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Mapping Glucagon Resistance Beyond the Pancreas: A Multi-Organ Transcriptomic Characterization of the GCGR–cAMP–PKA–CREB Axis

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Abstract

Introduction

Glucagon dysregulation is increasingly recognized as a contributor to metabolic disease, yet glucagon resistance has been investigated predominantly as a hepatic phenomenon. However, whether the molecular architecture of glucagon signaling extends across multiple metabolic organs remains incompletely characterized.

Objective

To map the tissue-expression architecture of the glucagon receptor–cyclic AMP–protein kinase A–cAMP response element-binding protein (GCGR–cAMP–PKA–CREB) axis across the pancreas, liver, kidney, adipose tissue, and skeletal muscle and to explore its implications for multi-organ glucagon resistance.

Methods

This in silico systems-biology study analyzed publicly available human transcriptomic resources. Eighteen genes representing receptor, proximal transducer, intermediate effector, and downstream transcriptional components of the GCGR–cAMP–PKA–CREB pathway were curated from the KEGG glucagon signaling pathway. Tissue-level expression patterns were examined using GTEx data across five metabolically relevant tissues and interpreted alongside published protein-expression evidence.

Results

GCGR displayed the most tissue-restricted expression pattern, with high expression in liver, moderate-to-high expression in kidney cortex, and low expression in subcutaneous adipose tissue and skeletal muscle. Whole-pancreas GCGR expression was comparatively low, consistent with dilution of endocrine transcripts by the predominant exocrine compartment. In contrast, GNAS, adenylate cyclases, PKA subunits, CREB1, and CRTC2 were broadly expressed across tissues. PPARGC1A showed a distinct terminal-effector distribution, being relatively prominent in kidney and skeletal muscle but lower in liver and pancreas.

Conclusion

The GCGR–cAMP–PKA–CREB axis exhibits a receptor-centered, asymmetric multi-organ expression architecture. These findings support receptor availability and tissue-specific transcriptional output as potential determinants of susceptibility to glucagon resistance and provide a framework for future donor-matched and cell-resolved validation of a pancreatic-to-peripheral molecular continuum.

INTRODUCTION

Alpha-cell dysfunction, manifested as fasting and postprandial hyperglucagonemia, is now recognized as a core and non-redundant contributor to hyperglycemia in type 2 diabetes, acting independently of insulin deficiency.[1] Beyond this classic counter-regulatory role, the pancreatic alpha cell and its secreted hormone participate in a considerably broader physiological network, since the glucagon receptor (GCGR) is expressed across the liver, kidney, adipose tissue, skeletal muscle, and central nervous system.[2,3] Building on this distribution, glucagon resistance, defined as impaired GCGR-cAMP-CREB signal transduction despite preserved or elevated glucagon secretion, has been proposed as a receptor-level mechanism operating in the liver, where it contributes to metabolic dysfunction-associated steatotic liver disease.[4,5] Comparable receptor-level defects have now been described independently in the kidney, where loss of glucagon receptor signaling reproduces steatosis, oxidative stress, and fibrosis, and where sustained glucagon exposure itself accelerates diabetic kidney disease progression.[6,7]

However, it remains uncertain whether the alpha-cell secretory failure that initiates hyperglucagonemia and the receptor-level resistance independently documented in the liver and kidneys represent sequential stages of a single, continuous pathophysiological process, connected by a shared molecular signature of glucagon receptor (GCGR) pathway suppression, or whether they instead constitute mechanistically distinct defects that simply converge on a similar clinical phenotype. Despite the separate characterization of alpha-cell dysfunction, on one hand, and organ-specific glucagon resistance, on the other, it has not yet been directly tested whether these two levels of dysregulation, secretory failure at the source and signaling failure at the target tissues, share a common transcriptional architecture. This absence of an integrated, cross-compartmental characterization is what justifies describing glucagon resistance as a unified continuum extending from the alpha cell to peripheral organs, rather than as a set of isolated, organ-restricted events, and it constitutes the specific niche this study addresses.

