Although their efforts to uncover *Hnf1b* expression heterogeneity in the ductal epithelium were unsuccessful, variability cannot be definitively ruled out. The cells that become marked could represent a population of duct cells with a higher activity of *Hnf1b* transcription or greater accessibility to Cre recombinase.

Data supporting a duct origin for islet cells postnatally in mice, rats, and humans exist, but the ductal origin hypothesis remains controversial and in need of definitive experiments. Growth of the exocrine pancreas from duct cells during branching morphogenesis remains an attractive hypothesis, which, surprisingly, is unsupported by this paper. If duct cells are not the origin of this increase in β cell number after PDL, what other candidates might produce so many β cells this quickly? The demonstrated increase in β cell replication after PDL must account for some of the increased β cell mass, with these replicating cells being from either newly formed or preexisting islets. If there are nonduct precursor cells, they must exist in reasonable numbers, but then why are they not easier to identify?

Assuming that the above caveats turn out to be groundless, the studies by Ferrer and colleagues considerably advance our understanding of pancreas development. *Hnf1bCreER* mice can be viewed as a novel tool to identify components of pancreas development. It can be concluded that *Hnf1b* floxed duct cells do not substantially contribute to endocrine or acinar pancreas. In the future, we imagine that *Hnf1bCreER* mice can be applied to exclude pancreatic lineages when searching for progenitors of β cell expansion. Ultimately, it will be important to confirm and expand the findings of Ferrer and colleagues with lineage tracing studies using additional markers that label either ducts or other candidate precursor cells.

In the end, the experiments by Ferrer and colleagues challenge the duct origin hypothesis, but the above caveats must be addressed. If future similarly rigorous experiments succeed in disproving the duct cell origin, where do we look next to explain the impressive regenerative potential of the β cells? We anticipate that the next few years will have many surprises in this exciting field.

REFERENCES

Brennand, K., Huangfu, D., and Melton, D. (2007). PLoS Biol. *5*, e163.

Dor, Y., Brown, J., Martinez, O.I., and Melton, D.A. (2004). Nature *429*, 41–46.

Granger, A., and Kushner, J.A. (2009). J. Intern. Med. *266*, 325–338.

Inada, A., Nienaber, C., Katsuta, H., Fujitani, Y., Levine, J., Morita, R., Sharma, A., and Bonner-Weir, S. (2008). Proc. Natl. Acad. Sci. USA *105*, 19915–19919.

Nir, T., Melton, D.A., and Dor, Y. (2007). J. Clin. Invest. *117*, 2553–2561.

Pittenger, G.L., Taylor-Fishwick, D., and Vinik, A.I. (2009). Diabetologia *52*, 735–738.

Rooman, I., and Bouwens, L. (2004). Diabetologia *47*, 259–265.

Solar, M., Cardalda, C., Houbracken, I., Martín, M., Maestro, M.A., De Medts, N., Xu, X., Grau, V., Heimberg, H., Bouwens, L., and Ferrer, J. (2010). Dev. Cell *17*, 849–860.

Teta, M., Rankin, M.M., Long, S.Y., Stein, G.M., and Kushner, J.A. (2007). Dev. Cell *12*, 817–826.

Xu, X., D'Hoker, J., Stangé, G., Bonné, S., De Leu, N., Xiao, X., Van de Casteele, M., Mellitzer, G., Ling, Z., Pipeleers, D., et al. (2008). Cell *132*, 197–207.

More Is Not Always Better: α2A-Adrenoceptor Expression in Type 2 Diabetes

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Various members of the G protein-coupled receptor (GPCR) superfamily are known to modulate the release of insulin from pancreatic β cells. Rosengren and colleagues have recently provided convincing evidence for a role of increased expression of the α2A-adrenoceptor in β cells in the pathogenesis of type 2 diabetes.

Type 2 diabetes (T2D) represents one of the major threats to human health in the 21st century. One key feature of T2D is that glucose fails to stimulate adequate release of insulin from pancreatic β cells to maintain normal blood glucose levels.

For this reason, therapies targeted at improving β cell function are predicted to be of considerable therapeutic benefit.

