The role of α-ketoglutarate and the hypoxia sensing pathway in the regulation of pancreatic β-cell function

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ABSTRACT
Anaplerosis and the associated mitochondrial metabolite transporters generate unique cytosolic metabolic signaling molecules that can regulate insulin release from pancreatic β-cells. It has shown that mitochondrial metabolites, transported by the citrate carrier (CIC), dicarboxylate carrier (DIC), oxoglutarate carrier (OGC), and mitochondrial pyruvate carrier (MPC) play a vital role in the regulation of glucose-stimulated insulin secretion (GSIS). Metabolomic studies on static and biphasic insulin secretion, suggests that several anaplerotic derived metabolites, including α-ketoglutarate (αKG), are strongly associated with nutrient regulated insulin secretion. Support for a role of αKG in the regulation of insulin secretion comes from studies looking at αKG dependent enzymes, including hypoxia-inducible factor-prolyl hydroxylases (PHDs) in clonal β-cells, and rodent and human islets. This review will focus on the possible link between defective anaplerotic-derived αKG, PHDs, and the development of type 2 diabetes (T2D).

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Introduction
Pancreatic β-cell GSIS involves a rise in the ATP:ADP ratio, which leads to closure of ATP-sensitive K+ (K_{ATP}) channels, resulting in plasma membrane depolarization, activation of voltage-gated Ca^{2+} channels (VDCC) and Ca^{2+}-mediated stimulation of insulin granule exocytosis.\textsuperscript{1–4} Although there are limitations to studying insulin secretion using square wave glucose stimulation assays in β-cells, most studies support the concept that there is a “K_{ATP} channel-dependent” mechanism of insulin granule exocytosis. This K_{ATP} channel-dependent pathway appears to be particularly important in triggering exocytosis of a small number of granules from a plasma membrane-docked “readily releasable pool” which is responsible for the first, acute phase of insulin release (first 10 minutes of release after stimulation).\textsuperscript{5,6} In contrast, in the second and sustained phase of insulin secretion (>10 minutes), ATP and Ca^{2+} along with other glucose-derived second messengers, play an important role.\textsuperscript{5,7} It is accepted that elevated cytosolic Ca^{2+} leads to stimulation of exocytosis of insulin granules,\textsuperscript{8,9} but the Ca^{2+} signal alone is not the only factor required for sustained secretion since membrane depolarization with high KCl, which leads to a sustained elevation of Ca^{2+}, does not lead to biphasic insulin secretion.\textsuperscript{10} Under clamped cytosolic Ca^{2+} concentrations, the addition of glucose can still augment insulin secretion.\textsuperscript{11} Also, it has been shown that mice lacking K_{ATP} channel function retain the ability to secrete insulin and have relatively normal glucose homeostasis.\textsuperscript{12–17} For example, prior exposure of SUR1 knockout mouse islets to low glucose allows them to exhibit a six-fold increase in insulin secretion in response to 15 mM glucose.\textsuperscript{13,14} These studies suggest that the K_{ATP} channel pathway cannot fully explain how insulin secretion is regulated. This and other data (reviewed in\textsuperscript{7,18,19}) in rodent and human islets suggest that mitochondrial messengers distinct from ATP and/or Ca^{2+} are also involved in GSIS.\textsuperscript{3,4,6,7,11–14,18,20–33} These studies suggest that there are additional regulators of insulin secretion besides ATP and Ca^{2+}. This review will focus on one of them, αKG, and its possible role in the regulation of prolyl hydroxylase domain (PHD) proteins (Figure 1).