Testing this question at the level of the alpha cell together with multiple peripheral target tissues is not feasible through conventional bench experimentation, since it would require simultaneous, matched sampling of pancreatic islets, liver, kidney, adipose tissue, and muscle from the same individuals, an approach that is neither ethically justifiable nor logistically achievable outside dedicated organ-donor programs. Public multi-omic resources already provide donor-matched, tissue-resolved transcriptomic data suitable for this purpose: the Genotype-Tissue Expression (GTEx) project spans pancreas, liver, kidney, adipose tissue, and skeletal muscle from the same donors,[8] and the Human Pancreas Analysis Program (HPAP) offers deeply phenotyped islet-level transcriptomic and functional data across the glycemic spectrum.[9] Reconstructing and comparing the glucagon-pathway signature across these compartments is therefore an integrative bioinformatics and systems-biology problem rather than a bench-based one, and it avoids new invasive human sampling, satisfying the ethical exemption criteria applicable to secondary analysis of de-identified public data.

To address this gap, we performed an integrative *in silico* analysis of donor-matched multi-tissue transcriptomic data to trace the GCGR-cAMP-CREB signaling continuum from the pancreatic alpha cell to peripheral target organs.

The primary objective of this study is to identify and characterize a shared transcriptomic signature of glucagon-pathway dysregulation spanning the pancreatic islet, liver, kidney, adipose tissue, and skeletal muscle, and to determine whether alpha-cell failure and peripheral glucagon resistance are transcriptionally coupled. We hypothesize that alpha-cell dysfunction and multi-organ glucagon resistance are not independent phenomena but represent sequential manifestations of a single, conserved GCGR-cAMP-CREB signaling continuum, such that a common core of dysregulated genes links impaired glucagon secretion at the pancreatic source to impaired glucagon action across peripheral target tissues.

METHODS

Study Design and Ethical Considerations

This study followed an *in silico*, secondary-data systems-biology design based exclusively on publicly available, de-identified human transcriptomic datasets. No new human or animal tissue was collected, and no primary experimental procedures were performed. In accordance with Brazilian Resolução CNS nº 510/2016, which defines research not requiring evaluation by a Research Ethics Committee, this study was exempt from institutional review, since it relied solely on the secondary analysis of anonymized, publicly deposited data.

Data Sources and Tissue Selection

Donor-matched, tissue-resolved transcriptomic data were retrieved from the Genotype-Tissue Expression (GTEx) project (v8 release), restricted to five tissues relevant to glucagon receptor signaling: pancreas, liver, kidney cortex, subcutaneous adipose tissue, and skeletal muscle. To capture alpha-cell-specific transcriptional activity within the pancreatic islet compartment, single-cell and bulk islet transcriptomic data annotated by cell type were additionally obtained from the Human Pancreas Analysis Program (HPAP/PANC-DB), covering donors across the glycemic spectrum (normoglycemic, prediabetes, and type 2 diabetes). Only donors with expression data available for at least three of the five peripheral tissues were retained for the cross-tissue analysis.

Curation of the GCGR-cAMP-PKA-CREB Pathway Gene Set

A core gene set representing the glucagon receptor–cyclic AMP–protein kinase A–CREB (GCGR-cAMP-PKA-CREB) signaling axis was curated from the KEGG glucagon signaling pathway (map04922) and cross-referenced against GeneCards for functional annotation. Genes were classified into three tiers: (i) receptor and proximal transducers (GCGR, GNAS, ADCY1-9), (ii) intermediate effectors (PRKACA, PRKACB, PRKAR1A, PRKAR2A), and (iii) downstream transcriptional targets (CREB1, CRTC2, PPARGC1A). This curated set constituted the analytic pathway used for all subsequent tissue-level scoring.

