TRPV4 acetylation supports prenatal anabolism

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A recent study published at *Vita* reports that acetylation of TRPV4 uncouples fetal mTORC1 from glucose sensing by blocking the inhibitory Aldolase-LKB1-AMPK axis. This finding identifies a unique metabolic adaptation that supports prenatal anabolism under maternal nutrient fluctuations.

The maintenance of metabolic homeostasis requires tight coupling between nutrient availability and cellular growth programs. Yet fetal development presents a unique physiological challenge: the demand for rapid anabolic growth must be met within a chronically low-glucose environment, a prerequisite for efficient transplacental nutrient transfer. How fetal tissues sustain anabolism under these conditions remains a fundamental question in developmental biology.

Central to metabolic coordination is the mechanistic target of rapamycin complex 1 (mTORC1), the master regulator of cell growth[1]. In adult tissues, mTORC1 integrates nutrient availability and growth factor signaling to promote anabolism while suppressing catabolic programs. In response to nutrients, mTORC1 is recruited to the lysosomal surface by the heterodimeric Rag guanosine triphosphatases (GTPases), which are anchored to the lysosomal membrane by the pentameric Ragulator complex. Dedicated sensing machineries for important amino acids such as leucine, arginine and methionine, as well as the lipid cholesterol, have been identified, and shown to converge on the GTPase activating protein, GATOR1, inhibiting its GAP activity and promoting the transition of the Rags into their active nucleotide-bound state, a conformational prerequisite for mTORC1 recruitment[1].

At the lysosome, growth factor-derived signals license mTORC1 kinase activity toward "canonical" substrates involved in anabolic regulation (including S6-kinase 1 and 4E-binding protein 1/2) via the PI3K-Akt axis, which inhibits the Tuberous Sclerosis (TSC) complex to release its GAP activity toward Rheb. This allows GTP-bound Rheb to directly stimulate mTORC1 catalytic activity only when the kinase complex is localized to the lysosomal membrane.

Another major input to mTORC1 is glucose, a major determinant of cellular energy levels that has been shown to regulate mTORC1 via both the nutrient- and growth factor branches[2,3].

Under low glucose, elevated AMP/ATP and ADP/ATP ratios activate AMP-dependent protein kinase (AMPK), which phosphorylates TSC to promote its mTORC1-inhibiting GAP activity, while carrying out inhibitory phosphorylation on the key mTORC1 subunit, Raptor[3]. In parallel, an AMPK-independent pathway monitors the levels of the glycolytic intermediate, dihydroxyacetone phosphate (DHAP), through a yet-unidentified lysosomal sensor[4].

Recent studies have delineated a further, AMPK-dependent glucose-sensing axis converging on the lysosome, which monitors glycolytic flux via the enzyme aldolase[5]. Under glucose-replete conditions, high levels of another glycolytic intermediate, fructose-1,6-bisphosphate (FBP), saturate aldolase, preventing its inhibitory association with the lysosomal signaling machinery. Conversely, glucose starvation leads to FBP depletion, at concentrations thought to be low enough to leave aldolase "unoccupied." This triggers a conformational shift that allows aldolase to bind and inhibit Transient Receptor Potential Vanilloid (TRPV) channels, which conduct calcium across the membrane of the endoplasmic reticulum (ER)[6]. The resulting cessation of local lysosomal calcium efflux induces TRPVs to interact with the vacuolar adenosine triphosphatase (v-ATPase), which, in turn, serves as a scaffold for the recruitment of the AXIN–LKB1 complex to the lysosome[7]. This assembly is thought to activate AMPK, enabling it to inhibit mTORC1 signaling during energy stress through a mechanism involving the Ragulator–Rag GTPase complex.

In a recent study published in *Vita*, Zhang and colleagues demonstrate that fetal tissues bypass the AMPK-dependent inhibitory machinery to prioritize anabolism over energy conservation[8]. The authors start from the observation that, in fetal hepatocytes, mTORC1 signaling remains active despite glucose withdrawal. They observe that, despite strong decrease of intracellular FBP levels and the resulting binding of aldolase to TRPV4 (the most highly expressed TRPV in fetal hepatocytes), the calcium-exporting activity of TRPV4 remained uninhibited. Consequently, lysosomal AMPK could not be activated and mTORC1 remained lysosome-bound and active.

Through mass spectrometry combined with systematic K-to-R mutagenesis, the authors identify TRPV4 acetylation at K608 as a critical metabolic checkpoint that functions as a molecular shield. Although K608 acetylation did not prevent the physical interaction between unoccupied aldolase and the TRPV4 channel, this modification maintains local Ca^{2+} efflux even in the presence of bound aldolase. Consequently, the v-ATPase–Ragulator complex remains in an active conformation, shielding fetal mTORC1 from the canonical starvation-induced dissociation.

The P300 acetyltransferase was shown to be required for K608 acetylation of TRPV4. Supporting the physiological importance of this regulatory mechanism, a liver-specific knockin of non-acetylatable K608R TRPV4 mutant led to increased embryonic lethality and decreased liver and overall size in surviving pups.

