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REVIEW

Elusive liver factor that causes pancreatic α cell hyperplasia: A review of literature

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Abstract

Tumors and cancers of the gastrointestinal tract and pancreas are commonly derived from precursor lesions so that understanding the physiological, cellular, and molecular mechanisms underlying the pathogenesis of precursor lesions is critical for the prevention and treatment of those neoplasms. Pancreatic neuroendocrine tumors (PNETs) can also be derived from precursor lesions. Pancreatic α cell hyperplasia (ACH), a specific and overwhelming increase in the number of α cells, is a precursor lesion leading to PNET pathogenesis. One of the 3 subtypes of ACH, reactive ACH is caused by glucagon signaling disruption and invariably evolves into PNETs. In this article, the existing work on the mechanisms underlying reactive ACH pathogenesis is reviewed. It is clear that the liver secretes a humoral factor regulating α cell numbers but the identity of the liver factor remains elusive. Potential approaches to identify the liver factor are discussed.

Key words: Pancreatic α cell hyperplasia; Humoral factor; Pancreatic neuroendocrine tumors; Digestive system hormone; Liver

Core tip: Tumors and cancers of the gastrointestinal tract and pancreas are commonly derived from precursor

lesions. One of the precursor lesions, reactive pancreatic α cell hyperplasia is caused by glucagon signaling disruption and invariably evolves into pancreatic neuroendocrine tumors. In this article, the existing work on the mechanisms underlying the novel precursor lesion is reviewed. It is clear that the liver secretes a humoral factor regulating pancreatic α cell numbers but the identity of the liver factor remains elusive. Potential approaches to identify the liver factor are discussed.

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INTRODUCTION

Tumors and cancers of the gastrointestinal tract and pancreas are commonly derived from precursor lesions[1-3]. For example, colon cancer is derived from polypoid or non-polypoid pre-neoplastic lesions in the colon, and pancreatic ductal carcinoma from pancreatic intraepithelial neoplasia. Neuroendocrine tumors in the gastrointestinal tract and pancreas (GEP-NETs) are relatively rare and indolent tumors with variable biological behaviors[4-6]. GEP-NETs can also be derived from precursor lesions[7-9]. In atrophic gastritis, hypergastrinemia drives entero-chromaffin-like cell hyperplasia, which in turn can give rise to gastric carcinoids[7,10]. In ulcerative colitis, microscopic neuroendocrine tumors can arise after long disease duration, probably in response to inflammation[7,11]. Recently, precursor lesions giving rise to pancreatic neuroendocrine tumors (PNETs) have drawn much attention and become more understood. It is well known now that diffuse precursor lesions including endocrine cell hyperplasia, dysplasia, and microadenomas are present in the pancreata of patients with familial tumor syndromes such as multiple endocrine neoplasia syndrome type 1 (MEN1) and von Hippel-Lindau disease, and of animal models of PNETs[12-16]. In the pancreata of patients with MEN1 and mice with heterozygous MEN1 inactivation, the hyperplastic endocrine cells are polyclonal and multi-hormonal and contain the normal menin allele, while microadenomas have to first lose the normal menin allele[17,18]. In contrast, uni-hormonal pancreatic endocrine cell hyperplasia such as pancreatic α cell hyperplasia (ACH) and pancreatic polypeptide cell hyperplasia has only been recognized in the last several years[8,9,19]. Although pancreatic polypeptide cell hyperplasia may be a physiological variation of normal pancreatic polypeptide cell distribution, ACH is clearly a pathologic precursor lesion leading to PNET pathogenesis[19].

In this article, we will summarize how the discovery of a novel hereditary tumor syndrome, Mahvash disease, has stimulated interest in the pathogenesis of ACH, and discuss the possible identify of an elusive liver factor that may cause the ACH.

The data we review are based on work in our own laboratories and PubMed and major endocrine conferences search using key words pancreatic α cell hyperplasia, glucagon receptor mutation, glucagon receptor antagonism, and hyperglucagonemia.

PANCREATIC ACH

ACH is defined as an overwhelming and specific increase of pancreatic α cell numbers[8,19]. Based on etiology and glucagon levels, 3 types of ACH are observed. Reactive ACH is caused in humans by inactivating glucagon receptor mutations and is associated with marked hyper-glucagonemia. Because the glucagon receptor is inactive, the severe hyperglucagonemia in reactive ACH does not result in glucagonoma syndrome. Non-functional ACH has an unknown cause and is associated with normal glucagon levels. Functional ACH also has an unknown cause but is associated with hyperglucagonemia that results in glucagonoma syndrome.