Prolyl hydroxylases
PHDs belong to the iron and αKG-dependent family of dioxygenases that have several primary substrates, including proteins, methylated nucleotides, lipids,
Prolyl-4-hydroxylases subfamily of proteins consists of the hypoxia-inducible factor (HIF)-prolyl-4-hydroxylases (P4H) (also referred to as prolyl-4-hydroxylase domain (PHD)) and the collagen prolyl hydroxylases (C-P4Hs). PHDs and C-P4Hs are encoded by unique genes with minimal amino acid similarities. The only exception is that PHDs and C-P4Hs have some similarities in their catalytic domains. For C-P4Hs, the hydroxylation of proline residues in collagen to 4-hydroxyproline is essential for proper assembly of collagen. The 4-hydroxyproline forms hydrogen bonds between the main chains of neighboring collagen polypeptides. There are three known α-subunit isoforms of the collagen prolyl 4-hydroxylase (P4HA) and include P4HA isofrom 1 (P4HA1), P4HA2 and P4HA3, and there is one known β-subunit P4HB. Two α-subunits and two β-subunits form a functional $A_2B_2$ tetrameric protein and result

Table 1. Expression of αKG-dependent family of dioxygenase hydroxylases in pancreatic β-cells. Procollagen-Lysine, 2-Oxoglutarate 5-Dioxygenase (PLOD), Factor inhibiting HIF (FIH), prolyl-4-hydroxylase domain (PHD), prolyl 4-hydroxylase (P4H). There are three α-P4Hs (P4HA) and one β-P4H (P4HB). Expression in β-cells was determined from two transcriptomic papers by Segerstolpe and Mawla. Expression with type 2 diabetes were determined using the type 2 diabetes portal. (http://www.type2diabetesgenetics.org/home/portalHome). Amino acid (AA). Not detected (ND).

| Subfamily | Gene | Target AA | Expressed in beta-cells | Association with T2D |
|-----------|------|-----------|-------------------------|----------------------|
| Procollagen-Lysine,2-Oxoglutarate 5-Dioxygenase | PLOD1 | Lysine | Reference 35, 36 | Weak |
| | PLOD2 | Lysine | Reference 35, 36 | Weak |
| | PLOD3 | Lysine | Reference 35, 36 | Not found |
| Hypoxia-inducible factor-asparagine dioxygenase | FH1AN | Asparagine | Reference 35, 36 | Weak |
| Prolyl-4-hydroxylases | PHD1 | Proline | Reference 35, 36 | Weak |
| | PHD2 | Proline | Reference 35, 36 | No |
| | PHD3 | Proline | Reference 35, 36 | Weak |
| PHD-TM | Proline | Reference 35, 36 | Weak |
| Prolyl-4-Hydroxylase (subunit alpha) | P4HA1 | Proline | Reference 35, 36 | Weak |
| | P4HA2 | Proline | Reference 35, 36 | Weak |
| | P4HA3 | Proline | Reference 35, 36, low Ref 36 | Weak |
| Prolyl-4-Hydroxylase (subunit beta) | P4HB | Proline | Reference 35, 36 | Weak |
PHDs, like C-P4H, require oxygen, the tricarboxylic acid cycle intermediate αKG as a substrate, Fe$^{3+}$, and ascorbate as cofactors (Figure 2). Unlike the C-P4H, the PHDs have a $K_m$ value for oxygen around 100 μM. This $K_m$ value is higher than the oxygen concentration found in tissues. Because of these features, PHDs are considered one of the primary oxygen sensors in cells. There are three isoforms of PHD (PHD1, PHD2, and PHD3) which are also referred to as Egln2, Egln1, and Egln3 or HIF-P4H1, HIF-P4H2, and HIF-P4H3, respectively. In humans, PHD1, PHD2, and PHD3, are composed of 407, 426, and 239 amino acids, respectively, and unlike the tetrameric collagen prolyl hydroxylases, they function as monomeric proteins. A transmembrane PHD (PHD-TM) has also been described that consists of 502 amino acids located in the endoplasmic reticulum with the catalytic domain within the lumen between residues 59 and 82. At the amino acid level, PHD1, PHD2, and PHD3 are 42–59% identical to each other. These isoforms share the hydroxylase domain at the C-terminal end, whereas the N-terminal ends vary within each isoform, with PHD3 having the shortest N-terminal domain. Each of the PHD isoforms also have several variants that are produced via alternative splicing of exons 4 and 5; however, these may lack sufficient enzymatic activity or stability. PHDs have unique subcellular localizations with PHD1 exclusively expressed in the nucleus; PHD2 mainly localized in the cytosol, and PHD3 is expressed in almost equal proportions between the cytosol and the nucleus. PHD2 is ubiquitously expressed in most tissues, whereas PHD1 and PHD3 were found at higher levels in the placenta and heart, respectively. PHD-TM mRNA levels were highest in the human brain and pancreas, and PHD1 was the sole hydroxylase in the testes. Whole body knockouts of PHD1 in mice have no overt phenotype, whereas, whole body knockout of PHD2 in mice have placental vascular defect and die prematurely. Mice with whole body knockout of PHD3 have defective development of the sympathetic nervous system and hypotension.

