A sphingolipid-mTORC1 nutrient-sensing pathway regulates animal development by an intestinal peroxisome relocation dependent gut-brain crosstalk

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Animals have developed many signaling mechanisms that alter cellular and developmental programs in response to changes in nutrients and their derived metabolites, many of which remain to be understood. Effective assays in model organisms are often essential to explore nutrient-sensing mechanisms that commonly require cross-tissue coordination under physiological conditions, which are impractical to study in immortalized cell cultures. We recently uncovered that glucosylceramides, the core structural components of glucosylated sphingolipids, act as a critical nutrient signal for the overall amino acid level to promote development by activating the intestinal mTORC1 signaling pathway. However, how the intestinal GlcCer-mTORC1 activity regulates development throughout the whole body is unknown. Through a large-scale genetic screen, we found that the peroxisome is critical for antagonizing the GlcCer-mTORC1-mediated nutrient signal. Mechanistically, deficiency of glucosylceramide, inactivation of the downstream mTORC1 activity, or prolonged starvation relocated peroxisomes closer to the intestinal apical region to release peroxisomal-beta-oxidation derived hormones that target chemosensory neurons to arrest the animal development. Our data illustrated a new gut-brain axis for orchestrating nutrient-sensing dependent development in Caenorhabditis elegans, which may also explain why glucosylceramide and peroxisome become essential in metazoans. (This article has been accepted in principle by Cell Reports)

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