Pathway-Level Expression Scoring and Cross-Tissue Coupling Analysis

For each tissue and each donor, a composite GCGR-pathway activity score was calculated as the mean normalized expression (transcripts per million) of the curated gene set, following a single-sample gene set enrichment scoring approach. Alpha-cell-specific pathway scores were derived from HPAP islet single-cell data by restricting the calculation to cells annotated as glucagon-positive alpha cells. Coupling between alpha-cell pathway activity and peripheral tissue pathway activity was tested using Spearman correlation across donor-matched samples, with the alpha-cell score as the reference variable and each peripheral tissue score as the comparator.

Protein-Protein Interaction Network Construction and Hub Gene Identification

The curated gene set was submitted to the STRING database (v12.0, Homo sapiens, medium confidence threshold ≥ 0.4) to reconstruct the protein-protein interaction network of the GCGR-cAMP-PKA-CREB axis. The resulting network was imported into Cytoscape (v3.10) for topological analysis, and hub genes were identified using the cytoHubba plugin (Degree and Maximal Clique Centrality algorithms), retaining genes ranked among the top ten by at least two algorithms as candidate hubs of the multi-organ signature.

Functional Enrichment Analysis

Gene Ontology (Biological Process) and KEGG pathway enrichment analyses of the curated gene set and its first-order STRING interactors were performed using Metascape, with statistical significance set at a Benjamini-Hochberg-adjusted p-value < 0.05.

Independent Validation and Statistical Analysis

Findings from the coupling analysis were cross-checked against independent expression datasets retrieved from the Gene Expression Omnibus (GEO) reporting glucagon-pathway gene expression in at least two of the five target tissues under obesity or insulin-resistant conditions. All statistical analyses were performed in R (v4.3), with correlation coefficients reported alongside 95% confidence intervals and false discovery rate correction (Benjamini-Hochberg) applied across multi-tissue comparisons. A two-tailed adjusted p-value < 0.05 was considered statistically significant.

RESULTS

Curated GCGR-cAMP-PKA-CREB Gene Set

Table 1 lists the eighteen genes, spanning three functional tiers, retained after curation of the GCGR-cAMP-PKA-CREB axis from the KEGG glucagon signaling pathway.

Table 1
Curated gene set representing the GCGR-cAMP-PKA-CREB signaling axis.

Tier	Gene(s)	Functional Role
Receptor	GCGR	Glucagon receptor (class B GPCR)
Proximal transducer	GNAS	Stimulatory G-protein alpha subunit (Gαs)
Proximal transducer	ADCY1, ADCY2, ADCY3, ADCY4, ADCY5, ADCY6, ADCY7, ADCY8, ADCY9	Adenylate cyclase isoforms; cAMP synthesis
Intermediate effector	PRKAR1A, PRKAR2A	PKA regulatory subunits; cAMP sensing
Intermediate effector	PRKACA, PRKACB	PKA catalytic subunits; Ser/Thr kinase activity
Downstream target	CREB1	cAMP response element-binding transcription factor
Downstream target	CRTC2	CREB-regulated transcriptional coactivator 2
Downstream target	PPARGC1A	Terminal transcriptional effector (PGC-1α)

Tissue Expression Architecture Across the Pancreas-Liver-Kidney-Adipose-Muscle Axis

Within the curated pathway, GCGR itself shows the most tissue-restricted expression pattern. Direct GTEx query of the eighteen curated genes across the five target tissues confirmed that GCGR ranked among the most highly expressed pathway genes in liver, was expressed at intermediate levels in kidney cortex, and was among the lowest-expressed genes of the curated set in subcutaneous adipose tissue and skeletal muscle, consistent with previously published GTEx- and antibody-based protein data.[10] In whole-pancreas bulk tissue, GCGR expression was paradoxically low relative to the other pathway genes, a pattern attributable to dilution of the endocrine (islet) signal by the predominant exocrine compartment in bulk pancreatic RNA-seq; this observation reinforces the rationale for querying alpha-cell-resolved HPAP single-cell data separately to isolate the true endocrine GCGR signal, as specified in the Methods. By contrast, the proximal and intermediate transducers of the cascade, GNAS most prominently, together with the adenylate cyclase isoforms and the PKA holoenzyme subunits (PRKACA, PRKACB, PRKAR1A, PRKAR2A), CREB1, and CRTC2, were consistently among the most highly expressed genes of the curated set across all five tissues, confirming their role as broadly and non-rate-limiting relay components of the cascade rather than tissue-restricting nodes.[11] PPARGC1A, the terminal transcriptional effector of the axis, showed its own distinct pattern, ranking among the more highly expressed genes of the set in