These findings add to a growing body of evidence suggesting that post-translational modifications can re-wire key nutrient-sensing pathways to support the unique demands of

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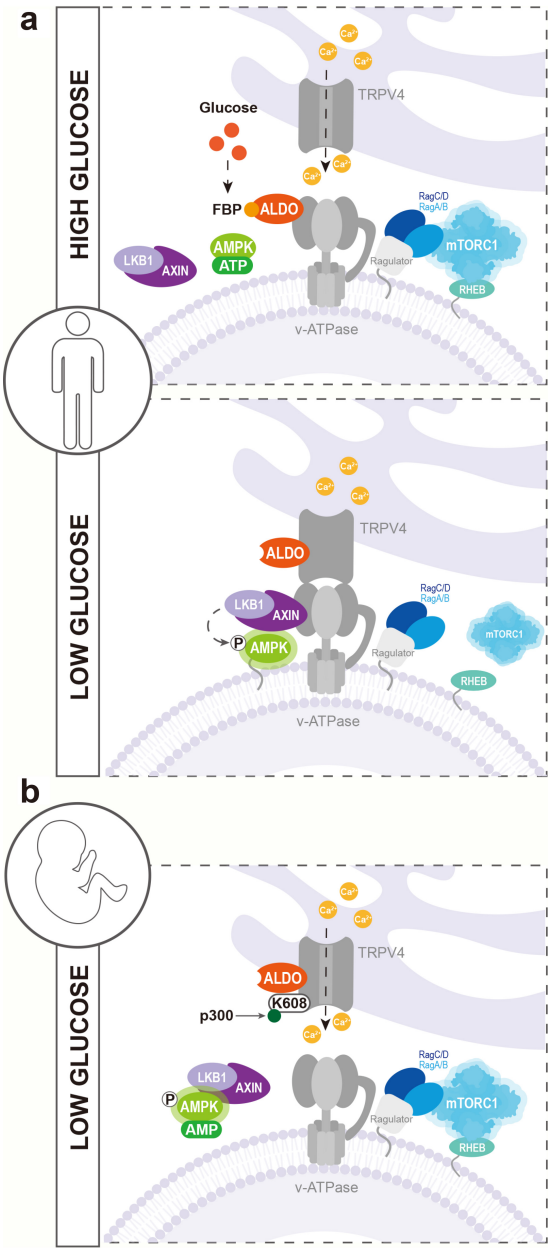

Fig. 1 Models of glucose-sensing pathways under high and low glucose conditions in adult and fetal cells. a Adult liver. High glucose (upper panel): when glucose is abundant, FBP binds to aldolase (ALDO), which associates with the lysosomal v-ATPase and supports its activity. The TRPV4 channel at ER–lysosome contact sites mediates local Ca^{2+} release. Under these conditions, v-ATPase remains active, enabling recruitment and activation of mTORC1 at the lysosomal surface via the Ragulator–Rag GTPases and RHEB. Low glucose (lower panel): unoccupied aldolase interacts with TRPV4 and inhibits its activity, leading to reduced local Ca^{2+} levels. This promotes a reorganization into an aldolase–TRPV4–v-ATPase complex that results in v-ATPase inhibition. Consequently, mTORC1 dissociates from the lysosome. In parallel, AXIN recruits LKB1, leading to phosphorylation and activation of AMPK at the lysosomal membrane. **b** Fetal liver under low glucose conditions. Reduced ATP levels increase the AMP/ATP ratio, resulting in allosteric activation of AMPK. Although FBP-unbound aldolase interacts with TRPV4, acetylation of TRPV4 at K608 (mediated by p300) prevents its inhibition. As a result, local Ca^{2+} release is maintained, v-ATPase remains active, and mTORC1 stays associated with the lysosome, maintaining its activity despite low glucose availability.

prenatal growth.

The implications of these findings extend beyond prenatal physiology, raising fundamental questions about the metabolic transitions occurring at birth. As previously reported by Efeyan et al., the prompt inactivation of mTORC1 post-partum is required to promote a systemic catabolic switch[9]. The consequent induction of autophagy is essential for *de novo* gluconeogenesis, ensuring neonatal survival during the transient systemic drop in glucose levels. This transition from a "glucose-insensitive" fetal state to a "sensing-competent" neonatal state is therefore critical. Whether the TRPV4-aldolase axis, and specifically the removal of the K608 acetyl shield, is a primary driver of this developmental reprogramming remains an open avenue for future exploration. Beyond development, the TRPV4-aldolase axis emerges as a compelling target for conditions characterized by metabolic "rigidity". In aged populations, where muscle malleability and fatigue resistance are often compromised, the ability to bypass the energetic requirements for AMPK activation through small-molecule modulation of TRPV channels could offer a novel strategy to restore metabolic fitness. Additionally, identification of pathways to decouple mTORC1 from nutrient sensing could play a major role also in cancer, as tumors often thrive in hypoxic, nutrient-depleted microenvironments that would normally trigger mTORC1 inhibition.

Ultimately, this work reinforces the view of the lysosome as a sophisticated metabolic hub where metabolite signals, both intrinsic and from non-lysosomal compartments, converge to dictate cellular fate via a multiplicity of mechanisms, including metabolite-driven post-translational modifications.

COMPETING INTERESTS

The author declares no competing interests.

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ADDITIONAL INFORMATION

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