Reactive ACH is most extensively studied due to the novel Mahvash disease and the existence of multiple animal models. We first described the Mahvash disease which is hyperglucagonemia, ACH, and PNETs but without glucagonoma syndrome, caused by an inactivating glucagon receptor mutation[20,21]. Later, we and others have confirmed the Mahvash disease (Tang L and Yu R, unpublished results)[19,22]. Currently, 8 inactivating glucagon receptor mutations are known.

We further established that the glucagon receptor knockout ($Gcgr^{-/-}$) mice are a murine model of Mahvash disease[23-25]. The $Gcgr^{-/-}$ mice exhibit ACH throughout their lifespan. Dysplastic islets consisted of mostly α cells are evident from 5-7 mo on and glucagonomas are detected from 10-12 mo to death. Hyperplasia is also observed in the exocrine compartment but dysplasia, carcinoma *in situ*, or frank exocrine carcinoma is not found. Large PNETs contribute at least partially to the premature demise of the $Gcgr^{-/-}$ mice. Three other murine models also mimic the Mahvash disease in some aspects. The prohormone convertase 2 knockout ($PC^{-/-}$) mice cannot make mature glucagon; they exhibit ACH and eventually develop PNETs[26,27]. The preproglucagon knockout ($Gcg^{-/-}$) mice cannot make any proglucagon-derived peptide hormones, including mature glucagon; they also exhibit ACH and eventually develop PNETs[28,29]. The liver-specific Gsα knockout mice cannot transduce the glucagon signaling in hepatocytes; they exhibit hyperglucagonemia and ACH, and eventually develop PNETs as well[30,31].

Thus both in humans and in mice, reactive ACH ensues whenever glucagon signaling is disrupted and evolves into PNETs eventually. Reactive ACH thus is clearly a precursor lesion leading to PNET pathogenesis.

PATHOGENESIS OF REACTIVE ACH

The pathogenesis of reactive ACH in $Gcgr^{-/-}$ mice is

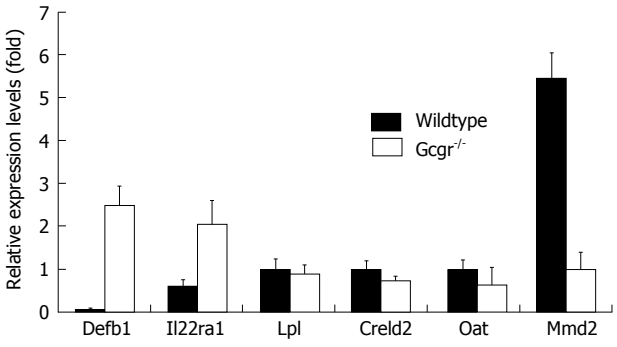

Figure 1 Realtime polymerase chain reaction of several genes differentially expressed in the Gcgr$^{-/-}$ mice. See text for details.

studied in detail. As increased pancreatic endocrine cell numbers can be due to proliferation, neogenesis, or reduced apoptosis, they are each examined at 6-7 mo[23]. α cell proliferation measured by proliferating cell nuclear antigen or Ki-67 labeling is very low and not significantly different in WT and Gcgr$^{-/-}$ mice. α cell neogenesis measured by counting singlet and doublet α cells and exocrine ducts harboring glucagon-positive cells is much higher in Gcgr$^{-/-}$ than in WT mice. α cell apoptosis measured by TUNEL labeling is very low in both Gcgr$^{-/-}$ and WT mice and not significantly different. While upregulated α cell neogenesis is also seen in the PC$^{-/-}$ mice throughout their lifespan, higher α cell proliferation is found at 3 mo[27].

The hyperplastic α cells in the Gcgr$^{-/-}$ mice exhibit abnormal differentiation. A few of these cells are positively labeled with both glucagon and insulin, and some express pancreatic and duodenal homeobox 1, a β cell marker[23]. Most α cells express embryonic α cell markers such as GLUT2[32]. Abnormal α cell differentiation is also seen in humans with mutated Gcgr and in the PC$^{-/-}$ mice as they both express glucagon-like peptide 1, which is normally not expressed in the α cells[21,27].