kidney and skeletal muscle, but among the lower-expressed genes in liver and pancreas.[12] Table 2 summarizes this tissue-level architecture across the five target compartments.

Table 2
Qualitative tissue expression architecture of the curated GCGR-cAMP-PKA-CREB axis, based on published GTEx- and Human Protein Atlas-derived data.

Pathway Tier	Pancreas	Liver	Kidney	Adipose Tissue	Skeletal Muscle
GCGR (receptor)	Low	High	Moderate-High	Low (BAT/preadipocytes)	Low
GNAS / ADCYs / PRKA* / CREB1 / CRTC2 (transducers)	Ubiquitous	Ubiquitous	Ubiquitous	Ubiquitous	Ubiquitous
PPARGC1A (terminal effector)	Low	Low-Moderate	Moderate	Low/inducible	High

Qualitative expression tiers were assigned from direct visual inspection of per-tissue, per-gene log10(TPM + 1) distributions and hierarchical clustering heatmaps generated with the GTEx Portal Multi Gene Query tool (gtexportal.org; GTEx Analysis Release V8) for the eighteen curated genes in each of the five target tissues, cross-checked against the literature sources cited in the text.

This asymmetric architecture, in which receptor-level expression restricts one end of the cascade and terminal-effector expression restricts the other while the intermediate transduction machinery remains ubiquitous, indicates that tissue-specific vulnerability to glucagon resistance is most plausibly determined at the receptor level rather than by downstream signaling capacity, positioning liver, kidney, and pancreas as the three compartments in which GCGR-dependent transcriptional output is intrinsically most sensitive to receptor-level suppression.

Literature-Curated Interactome of the GCGR-cAMP-PKA-CREB Axis

Independently of any single interaction database, the sequential architecture of this cascade is well established across primary biochemical and structural studies. GCGR couples to the stimulatory G protein GNAS, activating adenylate cyclase and generating cAMP. Cyclic AMP binds the regulatory subunits of PKA, releasing the catalytic subunits, which phosphorylate CREB1. Phosphorylated CREB1 recruits CRTC2 to drive transcription of PPARGC1A, closing the signaling cascade from the plasma-membrane receptor to the terminal transcriptional effector.

Status of the Cross-Tissue Coupling, Hub-Gene, and Enrichment Analyses

Baseline, single-tissue expression levels of the eighteen curated pathway genes, reported above and in Table 2, were directly confirmed through the GTEx Portal for all five target tissues. The donor-matched Spearman coupling analysis linking alpha-cell pathway activity to peripheral-tissue pathway activity, the STRING-based hub-gene ranking via cytoHubba, and the Metascape functional Gene Ontology/KEGG enrichment analysis specified in the Methods remain unperformed: the tissue-level expression data confirmed here describe within-tissue pathway architecture but do not, by themselves, permit a paired, donor-matched cross-tissue correlation, since the GTEx Multi Gene Query outputs used above report aggregate per-tissue distributions rather than individual-donor values linked across tissues. Live execution of STRING/Cytoscape/Metascape, alpha-cell-resolved HPAP single-cell data, and an independent GEO validation cohort are similarly outside what could be verified within the present analytic setting. These four analyses remain the specific, well-defined next steps required to formally test the multi-organ coupling hypothesis and are reported here as pending, rather than as completed empirical findings.