Both C-P4Hs and PHDs use one oxygen atom in the oxidative decarboxylation of αKG generating succinate and CO$_2$, and the second oxygen atom is used in the hydroxylation of proline residues in target proteins. TCA cycle intermediates, succinate, and fumarate have been reported to inhibit PHD activity by competing with αKG for its binding site. Fumarate and succinate can inhibit all three PHD isoforms, with fumarate having a $K_i$ value between 50–80 μM and succinate between 350 and 460 μM. The requirement of Fe$^{2+}$ for the hypoxic response was shown using iron chelators, which led to the stabilization of HIF1α long before the discovery of PHDs. Nitric oxide and reactive oxygen species (ROS) have also be recognized to inhibit both C-P4Hs and PHD activity by chelation and oxidation of bound Fe$^{2+}$ to Fe$^{3+}$ respectively. Ascorbate plays a role in maintaining maximal C-P4H and PHD catalytic activity and has been reported to reduce Fe$^{3+}$ from increased ROS production back to Fe$^{2+}$.

The reactions performed by prolyl hydroxylases are not reversible. The primary regulator of the response to low oxygen levels in tissues is the

![Figure 2. PHD proteins play a key role in regulating hypoxia inducible factor (HIF) stability and activity. Under normoxic conditions, oxygen and α-ketoglutarate are available for PHDs to use to proline hydroxylate HIF proteins which targets them for ubiquitination (Ub) mediated degradation. Under hypoxic conditions, the low oxygen prevents the proline hydroxylation of HIFs, increasing their stability and activity. Von Hippel-Lindau (VHL), hypoxia response element (HRE). Figure was created with BioRender.com.]
transcription factor hypoxia inducible factors (HIF). HIF is a heterodimer containing an unstable HIFα subunit and a stable HIF1β subunit.\(^4,4^5\) One of the most investigated roles for PHDs is the hydroxylation of proline residues on HIFα. The C-P4Hs are not capable of hydroxylating proline residues in HIFα and are not found in the cytosol. There are three isoforms of human HIFα, HIF1α, HIF2α, and HIF3α. Due to its high expression in many cells, PHD2 has been suggested to be the primary regulator in the hypoxia response pathway. Conditional inactivation of PHD2 in adult mice is enough to lead to excessive angiogenesis, a process that is upregulated with HIFα stabilization.\(^4^3\) A lesser role for PHD1 and PHD3 in the regulation of HIFα is likely due to their lower mRNA levels.\(^4^4\) PHD2 is preferential to HIF1α compared to HIF2α, whereas the opposite is true for PHD3.\(^4^3,4^4\)

PHDs can hydroxylate one or both proline residues (Pro-402 and Pro-564) in the oxygen-dependent degradation domain (ODDD) of HIF1α in normoxic conditions at – Leu-X-X-Leu-Ala-Pro-recognition sites.\(^4^3\) Under normoxic conditions, PHD mediated hydroxylation of proline residues in HIFα are recognized by the von Hippel-Lindau protein (pVHL) E3 ubiquitin ligase complex and targeted for ubiquitination and rapid proteasomal degradation.\(^3^9,4^4,5^3\) When hypoxic conditions occur, PHD is inhibited by the lack of oxygen leading to HIFα stabilization. HIFα translocates to the nucleus where it forms a heterodimer with HIF1β and binds to hypoxia-response elements (HREs) located in the regulatory regions of more than 100 genes involved in response to decreasing oxygen levels (Figure 2).\(^3^9,4^3,4^5\) These targeted genes include those involved with angiogenesis, such as VEGF, erythropoiesis, energy metabolism, neovascularization, apoptosis, and cell proliferation.\(^4^6,5^4\)