REACTIVE ACH AND THE LIVER

As reactive ACH universally occurs after glucagon signaling inhibition (see above), it is logical to hypothesize that glucagon signaling negatively feeds back on α cell number regulation and loss of the negative feedback causes the ACH[33]. A number of lines of evidence point to the liver as the organ which sends inhibitory signals to the α cells during normal glucagon signaling and a stimulatory signal to them when glucagon signaling is disrupted. First, liver is the natural target organ of glucagon signaling. Second, liver-specific Gsα deletion in mice recapitulates ACH pathogenesis[30]. Third, liver-specific glucagon receptor deletion in mice results in a phenotype very similar to that of mice with global glucagon receptor deletion[34]. Fourth, glucagon receptor re-expression in the liver of Gcgr$^{-/-}$ mice reduces glucagon levels by almost 99%[35]. Therefore, if the liver does not respond to glucagon but all other organs do, reactive ACH ensues; conversely, if the liver does respond to glucagon but all other organs do not, reactive ACH likely reverses. In other words, the liver is likely necessary and sufficient to be the organ regulating the number of α cells in response to glucagon signaling.

THE ELUSIVE LIVER FACTOR

The liver communicates with the pancreas *via* neuronal and humoral signals. It has been shown that the liver can regulate insulin secretion and pancreatic β cell proliferation through neuronal signals[36-38]. In a similar manner, the liver may regulate glucagon secretion and pancreatic α cell proliferation through neuronal connection, but there has not been any direct experimental evidence supporting or disputing that. In contrast, there is strong evidence that the liver regulates glucagon secretion and pancreatic α cell proliferation through a humoral factor as shown by islet transplantation experiments[34]. Transplanted wildtype islets in Gcgr$^{-/-}$ recipient mice exhibit higher α/β cell ratio and increased α cell proliferation, compared with those in wildtype recipient animals. Conversely, transplanted Gcgr$^{-/-}$ islets in wildtype recipient mice exhibited reduced α-cell proliferation compared with those in Gcgr$^{-/-}$ recipient animals.

The nature and identity of the liver factor that causes reactive ACH have been sought after. As the liver gene expression must be different between the wildtype and the Gcgr$^{-/-}$ mice, systems approaches such as DNA microarray studies are done to efficiently provide systemic and novel insights into the nature of the liver factor. We compared gene expression profile of 4 WT and 4 Gcgr$^{-/-}$ mouse livers at 2.5 mo (2 females and 2 males in each group) by Affymetrix GeneChip Mouse Gene 1.0 ST Array. The microarray data were analyzed using Genespring 11 (Tables 1 and 2). A total of 125 genes were significantly differentially expressed (> 2 fold change and $P < 0.05$). Since ACH occurs regardless of sex, we eliminated 47 genes with differential expression only limited in one sex, leaving 35 genes upregulated and 43 genes downregulated in both female and male Gcgr$^{-/-}$ mouse liver. The differential expression of some of the 78 genes was validated by realtime polymerase chain reaction (Figure 1). We reason that potential candidate genes should encode secretory proteins. Of the genes overexpressed in Gcgr$^{-/-}$ liver, Igfbp1, Defb1, Serpina7, Inhba, Cxcl13, Il1b, and Cxcl9 are secretory proteins and may stimulate α-cell differentiation and proliferation. Defb1 is particularly interesting as it is very significantly overexpressed in the Gcgr$^{-/-}$ liver (Table 1). Defensins are a group of cysteine-rich antimicrobial peptides that function to help defend against microbial infections[39]. They are mostly secreted by leukocytes and epithelial cells and their anti-microbial mechanisms are multiple. There are a few families of defensins according to their structures in mice and humans. Originally, defensin β1 (DB1, encoded by Defb1) is found to be expressed in the lung and urogenital epithelials cells[40-42]. Later, DB1 is also found