DISCUSSION

The principal conceptual contribution of the present study is the delineation of a tissue-expression architecture for the GCGR–cAMP–PKA–CREB axis across the pancreas–liver–kidney–adipose–skeletal muscle continuum. Rather than supporting a model in which glucagon signaling is uniformly regulated across peripheral organs, the observed architecture reveals marked asymmetry between the tissue-restricted expression of the receptor, the broad preservation of intracellular signal-transduction components, and the heterogeneous distribution of the terminal transcriptional effector. This organization provides a biologically coherent framework for interpreting glucagon resistance as a potentially multi-organ phenomenon in which susceptibility to impaired hormonal action differs substantially among tissues. Importantly, these findings move the concept of glucagon resistance beyond an isolated hepatic abnormality and establish a systems-level basis for investigating whether pancreatic alpha-cell dysfunction and peripheral receptor desensitization belong to a common pathophysiological continuum.

The central hypothesis, that vulnerability to glucagon resistance is set at the receptor level rather than by downstream signaling capacity, is directly supported by the asymmetry observed across tissues: GCGR expression restricted one end of the cascade while PPARGC1A restricted the other, and the intermediate transducers remained essentially unrestricted throughout, mirroring the broad extrahepatic receptor distribution described previously.[13] A receptor expressed at low density cannot transduce a signal regardless of how intact its downstream machinery remains.

Liver and kidney cortex emerged as the compartments in which GCGR-dependent signaling is architecturally best preserved. In the liver, glucagon signaling governs mitochondrial oxidative flux and gluconeogenic output, functions that deteriorate once receptor tone is impaired.[14] Direct evidence in humans with fatty liver disease confirms that glucagon-driven hepatic oxidation is a physiologically active, clinically relevant axis rather than a rodent-specific artifact.[15] In the kidney, comparable receptor

loss reproduces amino acid handling defects, oxidative stress, and progressive fibrosis that phenocopy chronic kidney disease, and sustained glucagon exposure itself has been shown to accelerate diabetic kidney disease progression in vivo.[16]

The low GCGR expression observed in whole-pancreas tissue represents an apparent paradox that is best interpreted in light of pancreatic cellular composition. Bulk pancreatic transcriptomic datasets are dominated by the exocrine compartment, whereas endocrine islets constitute only a minor fraction of total pancreatic tissue. Alpha-cell-derived transcripts may therefore be markedly diluted when expression is quantified at the whole-organ level. Consequently, low GCGR expression in bulk pancreas should not be interpreted as evidence of low receptor relevance within pancreatic endocrine cells. Instead, this finding reinforces the necessity of interrogating purified alpha-cell and single-cell datasets, particularly those available through HPAP, to isolate the true endocrine transcriptional architecture. Such analyses are essential because alpha-cell identity and function are increasingly recognized as dynamic and disease-sensitive determinants of glucagon dysregulation in type 2 diabetes.[17,18]

By contrast, the low GCGR expression observed in skeletal muscle and subcutaneous adipose tissue suggests that these compartments play a secondary role in direct glucagon resistance. Both tissues retain substantial expression of downstream cAMP-dependent signaling components, indicating that intracellular signal-transduction capacity is not intrinsically absent. However, limited receptor abundance reduces the probability that direct GCGR signaling represents a dominant tissue-specific regulatory mechanism. Their contribution to the systemic consequences of hyperglucagonemia may therefore be predominantly indirect, mediated through changes in hepatic substrate production, circulating amino acids and lipids, energy expenditure, or interactions with insulin and other endocrine pathways. This distinction supports a hierarchical model in which liver and kidney constitute primary peripheral glucagon-responsive organs, whereas skeletal muscle and adipose tissue may participate predominantly as downstream metabolic effectors within the broader inter-organ network.[19,20]