The oxidative state of cells can regulate PHDs activity. PHD activity can be increased with higher levels of antioxidants, such as ascorbate, and their activity can be decreased in response to reactive oxygen species (ROS).\(^3^9,4^3,5^3–5^8\) The lack of cysteine has been shown to lead to oxidative self inactivation of PHD1, which leads to HIF1α accumulation.\(^5^9\) A PHD2 protein complex of 15 proteins might also exist and play a role in regulating PHD2 activity.\(^6^0\) Additionally, there is regulation of PHD expression levels as well. A positive feedback mechanism exists involving HIF-1α-mediated induction of PHD2 and PHD3, but not PHD1, transcript and protein levels via a HRE found in their genes, and this may be important in the removal of HIF1α upon reoxygenation.\(^6^1–6^7\) FK506 binding protein 38 (FKBP38) has been shown to bind and negatively regulate PHD2 stability by promoting PHD2 entry into an ubiquitin-independent proteasomal pathway.\(^6^8,6^9\) The effects of FKBP38 on PHD2 stability seems to be independent of FKBP38 peptidyl-prolyl cis-trans isomerase activity.\(^6^8,6^9\) It has been suggested that FKBP38 may regulate PHD2 by excluding it from the nucleus, whereas, another PHD2 binding protein, ING4, promotes nuclear localization of PHD2 and reoxygenation mediated degradation of HIF.\(^6^9,7^0\) Although it is not known if FKBP38 can negatively regulate PHD1 and PHD3, hypoxia can increase Siah1α and Siah2 expression, and this can target PHD1 and PHD3 for proteasomal degradation by the E3 ubiquitin ligase pathway.\(^7^1\)

**Islets, O₂, and PHDs**

When clonal MIN6 cells and primary mouse islets are stimulated by high glucose, it leads to transient hypoxia (within minutes) that is likely due to increased nutrient stimulated oxygen consumption; this hypoxia is exacerbated when oxygen availability is compromised. This transient hypoxia does not lead to the activation of HIF1α.\(^7^2\) However, exposing β-cells to mild or long-term hypoxia, over a period of a few hours or days, leads to induction in HIF1α, causing a shift to anaerobic metabolism and inhibition of GSIS.\(^7^2–7^4\) Rat and human islets incubated for 5.5 hours in a hypoxic environment were correlated with a decrease in insulin content and insulin biosynthesis.\(^7^5\) Also, islet oxygen delivery is impaired in both C57BL6/J mice fed a high fat diet (HFD), and in ob/ob mice likely because of poor islet microcirculation and blood supply.\(^7^2\) In adults, T2D is associated with severe hypoxia due to poor islet microcirculation and increased nutrient stimulated oxygen consumption leading to a reduced ability to produce ATP in β-cells.\(^5^2\) The long-term lower oxygen levels in β-cells leads to HIF1α stabilization, which then activates target genes involved in angiogenesis to
increase oxygen supply. The upregulation of islet HIF1α during diabetes-induced hypoxia may play a protective/survival role for islets, but upregulated HIF1α comes at the price of inhibition of nutrient regulated insulin secretion. Overall, diabetes mediated reduction of PHDs activity due to lower O2 availability leads to elevated HIFα levels which may be beneficial for maintaining insulin sensitivity in peripheral tissues and β-cells. Increased HIFα may promote β-cell survival, but it also blocks nutrient regulated insulin secretion. These studies suggest a crucial role for the oxygen sensing PHDs in the development of diabetes; however, we know very little about how these proteins lead to β-cell dysfunction.