The activity of pancreatic β cells is modulated by several neurotransmitters released from peripheral autonomic nerves (Ahrén, 2000; Gilon and Henquin, 2001). The major neurotransmitter of the peripheral parasympathetic nervous system, acetylcholine, facilitates insulin secretion from pancreatic β cells via activation of the M_3 muscarinic receptor
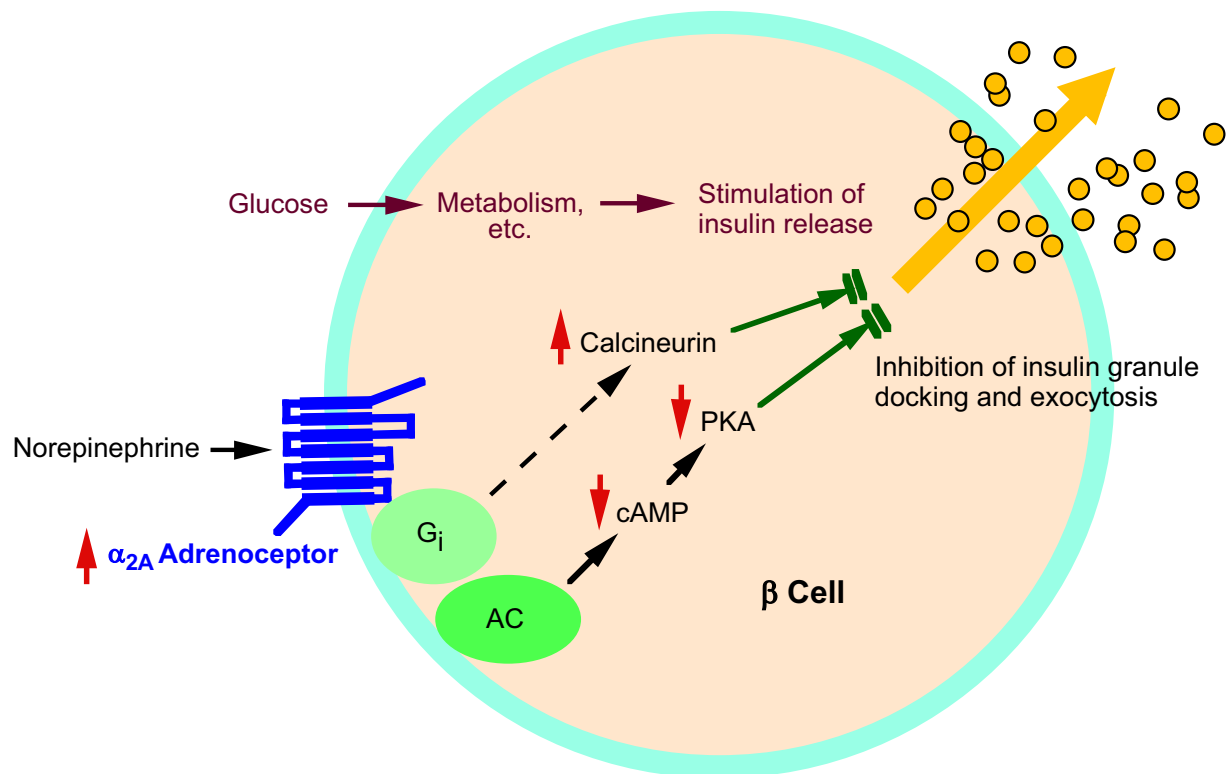
Figure 1. Overexpression of the α_{2A} Adrenoceptor in Pancreatic β Cells Results in Impaired Insulin Release
The α_{2A}-adrenoceptor subtype is expressed on the surface of pancreatic β cells. Norepinephrine-mediated activation of the α_{2A} adrenoceptor leads to the activation of G proteins of the G_i family, ultimately triggering reduced insulin release. Increased expression of the α_{2A} adrenoceptor in β cells of rats or humans causes impairments in insulin granule docking to the plasma membrane and exocytosis. These latter deficits are due, at least in part, to increased activation of the protein phosphatase, calcineurin (see text for details). AC, adenylyl cyclase; PKA, protein kinase A.

subtype (Gilon and Henquin, 2001; Gautam et al., 2006).