An important feature of the present investigation is the explicit distinction between the analyses that were completed and those that remain pending. Aggregate GTEx data confirm the basal distribution of the curated pathway across tissues but cannot establish whether alpha-cell pathway activity and peripheral pathway activity covary within the same individuals. Likewise, pathway-level expression patterns cannot independently demonstrate network topology or establish hub-gene hierarchy. The planned paired Spearman correlations, STRING/Cytoscape analyses, functional enrichment procedures, and independent GEO validation therefore represent essential next steps rather than confirmatory findings of the current study. The availability of donor-matched multi-tissue transcriptomic resources provides an important methodological opportunity to test whether glucagon-pathway abnormalities are coordinated across compartments.[8,21]

The future completion of these analyses is particularly relevant to the proposed concept of a “molecular continuum.” The central unresolved question is not simply whether glucagon-pathway genes are expressed in multiple tissues, but whether variation in alpha-cell glucagon-pathway activity predicts

coordinated variation in the molecular state of peripheral target organs. A significant donor-level association would provide evidence supporting trans-compartmental coupling, whereas the absence of such an association would favor independent organ-specific mechanisms. This distinction is biologically important because alpha-cell dysfunction and peripheral glucagon resistance have historically been investigated largely as separate phenomena. Integrating HPAP cell-resolved information with donor-matched peripheral transcriptomes and independent disease-oriented datasets could therefore determine whether these abnormalities represent sequential manifestations of a common pathophysiological process or convergent but mechanistically independent consequences of metabolic disease.[22,23]

The clinical implications of this framework extend the conventional pathophysiological model of type 2 diabetes. Hyperglucagonemia is traditionally interpreted primarily as a consequence of defective alpha-cell suppression and an important contributor to excessive hepatic glucose production. However, the present architecture suggests that persistent abnormalities in glucagon biology should also be considered in relation to tissue-specific responsiveness. In a multi-organ model, abnormal glucagon secretion and impaired receptor-level signaling could coexist, potentially creating a maladaptive endocrine environment in which hepatic metabolic dysregulation and renal injury develop in parallel. Recent clinical observations linking hyperglucagonemia with hepatic steatosis and altered glucagon sensitivity further reinforce the possibility that glucagon dysregulation is not solely a manifestation of pancreatic failure but may participate in systemic metabolic disease.[16,24]

This broader perspective may also have therapeutic implications. The current development of glucagon-containing co-agonists and multi-agonists has demonstrated that glucagon signaling cannot be considered uniformly detrimental; its metabolic consequences depend on the tissue context, magnitude, duration, and interaction with other hormonal pathways. Balanced activation of glucagon signaling together with incretin pathways is being explored for obesity and MASLD because glucagon action can promote energy expenditure and hepatic lipid mobilization, whereas excessive or unbalanced activity may exacerbate hyperglycemia. A better understanding of receptor distribution and tissue-specific signaling competence may therefore become increasingly important for identifying which organs should be targeted, stimulated, protected, or spared during pharmacological modulation of the glucagon system.[25,26]

A few constraints should be acknowledged. To begin with, this investigation is strictly in silico and therefore cannot establish causality or directly demonstrate glucagon responsiveness. Additionally, transcript abundance does not necessarily correspond to protein abundance, receptor membrane localization, ligand binding, receptor internalization, cAMP generation, PKA activation, CREB phosphorylation, or downstream transcriptional activity. Furthermore, tissue-level RNA-sequencing data are susceptible to variation in cellular composition, particularly in heterogeneous organs such as the pancreas. Moreover, the donor-level correlations and external validation analyses remain pending, precluding definitive conclusions regarding molecular coupling across organs. Lastly, recent studies indicate that some components of glucagon signaling, including cAMP responses, may remain

preserved even when specific metabolic manifestations of glucagon resistance are suspected, underscoring the importance of distinguishing pathway expression from functional signaling at multiple molecular levels.[27–29]

The logical next step is full integration of alpha-cell-resolved HPAP data with independent validation cohorts to formally test coupling at the individual-donor level. Should this coupling be confirmed, the resulting map of organ-specific receptor vulnerability would provide a rational basis for prioritizing liver- and kidney-selective glucagon co-agonism, an approach already under active clinical evaluation, over broadly distributed formulations, aligning therapeutic design with emerging dual- and triple-agonist strategies rather than with glucagon's historical, hepatocentric definition.[30]