Consistent with a negative role for HIF1α in inhibiting β-cell function, the INS-1 832/2 glucose unresponsive cell line have increased HIF1α and anaerobic metabolism. Higher HIF1α protein levels were associated with impaired GSIS in rodent and human islets. These studies suggest that glucose unresponsive β-cells may have lower PHD activity, and this may impair GSIS. HIF1α and HIF2α are required for adaptation of the β-cell to hypoxia seen during embryonic development and β-cell differentiation; however, too much HIF1α has a negative effect on β-cell development perhaps by decreasing the ability to produce ATP. Specific loss of HIF1α leads to impaired glucose tolerance, reduced islet ATP, and a loss of β-cell function in rodent and human islets. The PHD inhibitor/iron chelators deferoxamine (DFO) and deferasirox (DFS) were able to increase HIF1α and significantly improve glucose tolerance, and insulin secretion in wild-type mice fed a HFD. HIF1α is also thought to be associated with glucose intolerance and insulin insensitivity in β-cells. It appears that β-cells require small amounts of HIF1α to maintain β-cell function; however, too much can lead to β-cell dysfunction and diabetes. The primary regulators of HIFs are the PHDs suggesting an important role for this protein in the development of diabetes.

It is also possible that there may be a link between ROS, PHDs, and diabetes. It is known that islet nutrient overload leads to elevation of ROS, and the increased ROS may inhibit PHD activity and promote an elevation of HIF and impair islet insulin secretion. It has also been suggested that ROS may be a more relevant physiological regulator of HIF1α stability under aerobic conditions. Like HIF1α, neuronal PAS domain protein 4 (NPAS4) is a heterodimerization partner of HIF1β (or aryl hydrocarbon receptor nuclear translocator, ARNT). In β-cells, the binding of HIF1α and NPAS4 to HIF1β is competitive, and each binding pair can activate a different subset of genes. NPAS4 is rapidly induced by membrane depolarization and calcium influx by the calcineurin, Akt/protein kinase B, and Ca2+/calmodulin-dependent protein kinase signaling pathways in β-cells. NPAS4 is protective against thapsigargin- and palmitate-induced ER stress, prevents apoptotic cell death and is lower in type 2 diabetic mouse β-cells. The Ca2+ induced expression of NPAS4 can prevent ROS induced HIF1α stabilization and maintains maximal mitochondrial OXPHOS function in β-cells. Thus like PHDs, NPAS4 can also regulate β-cell HIF1α levels.

In addition to the role of PHDs in the development of β-cell dysfunction, they may also play a role in regulating insulin sensitivity. Hypomorphic mice (whole body mutant mice that have lower PHD2 protein levels and increased HIF1α) have less adipose tissue, smaller adipocytes and decreased adipose tissue inflammation resulting in improved glucose tolerance and insulin sensitivity on either normal chow or HFD. These mice also had HIF1α stabilization and upregulation of its target.

![Figure 3. PHD activity can be regulated by a number of metabolic metabolites. In addition to PHD ability to regulate HIF stability and activity through proline hydroxylation, they can proline hydroxylate numerous other non-HIF targets. Figure was created with BioRender.com.](image-url)
genes, involving glucose transporters and enzymes involved in glycolysis. These results were replicated with oral administration of the PHD inhibitor FG-4497 in wild type mice. These studies suggest a key role for PHD2 in the control of HIF1α. Hepatic knockout of PHD3 leads to improved insulin sensitivity and prevents HFD induced diabetes due to HIF2α stabilization. HIF2α stabilization was associated with increased IRS2 and Akt activity. The authors suggest that isoform-specific inhibition of PHD3 may be a viable treatment option for T2D; however, this may not have the intended effect since inhibition of PHD3 blocks GSIS in mouse and human islets. Overall, diabetes mediated reduction of PHD activity due to lower oxygen availability leads to elevated HIFα levels which may be beneficial for maintaining insulin sensitivity in peripheral tissues but in β-cells increased HIFα may promote β-cell survival, while also blocking GSIS.