Table 1 Genes significantly overexpressed in the Gcgr$^{-/-}$ mouse liver

Gene symbol	mRNA description	GO biological process term	Fold increase
Cdkn1a	Cyclin-dependent kinase inhibitor 1A (P21), transcript variant 1	Response to DNA damage stimulus/cell cycle/cell cycle arrest/negative regulation of cell proliferation	5.6
Igfbp1	Insulin-like growth factor binding protein 1	Regulation of cell growth	5.5
Defb1	Defensin beta 1	Defense response/response to bacterium/defense response to bacterium/innate immune response	5.2
Gpr64	G protein-coupled receptor 64, transcript variant 1	Signal transduction/cell surface receptor linked signaling pathway/G-protein coupled receptor protein signaling pathway/neuropeptide signaling pathway	5.1
Serpina7	Serine (or cysteine) peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 7	Post-embryonic development/response to vitamin A/response to drug	4.9
Cpt1b	Carnitine palmitoyltransferase 1b, muscle, nuclear gene encoding mitochondrial protein	Lipid metabolic process/fatty acid metabolic process/transport/long-chain fatty acid transport/long-chain fatty acid transport	4.6
Chac1	ChaC, cation transport regulator-like 1 (*E. coli*)	Apoptosis/response to unfolded protein/biological_process	4.3
Npas2	Neuronal PAS domain protein 2	Transcription/regulation of transcription, DNA-dependent/signal transduction/circadian sleep/wake cycle/regulation of transcription/locomotor rhythm/positive regulation of transcription from RNA polymerase Ⅱ promoter/rhythmic process	3.9
Slc34a2	Solute carrier family 34 (sodium phosphate), member 2	In utero embryonic development/transport/ion transport/sodium ion transport/phosphate transport/phosphate transport/phosphate transport	3.6
Fabp5	Fatty acid binding protein 5, epidermal	Glucose metabolic process/lipid metabolic process/phosphatidylcholine biosynthetic process/transport/glucose transport	3.5
BC023105	cDNA sequence BC023105	Unknown	3.1
Cav1	Caveolin 1, caveolae protein	MAPKKK cascade/inactivation of MAPK activity/vasculogenesis/response to hypoxia/negative regulation of endothelial cell proliferation/negative regulation of cytokine-mediated signaling pathway/triglyceride metabolic process/calcium ion transport/cellular calcium ion homeostasis/cellular calcium ion homeostasis/endocytosis/regulation of smooth muscle contraction	2.8
Lpl	Lipoprotein lipase	Lipid metabolic process/positive regulation of macrophage derived foam cell differentiation/lipid catabolic process/triglyceride biosynthetic process/triglyceride catabolic process	2.7
Il22ra1	Interleukin 22 receptor, alpha 1	Blood coagulation	2.6
Acaca	Acetyl-Coenzyme A carboxylase alpha	Tissue homeostasis/acetyl-CoA metabolic process/lipid metabolic process/fatty acid biosynthetic process/metabolic process/lipid biosynthetic process/response to organic cyclic substance/multicellular organismal protein metabolic process	2.6
Inhba	Inhibin beta-A	Mesoderm formation/hemopoietic progenitor cell differentiation/growth/positive regulation of transcription from RNA polymerase Ⅱ promoter/mesodermal cell differentiation/negative regulation of hair follicle development	2.6
Gadd45b	Growth arrest and DNA-damage-inducible 45 beta	Activation of MAPKK activity/negative regulation of protein kinase activity/apoptosis/multicellular organismal development/cell differentiation/regulation of cell cycle	2.4
Tgtp1	T-cell specific GTPase 1	Immune response/response to virus	2.4
Rassf4	Ras association (RalGDS/AF-6) domain family member 4	Cell cycle/signal transduction	2.4
Cxcl13	Chemokine (C-X-C motif) ligand 13	Chemotaxis/inflammatory response/immune response/lymph node development	2.4
Il1b	Interleukin 1 beta	Angiogenesis/fever/inflammatory response/immune response/elevation of cytosolic calcium ion concentration/aging	2.4
Tgtp1	T-cell specific GTPase 1	Immune response/response to virus	2.3
Asns	Asparagine synthetase	Asparagine biosynthetic process/glutamine metabolic process/metabolic process/cellular amino acid biosynthetic process	2.3
Socs2	Suppressor of cytokine signaling 2, transcript variant 1	Lactation/regulation of growth/regulation of multicellular organism growth/negative regulation of multicellular organism growth/negative regulation of multicellular organism growth/positive regulation of neuron differentiation/negative regulation of JAK-STAT cascade/mammary gland alveolus development	2.3
Meig1	Meiosis expressed gene 1	Meiosis	2.3
Cxcl9	Chemokine (C-X-C motif) ligand 9	Inflammatory response/immune response	2.2
Vtcn1	V-set domain containing T cell activation inhibitor 1	Negative regulation of T cell activation	2.2
H2-Ab1	Histocompatibility 2, class Ⅱ antigen A, beta 1	Antigen processing and presentation of peptide or polysaccharide antigen *via* MHC class Ⅱ/immune response/antigen processing and presentation/antigen processing and presentation of exogenous peptide antigen *via* MHC class Ⅱ	2.2