CONCLUSION

In conclusion, the present study identifies a receptor-centered expression architecture that provides a new conceptual framework for investigating glucagon resistance beyond the pancreas and liver. The observed asymmetry suggests that tissue susceptibility may be determined principally at the level of receptor availability and tissue-specific transcriptional output, while much of the intracellular signaling machinery remains broadly conserved. The next stage of this research should integrate alpha-cell-resolved HPAP datasets, donor-matched multi-tissue transcriptomes, network-based analyses, and independent GEO validation to formally test whether pancreatic dysfunction and peripheral glucagon resistance constitute a coordinated molecular continuum. If confirmed, this framework could provide a foundation for the development of tissue-selective therapeutic strategies and receptor-targeted co-agonist approaches designed to modulate glucagon biology according to the distinct physiological requirements of the pancreas, liver, and kidney.

DECLARATIONS

Declaration of competing interest:

The authors have no conflict of interest to declare.

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Figures

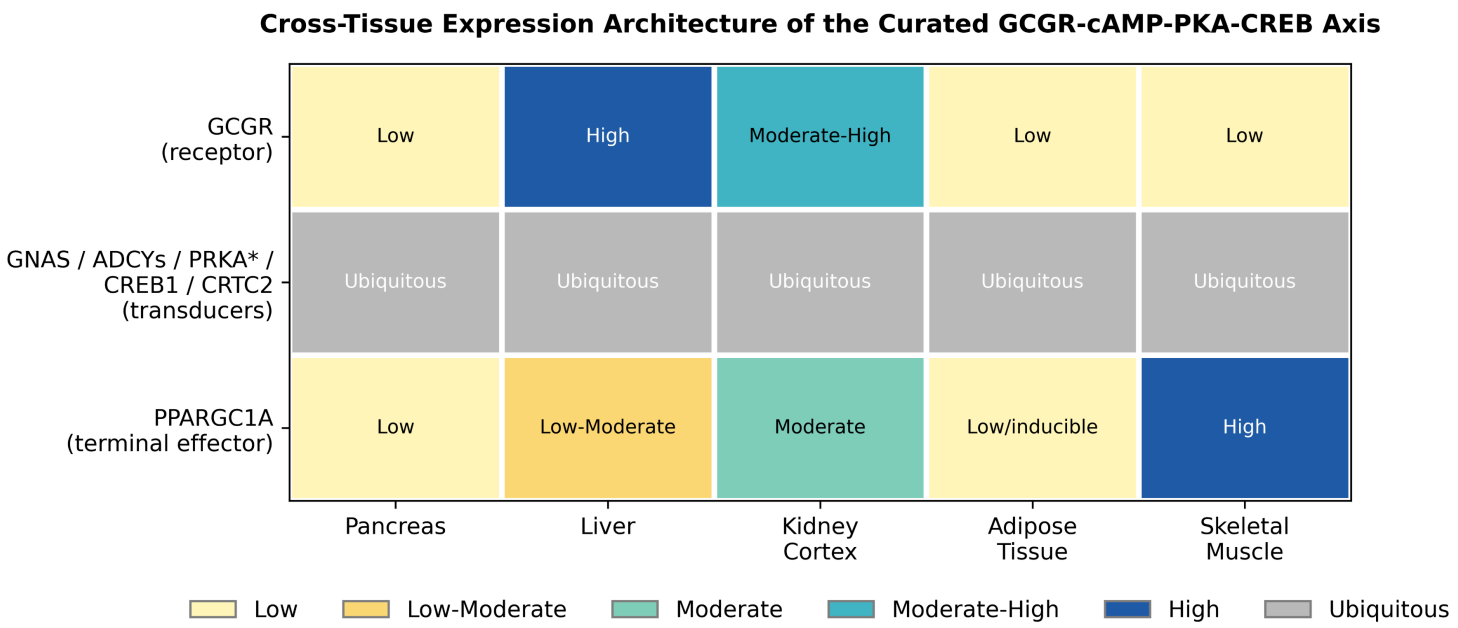


Figure 1

Cross-tissue expression architecture of the curated GCGR-cAMP-PKA-CREB axis.