The endocrine pancreas is also richly innervated by sympathetic nerves (Ahrén, 2000). Electrical stimulation of these nerves or norepinephrine administration results in a pronounced inhibition in insulin release (Ahrén, 2000). Various lines of evidence suggest that this effect is mediated by activation of postsynaptic α_2-adrenoceptors expressed by pancreatic β cells (Ahrén, 2000). Molecular cloning studies have revealed the existence of three molecularly distinct α_2-adrenoceptor subtypes (α_{2A}, α_{2B}, and α_{2C}). The α_2-adrenoceptors are prototypic members of the GPCR superfamily and exert most of their physiologic actions via coupling to G proteins of the G_i family (Philipp and Hein, 2004) (Figure 1). Accumulating evidence suggests that β cell α_{2A} adrenoceptors play a central role in mediating inhibition of insulin release following treatment with α_2-adrenoceptor agonists or stimulation of sympathetic

pancreatic nerves (Devedjian et al., 2000; Peterhoff et al., 2003).

Despite the known inhibitory role of α_{2A} adrenoceptors in mediating inhibition of insulin release from pancreatic β cells, the role of this receptor subtype in the pathogenesis of T2D was unclear. Rosengren et al. (2009) now provide strong evidence that the α_{2A}-adrenoceptor subtype plays an important role in the pathophysiology of T2D. Initially, the authors analyzed congenic strains from the Goto-Kakizaki (GK) rat, a widely used model for T2D exhibiting insulin resistance, impaired insulin secretion, as well as various late complications associated with T2D. Rosengren et al. (2009) convincingly demonstrated that a 1.4 Mb genomic locus of the GK rat is linked to reduced insulin release, due to impairments in insulin granule docking at the plasma membrane and granule exocytosis. This 1.4 Mb GK-derived genetic segment contains five known protein-coding genes Whereas expression of

four of these genes was unchanged in pancreatic islets from congenic rats containing the 1.4 Mb GK-derived sequence (N115 rats), interestingly the expression of the fifth gene, *Adra2a*, encoding the α_{2A} adrenoceptor was found to be significantly upregulated in these islets, both at the mRNA and protein level. Consistent with the in vitro studies, in vivo experiments demonstrated that N115 rats showed impaired glucose tolerance, associated with a pronounced reduction in glucose-stimulated insulin release (GSIS).

Incubation of N115 islets with the α_2-adrenoceptor antagonist yohimbine greatly enhanced GSIS. Moreover, treatment of N115 islets with *Adra2a* siRNA increased GSIS to levels similar to those seen with control islets. Taken together, these observations strongly support the concept that the impaired insulin secretion observed with N115 islets is caused by overexpression of the α_{2A}-adrenoceptor subtype. Additional in vitro studies

showed that the ability of β cell $α_{2A}$ adrenoceptors to inhibit insulin release results from the activation of pertussis toxin-sensitive G proteins (G proteins of the G_i family), and that overexpression of $α_{2A}$ adrenoceptors leads to increased activation of the protein phosphatase, calcineurin, which interferes with insulin granule recruitment.

On the basis of these findings, SNP analysis of the human *ADRA2A* gene was undertaken, and demonstrated a linkage between the minor allele (A) of rs553668, located in the 3′ UTR region of *ADRA2A*, and impaired insulin secretion in humans. This SNP was associated with reduced fasting insulin levels, and reduced insulin secretion following oral glucose administration. In addition, studies with a large cohort of nondiabetic and diabetic individuals indicated that *ADRA2A* rs553668 was associated with increased risk of T2D.

Importantly, Rosengren et al. (2009) went on to demonstrate that pancreatic islets from risk A-allele carriers for rs553668 overexpressed the $α_{2A}$-adrenoceptor subtype, both at the mRNA and protein level. Moreover, pancreatic islets from risk carriers showed reduced basal insulin secretion and a pronounced reduction in GSIS, probably due to a decrease in the number of docked insulin granules. In agreement with the results obtained with congenic rats (see above), these impairments in insulin secretion and insulin granule distribution could be rescued by treatment with the $α_2$-adrenoceptor antagonist, yohimbine. Taken together, these findings strongly suggest that impaired insulin secretion in rs553668 risk carriers results from

enhanced signaling through β cell $α_{2A}$ adrenoceptors, suggesting the possibility of tailoring specific treatments to individual T2D patients.