Spon2	Spondin 2, extracellular matrix protein	Cell adhesion/innate immune response	2.2
Rgs16	Regulator of G-protein signaling 16	G-protein coupled receptor protein signaling pathway/negative regulation of signal transduction	2.1
Il2rg	Interleukin 2 receptor, gamma chain	Regulation of gene expression/positive regulation of CD4-positive, CD25-positive, alpha-beta regulatory T cell differentiation/positive regulation of T cell differentiation in the thymus/positive regulation of B cell differentiation	2.1
Wdr67	WD repeat domain 67, transcript variant 1	Regulation of Rab GTPase activity	2.1
Prss8	Protease, serine, 8 (prostasin)	Hair follicle development/proteolysis	2.1
Bach2	BTB and CNC homology 2	Transcription/regulation of transcription, DNA-dependent/regulation of transcription	2.0
Serpina12	Serine (or cysteine) peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 12	Unknown	2.0

E. coli: *Escherichia coli*.

in the liver, especially in the biliary epithelial cells under obstructive jaundice[40,43,44]. DB1 released in circulation may result in ACH. Serpina7 encodes thyroxine-binding globulin (TBG) which binds thyroxine and increases total thyroxine levels[45]. As the index patient with Mahvash disease has normal thyroid functions, suggesting normal TBG levels, it is unlikely that TBG is the liver factor that causes ACH. For Cxcl13, Il1b, and Cxcl9, please see below. Literature review does not give us any clues on which underexpressed genes in Gcgr$^{-/-}$ mouse liver might encode a secretory protein that acts as inhibitor of α-cell differentiation and proliferation.

Pathway analysis suggested that WT and Gcgr$^{-/-}$ liver exhibit different metabolic profiles. As expected, genes involved in gluconeogenesis, glycogen synthesis, and glycogenolysis were downregulated in the Gcgr$^{-/-}$ liver, compared with those in WT (Table 3). Interestingly, genes involved in inflammation and cell proliferation were upregulated in the Gcgr$^{-/-}$ liver. The protein products of genes regulating cell proliferation unlikely diffuse out of the liver thus are improbable signals for regulating α cell mass. In contrast, the protein products of genes regulating inflammation are mostly cytokines which are secreted into the circulation and can reach the α cells, such as Cxcl13, Il1b, and Cxcl9. Interestingly, interleukin-6 (IL6), a cytokine secreted by T cells and macrophages (but not by the liver), upregulates α-cell mass but circulating IL6 levels are normal in the Gcgr$^{-/-}$ mice[34,46]. Alternatively, multiple liver-elaborated cytokines may act synergistically to cause ACH.

The liver may indirectly regulate α cell differentiation and proliferation by metabolic signals. Not surprisingly, the metabolic profile of Gcgr$^{-/-}$ mice and wildtype counterparts are vastly different, as shown by polyomic metabolic profiling[47]. Similar to our results, genes involved in gluconeogenesis and amino acid catabolism are downregulated. Furthermore, genes involved in fatty acid oxidation processes are also downregulated and genes involved in glycolysis, fatty acid synthesis, and cholesterol synthesis are upregulated. More pertinent to the potential mechanisms for ACH pathogenesis are the dramatic changes in the levels of metabolites[47]. As reported before[21,23], glucose levels are decreased by 1.4-fold. Consistent with decreased gluconeogenesis in the Gcgr$^{-/-}$ mice, amino acids and amino acid derivatives levels are significantly elevated. The most upregulated amino acids are threonine (9.6-fold), serine (8.7-fold), and asparagine (8.1-fold). Amino acid derivatives levels are also higher in the Gcgr$^{-/-}$ mice, the highest being 2-aminodipic acid and ornithine (both 5.4-fold). Levels of certain nucleotides and their derivatives are elevated, *e.g.*, pyridoxine levels are 3.6-fold elevated. Levels of some vitamins are different; those of dihydrofolic acid are 5.3-fold elevated. Glycerol and glycerol derivatives levels are about 2-fold lower. Intriguingly, the levels of cholic acid and glycocholic acid, two bile acids, are markedly and unexpectedly elevated (244- and 154-fold, respectively). There have been only a few studies addressing glucagon signaling and bile acids. In the rats, glucagon increases cholic acid levels[48]; in cultured cells, one bile acid, chenodeoxycholic acid, desensitizes the glucagon receptor[49]. Bile acids, however, are recognized recently as metabolic regulators[50]. Wildtype mice fed with cholic acid exhibit markedly elevated bile acid levels but their pancreas weight and glucagon levels are not changed[34]. Interestingly, α cell mass is somewhat increased (approximately 80%) by cholic acid feeding. Thus a metabolic signal that causes ACH has not been identified yet.

