

INSIGHTS

Who gets the calories? An endothelial checkpoint for fat expansion

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MYCT1–IFITM2/3 interaction links endothelial endolysosomal trafficking to white adipose tissue expansion and exposes the endothelium as a decisive regulator of systemic energy partitioning, not a passive conduit for nutrient delivery (Wetterwald et al., 2026, <https://doi.org/10.1084/jem.20251497>).

The vasculature is traditionally viewed as a conduit, the infrastructure that enables immune cell trafficking, nutrient distribution, and oxygen delivery to tissues. Although accurate, this definition is incomplete and underestimates the instructive and regulatory power of blood vessels. Far from being passive pipelines, endothelial cells (ECs) actively shape organ physiology. From early development onward, angiocrine cues and reciprocal vascular–parenchymal interactions guide tissue patterning and differentiation (Gomez-Salinerio et al., 2021; Hofmann et al., 2010; Ryan and Cleaver, 2022). Later in life, dynamic changes in vascular density and function influence tissue growth, regeneration, and pathological expansion, including tumor progression (Pasquier et al., 2020).

As molecular insight into nutrient transport and endothelial signaling deepens, it has become increasingly clear that the endothelium is not merely a distributor of resources but a decisive regulator of how those resources are sensed, allocated, and utilized. The vasculature operates as an integrative organ capable of coordinating local tissue demands with systemic metabolic states. Thereby, exerting far-reaching control over organ homeostasis and disease.

In the context of nutrient transfer, the interface between adipose tissue and the vasculature represents a particularly compelling focal point (Aizaim et al., 2023). Traditionally, white adipose tissue expansion has been attributed primarily to adipocytes, immune cells, and systemic hormonal cues, with the

vasculature cast largely as a structural scaffold and delivery network. Even when ECs are implicated in metabolic regulation, their influence is typically framed in terms of vessel density, angiogenic remodeling, inflammation, or barrier integrity. The study by Wetterwald et al. (2026) departs from this paradigm by proposing that endothelial mTORC1 activity itself functions as a metabolic checkpoint that determines how much energy ultimately becomes available for storage in adipocytes.

Specifically, the investigators uncovered that MYCT1, a transmembrane phosphoglycoprotein highly abundant in ECs, is a critical negative regulator of mTORC1 signaling. Their data demonstrate that endothelial-specific deletion of Myct1 reduced adiposity in a manner that was independent of vascular density, adipogenesis, or systemic metabolic activity (Wetterwald et al., 2026). Furthermore, using scRNAseq analysis from the endothelial-specific MYCT1 null mice and in vitro experiments, the authors noted a clear increase in mTORC targets and p70/S6 kinase phosphorylation, indicating a higher activation of mTORC1 signaling.

But, how does a transmembrane protein like MYCT1 control mTORC1? Using immunoprecipitation followed by MS, the authors first identified interferon-induced transmembrane protein 2 and 3 (IFITM2/3) as direct interactors of MYCT1. Interestingly, MYCT1 and IFITM2/3 are colocalized in early endosomes, and in the absence of MYCT1, there is an expansion of the early endosomal compartment with a significant increase in



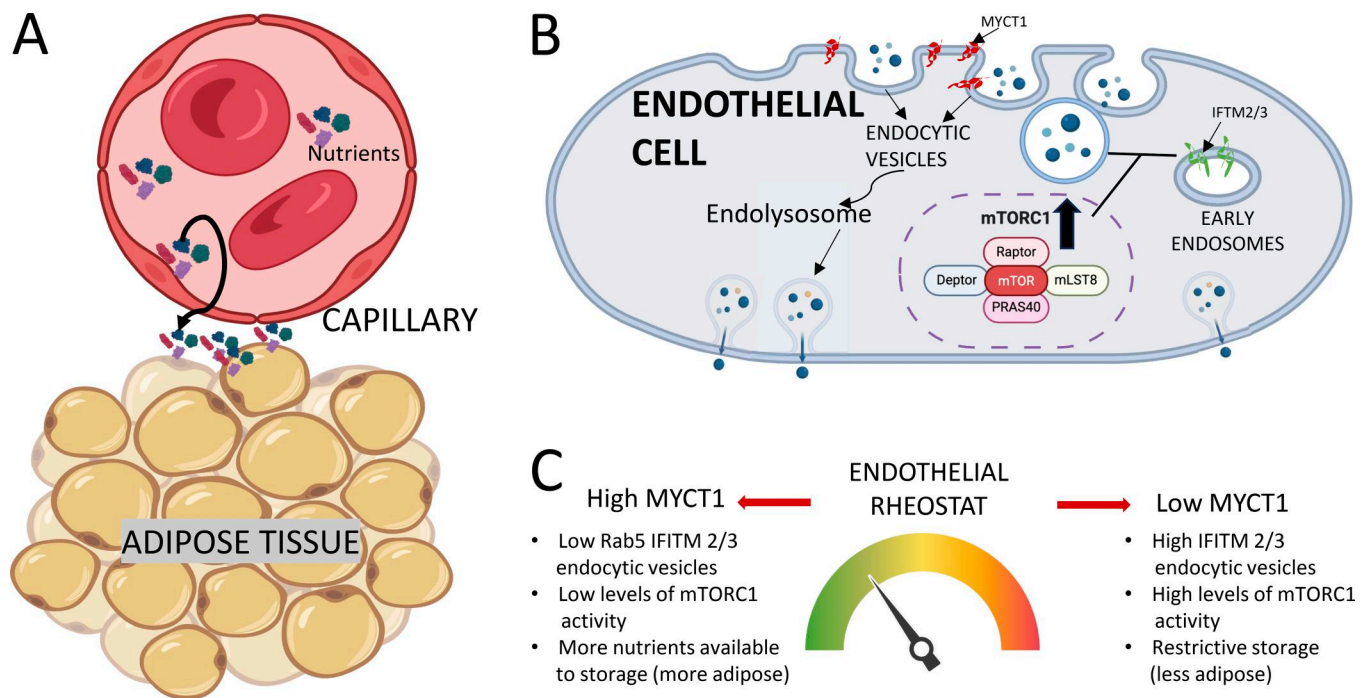
M. Luisa Iruela-Arispe.