As the $α_{2A}$ adrenoceptor is expressed in many peripheral and central tissues, it is not surprising that this receptor subtype modulates many diverse physiological functions, including regulation of blood pressure and various metabolic processes (Philipp and Hein, 2004). Enhanced signaling through $α_{2A}$-adrenoceptors may therefore also contribute to other pathophysiological conditions. The widespread expression of the $α_{2A}$-adrenoceptor, however, suggests that the use of $α_{2A}$-adrenoceptor antagonists for the treatment of T2D is likely to be associated with significant side effects. Clearly, targeting drugs more specifically to β cell $α_{2A}$ adrenoceptors or downstream signaling proteins remains a major challenge for future research.

Besides the $α_{2A}$ adrenoceptor, pancreatic β cells express a multitude of other GPCRs, many of which are known to modulate insulin release (Regard et al., 2007; Ahrén, 2009). Since GPCRs are mostly found on the cell surface, these receptors could represent excellent drug targets for small molecule ligands. Receptors that are coupled to the activation of G_q- and G_s-type G proteins have attracted considerable interest as potential drug targets, primarily due to their ability to stimulate insulin release (Ahrén, 2009; Guettier et al., 2009). For example, the GLP-1 receptor is a G_s-coupled receptor that is highly enriched in pancreatic islets (Regard et al., 2007), and drugs that act as agonists at this receptor (e.g., exendin 4) or compounds that inhibit the enzymatic breakdown of GLP-1 (dipep-

tidyl peptidase 4 inhibitors) have recently been approved for the treatment of T2D (Ahrén, 2009).

Given the findings by Rosengren et al. (2009), it is likely that sequence variations in other GPCRs may also contribute to the pathogenesis of T2D. Clearly, this subject provides fertile ground for future research. Hopefully, these efforts will lead to the development of novel, more specific GPCR-based therapies for the treatment of T2D.

REFERENCES

Ahrén, B. (2000). Diabetologia *43*, 393–410.

Ahrén, B. (2009). Nat. Rev. Drug Discov. *8*, 369–385.

Devedjian, J.C., Pujol, A., Cayla, C., George, M., Casellas, A., Paris, H., and Bosch, F. (2000). Diabetologia *43*, 899–906.

Gautam, D., Han, S.J., Hamdan, F.F., Jeon, J., Li, B., Li, J.H., Cui, Y., Mears, D., Lu, H., Deng, C., et al. (2006). Cell Metab. *3*, 449–461.

Gilon, P., and Henquin, J.C. (2001). Endocr. Rev. *22*, 565–604.

Guettier, J.M., Gautam, D., Scarselli, M., de Azua, I.R., Li, J.H., Rosemond, E., Ma, X., Gonzalez, F.J., Armbruster, B.N., Lu, H., et al. (2009). Proc. Natl. Acad. Sci. USA *106*, 19197–19202.

Peterhoff, M., Sieg, A., Brede, M., Chao, C.M., Hein, L., and Ullrich, S. (2003). Eur. J. Endocrinol. *149*, 343–350.

Philipp, M., and Hein, L. (2004). Pharmacol. Ther. *101*, 65–74.

Regard, J.B., Kataoka, H., Cano, D.A., Camerer, E., Yin, L., Zheng, Y.W., Scanlan, T.S., Hebrok, M., and Coughlin, S.R. (2007). J. Clin. Invest. *117*, 4034–4043.

Rosengren, A.H., Jokubka, R., Tojjar, D., Granhall, C., Hansson, O., Li, D.-Q., Nagaraj, V., Reinbothe, T.M., Tuncel, J., Eliasson, L., et al. (2009). Science. Published online November 19, 2009. 10.1126/science.1176827.