FUTURE DIRECTIONS

The elusive, yet-to-be identified liver factor that causes ACH fulfills the definition of a novel digestive system hormone (Figure 2). The liver factor is produced by the liver and released into the circulation; it then acts remotely on the pancreas to result in ACH. The liver factor could be more than one molecule but we use singular form here for conciseness. To identify this liver factor, the process of discovering leptin may offer some insights. When the first obese mouse models were described, it was not clear why they are obese. A circulating factor was hypothesized[51]. In the obese mouse models, the factor may either stimulate appetite and be overproduced or inhibit appetite and be under-produced. The circulating factor hypothesis was tested by parabiosis which joins the circulation of two mice of various lean and obese phenotypes. Eventually it was found that the *ob/ob* obese mice lack an inhibitor of appetite (leptin) and the *db/db* obese mice lack the

Table 2 Genes significantly underexpressed in the Gcgr$^{-/-}$ mouse liver

Gene symbol	mRNA description	GO biological process term	Fold decrease
Mmd2	Monocyte to macrophage differentiation-associated 2	Cytolysis	9.7
Nnmt	Nicotinamide N-methyltransferase	Unknown	6.2
Gcgr	Glucagon receptor	Exocytosis/signal transduction/cell surface receptor linked signaling pathway/G-protein coupled receptor protein signaling pathway/G-protein signaling, coupled to cAMP nucleotide second messenger/activation of adenylate cyclase activity by G-protein signaling pathway	5.3
Mfsd2a	Major facilitator superfamily domain containing 2A	Transport/transmembrane transport	4.2
Oat	Ornithine aminotransferase, nuclear gene encoding mitochondrial protein	Unknown	4.1
Slc10a2	Solute carrier family 10, member 2	Transport/ion transport/sodium ion transport/organic anion transport/bile acid and bile salt transport	3.9
A1bg	Alpha-1-B glycoprotein	Unknown	3.5
Gm129	Gene model 129 (NCBI)	Unknown	3.3
Sds	Serine dehydratase	Gluconeogenesis/cellular amino acid metabolic process/metabolic process	3.1
Pck1	Phosphoenolpyruvate carboxykinase 1, cytosolic	Gluconeogenesis/gluconeogenesis/oxaloacetate metabolic process/lipid metabolic process/glycerol biosynthetic process from pyruvate	3.0
Lrtm1	Leucine-rich repeats and transmembrane domains 1	Unknown	3.0
Ntrk2	Neurotrophic tyrosine kinase, receptor, type 2, transcript variant 1	Vasculogenesis/protein amino acid phosphorylation/transmembrane receptor protein tyrosine kinase signaling pathway/multicellular organismal development/nervous system development/feeding behavior/glutamate secretion/regulation of metabolic process/cell differentiation/brain-derived neurotrophic factor receptor signaling pathway/mechanoreceptor differentiation	3.0
Gls2	Glutaminase 2 (liver, mitochondrial), nuclear gene encoding mitochondrial protein	Gutamine metabolic process	3.0
Susd4	Sushi domain containing 4	Unknown	2.9
Slc16a5	Solute carrier family 16 (monocarboxylic acid transporters), member 5	Unknown	2.9
Ccrn4l	CCR4 carbon catabolite repression 4-like (*S. cerevisiae*)	Rhythmic process	2.9
Lhpp	Phospholysine phosphohistidine inorganic pyrophosphate phosphatase	Metabolic process	2.7
Neb	Nebulin	Regulation of actin filament length/sarcomere organization	2.6
Got1	Glutamate oxaloacetate transaminase 1, soluble	Oxaloacetate metabolic process/glycerol biosynthetic process/cellular amino acid metabolic process/aspartate metabolic process/aspartate biosynthetic process/biosynthetic process/glutamate catabolic process to aspartate/glutamate catabolic process to 2-oxoglutarate/dicarboxylic acid metabolic process/fatty acid homeostasis	2.6
Sult5a1	Sulfotransferase family 5A, member 1	Unknown	2.6
Hapln1	Hyaluronan and proteoglycan link protein 1	Cell adhesion	2.5
Mt2	Metallothionein 2	Cellular zinc ion homeostasis/nitric oxide mediated signal transduction/detoxification of copper ion	2.5
Mt1	Metallothionein 1	Cellular metal ion homeostasis/cellular zinc ion homeostasis/nitric oxide mediated signal transduction/detoxification of copper ion	2.4
Slc3a1	Solute carrier family 3, member 1	Amino acid transport	2.4
Trdn	Triadin	Cellular calcium ion homeostasis/regulation of release of sequestered calcium ion into cytosol by sarcoplasmic reticulum/negative regulation of calcium ion transport via store-operated calcium channel activity	2.4
Bhlhe41	Basic helix-loop-helix family, member e41	Negative regulation of transcription from RNA polymerase Ⅱ promoter/transcription/regulation of transcription, DNA-dependent/circadian rhythm/entrainment of circadian clock/regulation of transcription	2.3
Usp2	Ubiquitin specific peptidase 2, transcript variant 3	Ubiquitin-dependent protein catabolic process	2.3
Derl3	Der1-like domain family, member 3	Unknown	2.3
Mrap2	Melanocortin 2 receptor accessory protein 2, transcript variant 1	Unknown	2.2
Ncam2	Neural cell adhesion molecule 2, transcript variant 1	Cell adhesion	2.2
S1pr5	Sphingosine-1-phosphate receptor 5	Signal transduction/G-protein coupled receptor protein signaling pathway	2.2
1810046K07Rik	RIKEN cDNA 1810046K07 gene	Unknown	2.2
Nrg4	Neuregulin 4	Unknown	2.2