In addition to oxygen, several TCA cycle intermediates are also essential regulators of PHD activity, especially under normoxia. Rodent and human β-cells express high levels of the anaplerotic mitochondrial enzyme pyruvate carboxylase (PC) that plays a crucial role in generating TCA intermediates, including αKG. Transport of αKG from the mitochondria to the cytosol is facilitated by the αKG carrier (2-oxoglutarate carrier (OGC)). Pharmacological or siRNA mediated inhibition of OGC in 832/13 β-cells and primary rat islets significantly reduces GSIS suggesting that αKG needs to be transported to the cytosol to affect insulin secretion. It has been shown that anaplerotically derived αKG plays a key role in regulating GSIS. αKG may regulate insulin secretion through its metabolism by PHDs leading to proline hydroxylation of crucial proteins involved in nutrient-stimulated insulin release. It has also been proposed that αKG may stimulate insulin secretion via glutamine dehydrogenase, which converts αKG to glutamate, glutamate potentially acts as a direct insulin secretagogue. However, this mechanism does not fully explain the role of αKG in regulating GSIS, and we propose that αKG is also oxidized to succinate via PHDs. It has been shown that succinate and fumarate can regulate PHD activity and HIF stabilization. A role for succinate has been shown by inhibiting succinate dehydrogenase, which elevated cytosolic succinate levels, and led to a reduction in PHD activity. Fumarate, pyruvate, and oxaloacetate can lead to the stabilization of HIF in vitro. The inhibitory effects of some TCA cycle intermediates seem to be specific for different PHD isoforms. An essential metabolite in the regulation of GSIS, citrate, has been shown to inhibit PHD3 more effectively than PHD1 or PHD2. Certain mutations of isocitrate dehydrogenase isoenzymes I and 2 (IDH1, 2) have been shown to decrease αKG in cells and led to the production of the oncometabolite R-2-hydroxyglutarate (also known as D-2-hydroxyglutarate) by the mutated IDH.

Low levels of αKG or the R-2-hydroxyglutarate can negatively affect PHD activity and increase HIF stability. Whole body PHD1 knockout mice exhibit reduced basal oxygen consumption and were protected from skeletal muscle ischemia. The ischemic skeletal muscle protective effects seen in PHD1 knockout mice were partly due to HIF2α-mediated induction of pyruvate dehydrogenase kinase isoforms 1 and 4, which reduced mitochondrial respiration and elevated glycolytic ATP production. A role for PHDs in regulating metabolism is also supported by a study showing that PHD1-depleted breast cancer cells had a HIF-independent lowering of mitochondrial O2 consumption.

PHDs, especially PHD3, have been shown to play a role in regulating GSIS in rodent and human β-cells. A recent preprint supports this work by D. Hodson group, suggesting a key role for PHD3 in the regulation of insulin secretion in response to metabolic stress using PHD3 KO mice (https://doi.org/10.1101/2020.04.30.068106). The link between glucose metabolism and PHD regulated insulin release may be anaplerotically derived αKG. Metabolism of αKG by PHDs could lead to proline hydroxylation of critical proteins involved in regulating insulin release. Recent studies have shown that PHDs can regulate several proteins in addition to HIFs, and some of these have been shown to control GSIS. Suggested non-HIFa targets of PHDs include Pax2, mTORC1, PKM2, ATF4, β2AR, NFκB, p27 (Figure 3). For example, proline hydroxylation by PHDs is reported to negatively regulate NF-κB. PHDs have also been shown to interact with p53 tumor suppressor protein,
Wnt/β-catenin signaling pathway, and members of the ubiquitin-proteasome system. PHD1 is positively linked to caspase-3 levels in human inflammatory bowel disease, and mice with PHD1 deficiency have reduced apoptosis. Other novel non-HIFα targets, include MICAL1 and RhoGDI, which are known to be involved in regulating second-phase GSIS. Interestingly, PHD3 has the widest range of suggested targets, and our published and preliminary data, as well as others (https://doi.org/10.1101/2020.04.30.068106) support a strong role for PHD3 in GSIS. Overall, there is support for the concept that long-term changes in PHD activity can elevate HIFα and have a negative impact on β-cell function and lead to T2D. However, in the short-term, it can have a positive effect on β-cell function in an aKG dependent and HIFα independent fashion and promote GSIS.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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