total IFITM2/3 protein levels. The convergence of MYCT1 and IFITM2/3 seems to occur shortly after endocytosis and appears to regulate the process. In fact, MYCT1 was shown to restrict endocytic rate in hematopoietic stem cells (Agudé-Gorgorió et al., 2024) and, in the Wetterwald study, the authors showed that this effect is also conserved on ECs. In fact, absence of MYCT1 in the endothelium significantly increases plasma protein uptake by endocytosis, which leads to an expansion in endolysosomal trafficking and increase in mTORC1 activity. Thus, under wild-type conditions, MYCT1 limits mTORC1 activation in the endothelium, making more nutrients available for storage in the adipose tissue. The key conceptual advancement is the assertion that endothelial intracellular nutrient sensing, not vascular growth or perfusion, can shape systemic energy partitioning.

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ECs can regulate systemic energy allocation through MYCT1-IFITM2/3-mTORC1. (A) Delivery of nutrients to adipose tissue requires trafficking through ECs (arrow). (B) Nutrients are endocytosed by ECs in a regulated fashion, controlled by MYCT1. Once endocytosed, MYCT1 vesicles fused with early endosomes and lysosomes, promoting activation of mTORC1. Modified nutrients are released to tissues in the abluminal side of the EC. However, levels of MYCT1 control the type of endolysosomal trafficking, resulting in more or less transfer of nutrients to adipose tissue. (C) MYCT1 levels in the endothelium functions as a metabolic rheostat by controlling levels of mTORC1. Figure generated in BioRender.

A second conceptual advance lies in the mechanistic link between membrane trafficking and metabolic signaling. By identifying MYCT1-IFITM2/3 complexes as modulators of endocytic routing and lysosomal dynamics, the study connects processes traditionally associated with membrane biology to the regulation of mTORC1-driven metabolism. In doing so, it reframes endolysosomal trafficking as a metabolic rheostat within ECs, with consequences that extend beyond the vessel wall (figure).

Taken together, these findings reposition the endothelium as an active metabolic gatekeeper that influences systemic energy allocation by regulating its own nutrient consumption, in addition to classical angiocrine or structural mechanisms. Importantly, the work also challenges the assumption that meaningful metabolic phenotypes must arise from overt systemic alterations. Instead, it suggests that subtle, cell-autonomous shifts in endothelial nutrient handling, which might be undetectable by conventional metabolic assays, may cumulatively redirect energy distribution at the tissue level. If substantiated and generalized, this framework establishes the endothelium as a

competitive metabolic compartment capable of modulating adipose expansion independently of angiogenesis or endocrine control.

Taken together, this work opens a series of fundamental questions that extend well beyond MYCT1. For example: Is endothelial nutrient consumption sufficient to measurably influence systemic energy balance? Does endothelial mTORC1 function as a general metabolic rheostat across tissues and physiological states (fasting, obesity, exercise, and tumor growth) or is this mechanism context dependent?

Finally and more broadly, the study invites us to reconsider the metabolic autonomy of the endothelium. Are MYCT1-IFITM2/3 complexes part of a larger trafficking-based network that links membrane organization to nutrient sensing? Do endothelial endolysosomal dynamics regulate additional metabolic pathways beyond mTORC1? And could similar endothelial metabolic checkpoints influence diseases ranging from obesity and insulin resistance to cancer and cachexia? Perhaps most provocatively, the work shifts the central question in vascular biology from how blood vessels enable tissue growth to whether ECs actively determine how energy is partitioned within the

organism. If generalized, this would represent a substantial conceptual pivot for the field.

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