Gas2	Growth arrest specific 2	Apoptosis/cell cycle/cell cycle arrest/regulation of cell shape	2.2
Ttc39b	Tetratricopeptide repeat domain 39B	Unknown	2.2
Cyp17a1	Cytochrome P450, family 17, subfamily a, polypeptide 1	Steroid biosynthetic process/glucocorticoid biosynthetic process/oxidation reduction	2.1
Creld2	cysteine-rich with EGF-like domains 2	Unknown	2.1
Upp2	Uridine phosphorylase 2	Nucleoside metabolic process/nucleotide catabolic process	2.1
Ar	Androgen receptor	*In utero* embryonic development/transcription/regulation of transcription, DNA-dependent/regulation of transcription from RNA polymerase Ⅱ promoter/male gonad development/cellular process/regulation of gene expression/male somatic sex determination/androgen receptor signaling pathway/androgen receptor signaling pathway/positive regulation of estrogen receptor signaling pathway/positive regulation of MAPKKK cascade/positive regulation of insulin-like growth factor receptor signaling pathway	2.1
Gm10419	Lung RCB-0558 LLC cDNA, RIKEN full-length enriched library, clone: G730014J15 product: Hypothetical protein	Unknown	2.1
Sdf2l1	Stromal cell-derived factor 2-like 1	Unknown	2.0
Trdn	Triadin	Cellular calcium ion homeostasis/regulation of release of sequestered calcium ion into cytosol by sarcoplasmic reticulum/negative regulation of calcium ion transport *via* store-operated calcium channel activity	2.0
Antxr2	Anthrax toxin receptor 2	Unknown	2.0

S. cerevisiae: *Saccharomyces cerevisiae*.

Table 3 Pathway analysis of differentially expressed genes in the Gcgr$^{-/-}$ mouse liver

