i>-glycosylation defects that mimicked the effects of glucose deprivation. We found that mannose deprivation did not reduce the viability of <i>MPI</i>-KO cells. Mechanistically, mannose deprivation-induced <i>N</i>-glycosylation defects activated unfolded protein response (UPR) in the ER, among which PERK-eIF2α axis was required to maintain the viability of mannose-deprived <i>MPI</i>-KO cells. Our metabolic compartmentalization approach allowed for specific inactivation of glucose metabolism by depleting glucose from culture of <i>MPI</i>-KO cells, revealing that this metabolic stress was lethal and inhibited translation. Moreover, we performed label-free glycoproteomics and gene ontology (GO) analysis to further dissect the role of mannose deprivation-induced <i>N</i>-glycosylation defects in cell survival. The analyses revealed lysosome as a GO term in the top 10 hits. Functionally, mannose deprivation-induced <i>N</i>-glycosylation defects still preserved glycocalyx layer in the luminal side of the lysosomes, which was critical for cell survival. 〔総 括(Conclusion)〕 In conclusion, we demonstrated that low metabolic flux of glucose into mannose pathway initiates alterations in homeostasis of the ER and lysosomes, at least in part through <i>N</i>-glycosylation defects, leading to cell fate decisions. The context-dependent role of <i>N</i>-glycosylation may fulfill the spatial and temporal regulation of cell fate during different phases of glucose deprivation. This study also reveals a clear functional segregation between the glucose and mannose pathways in stress signaling pathways, which enables cells to fine-tune their responses to specific metabolic perturbations. Thus, exploiting a compartmentalization-based approach to dissect metabolic stress may provide valuable insights into how cells coordinate complex metabolic programs to regulate their fate under nutrient-limited conditions. However, not all <i>MPI</i>-KO cell lines tested in this study reacted to sugar deprivation in the same manner. Thus, further studies are necessary to elucidate the mechanisms that determine cell fates during glucose deprivation, which might offer novel therapeutic strategies that target tumor microenvironment.	

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

This dissertation investigates how mammalian cells regulate cell fate under conditions of glucose deprivation, focusing on the interplay between cellular metabolism and protein glycosylation. The author established a genetically engineered cell system in which the GDP-mannose biosynthesis pathway was uncoupled from glycolysis, thereby enabling precise manipulation of asparagine-linked glycosylation (*N*-glycosylation) through mannose supply independent of glucose availability. This experimental strategy allowed the author to dissect the specific contribution of the mannose pathway to cellular stress responses without the confounding effects of global glucose starvation.

Using this system, the author demonstrated that glucose deprivation limits GDP-mannose production and induces a moderate suppression of *N*-glycosylation, which in turn promotes cell survival. Mechanistically, this protective effect is mediated by activation of the pro-survival branch of the unfolded protein response in the endoplasmic reticulum, particularly the PERK-eIF2 signaling pathway, which helps cells adapt to metabolic stress. In contrast, when *N*-glycosylation is suppressed more severely, the protective glycocalyx within the lysosomal lumen is depleted, resulting in compromised lysosomal membrane integrity and increased sensitivity to lysosome-damaging agents. These findings reveal a context-dependent, biphasic role of *N*-glycosylation in the regulation of cell fate, whereby distinct levels of glycosylation control different adaptive and maladaptive cellular responses. Importantly, this study proposes that such spatial and temporal regulation of *N*-glycosylation may contribute to cell fate decisions during different phases of glucose deprivation. The results further provide new insights into how cancer cells may fine-tune *N*-glycosylation to adapt to low-glucose environments. Overall, these findings offer important mechanistic insight into how metabolic flux through the mannose pathway governs endoplasmic reticulum and lysosomal homeostasis and thereby influences cell fate decisions. The study is technically sound, conceptually original, and of significant academic value. This research is worth being granted a doctoral degree (medicine).