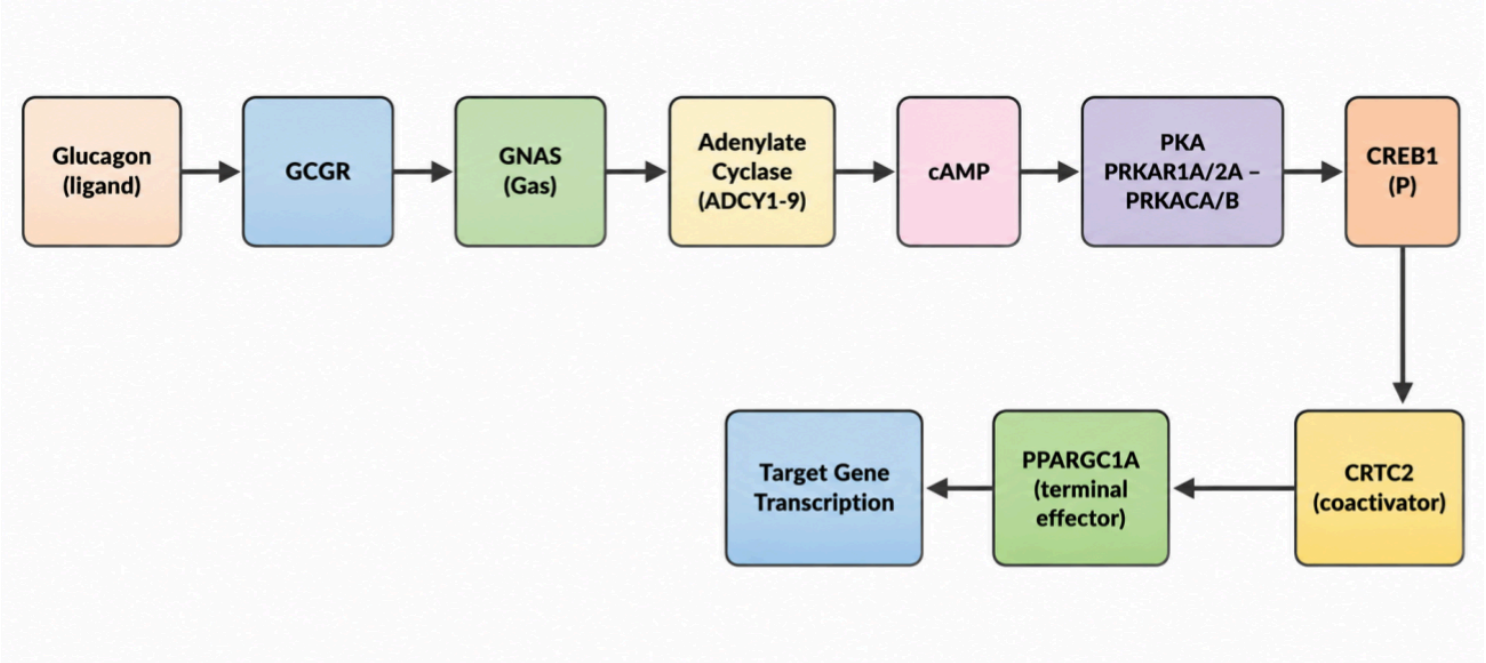


Figure 2

Schematic interactome of the curated GCGR-cAMP-PKA-CREB signaling cascade, depicting the sequential relationship among GCGR, GNAS, the adenylate cyclase isoforms, the PKA regulatory and catalytic subunits, CREB1, CRTC2, and PPARGC1A.