COMMENTARY

CaSR-Gq-ERK1/2: A New Addition to the Liver-α Cell Axis in Hyperaminoacidemia-Triggered α Cell Proliferation

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DESCRIPTION

Glucagon was discovered 100 years ago by Kimball and John due to its potent glucogenic activity [1]. Aside from promoting glucose production using glucogenic Amino Acids (AA) and other substrates, glucagon is also a crucial hormone in stimulating Amino Acids (AA) catabolism by activating ureagenesis in the liver [2-4]. Loss of Glucagon Receptor (GCGR) function results in marked increase of plasma AA concentration (hyper aminoacidemia) from zebrafish to humans. Hyper aminoacidemia in turn promotes compensatory proliferation of glucagon-producing α cells [5-8], revealing a liver-α cell axis that tunes α cell mass and function with glucagon signaling in the liver [9,10]. How hyperaminoacidemia promotes α cell proliferation specifically is not well understood.

Not surprisingly, previous studies have identified an essential role for the AA sensor mTORC1 in hyperaminoacidemia-induced α cell proliferation [8]. In zebrafish and mice, the small neutral AA transporter Slc38a5, or SNAT5, is also important for the compensatory α cell proliferation. However, genetic activation of mTORC1 alone in mouse α cells failed to induce α cell hyperplasia in neonatal islets. Although increased proliferation was detected in adult mice due to impaired GCGR function in the liver, the increase is significantly lower than in Gcgr-/- islets [11]. Thus, other cell intrinsic signals may also be involved in the compensatory α cell proliferation. Identification of the additional pathways is therefore important for understanding how hyperaminoacidemia stimulates α cell proliferation. Our recent study uncovered that the AA-sensitive Calcium Sensing Receptor (CaSR), via Gq signaling pathway, synergized with mTORC1 in promoting α cell proliferation. Notably, co-activation of Gq and mTORC1 is sufficient for inducing pancreatic α cell proliferation in the absence of hyperaminoacidemia [12].

CaSR is a class C G-protein-coupled Receptor (GPCR) that senses L-AA and Ca2+ among other endogenous ligands [13,14]. CaSR is expressed not only in calcitropic tissues (eg. parathyroid glands, kidney and breast), but also in noncalcitropic tissues including enteroendocrine and pancreatic islets [13]. In the pancreatic islets, CaSR is highly expressed in α and β cells, and regulates the secretion of these pancreatic endocrine cells [15,16]. Importantly, CaSR also regulates cell proliferation, as its mutation or aberrant activation is associated with various cancers and alters pancreatic islet mass [17-19]. These clues advanced CaSR as a candidate in mediating hyperaminoacidemia-induced pancreatic α cell proliferation.

In our study, we first identified that CaSR is cell-autonomously required for hyperaminoacidemia-induced α cell proliferation in zebrafish and mouse islets [12]. CaSR couples to multiple heterotrimeric G-proteins (Gq/11, Gi/o, or G12/13) to regulate intracellular signal transduction cascades [20,21]. Using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) in zebrafish, we found that CaSR signals through Gq not Gi, to mediate α cell proliferation. Importantly, co-activation of Gq and mTORC1 was sufficient for α cell proliferation in normal aminoacidemia [12]. CaSR-Gq cascades induce elevated cytosolic calcium concentrations and activate the Mitogen Activated Protein Kinase (MAPK) pathway, which ultimately phosphorylate and activate ERK1/220. Our study also demonstrated that Mek1/2-ERK1/2 was the downstream effector of CaSR-Gq. Unexpectedly, we also found that CaSR-Gq-ERK1/2 was required for mTORC1 activation in mediating hyper aminoacidemia-induced α cell proliferation [12]. We therefore identified the two major necessary and sufficient pathways activated by hyperaminoacidemia to promote α cell proliferation. As such, we revealed a previously unknown physiological role of CaSR in the liver-α cell axis.

Our recent study also raises further questions: 1.

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What is the exact interplay between CaSR-Gq-ERK1/2 and mTORC1 during hyper aminoacidemia inducing α cell proliferation? 2. Why α cell is specifically sensitive to hyper aminoacidemia? We believe the upcoming studies by us or others will answer these questions soon.

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