	Glucose homeostasis	Inflammation	Cell proliferation	Metabolism
Underexpressed in Gcgr$^{-/-}$ mouse liver	Nnmt, Got1, Sds, Pck1		Gas2	Slc10a2, Ntrk2, Gls2, Lhpp, Sult5a1, Mt2, Mt1, Slc3a1, Trdn, Usp2, Cyp17a1, Upp2
Overexpressed in Gcgr$^{-/-}$ mouse liver		Il1b, Cxcl13, Tgtp1, Cxcl9, Defb1, Vtcn1, H2-Ab1, Spon2, Il2rg	Cdkn1a, Igfbp1, Chac1, Cav1, Inhba, Gadd45b, Rassf4, Socs2, Meig1	Serpina7, Cpt1b, Slc34a2, Fabp5, Lpl, Acaca, Asns

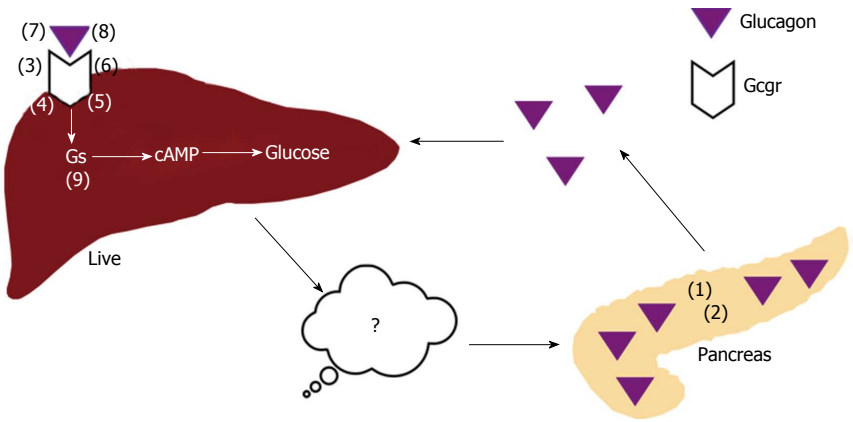

Figure 2 Schematic drawing of regulation of pancreatic α cell number by a humoral liver factor. The numbers indicate specific ways to disrupt glucagon signaling. (1) Glucagon deletion; (2) PC2 deletion; (3) Glucagon receptor (Gcgr) global deletion; (4) Gcgr liver-specific deletion; (5) Gcgr inactivating mutation; (6) Gcgr antisense RNA; (7) Gcgr antagonists; (8) Gcgr antibodies; and (9) Gsa liver-specific deletion. See text for details.

receptor for the inhibitor (leptin receptor). Analogously, the Gcgr$^{-/-}$ mice liver could produce a stimulator or lack an inhibitor of α cell mass. Whether the liver factor is a stimulator or an inhibitor in nature is critical in guiding the search for the identity of the liver factor that causes ACH. As parabiosis is technically challenging, it probably should be used as a last resort. Alternative approaches such as primary pancreatic islet culture[52,53] may be used first to resolve the stimulator/inhibitor question and later used as a high-throughput model for identifying the factor. For example, if a 10:1 mixture of wildtype and Gcgr$^{-/-}$ serum stimulates α cell proliferation of the wildtype islets, then it is likely that the Gcgr$^{-/-}$ mice have a stimulator of α cell mass. Another potential systems approach is to compare the liver gene expression and metabolic profile of multiple animal models of reactive ACH. As all the models develop reactive ACH, any differentially expressed genes unlikely encode the liver

factor and metabolites of various levels unlikely cause ACH, thus greatly narrowing down the list of candidate genes or metabolites. It is also important to point out that other subtypes of ACH exist and not all ACH is associated with glucagon receptor mutation[22,54].

CONCLUSION

Pancreatic ACH is a precursor lesion that gives rise to PNETs. Reactive ACH is associated with hyperglucagonemia and invariably evolves into PNETs in both humans and animal models. The glucagon receptor knockout ($Gcgr^{-/-}$) mice are one of the murine model of reactive ACH and current research has shown that the liver produces a factor that regulates pancreatic α cell mass. Liver gene expression arrays and metabolic profiling suggest a number of potential candidates for the novel liver hormone but none of them so far tested has been confirmed. As understanding the physiological, cellular, and molecular mechanisms underlying reactive ACH pathogenesis is important to the prevention and treatment of PNETs, the search for the elusive liver factor is worthwhile but may require a substantial effort to find it.

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