Review

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Cellular communication and heterogeneity in pancreatic islet insulin secretion dynamics

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Coordinated pulses of electrical activity and insulin secretion are a hallmark of the islet of Langerhans. These coordinated behaviors are lost when β cells are dissociated, which also leads to increased insulin secretion at low glucose levels. Islets without gap junctions exhibit asynchronous electrical activity similar to dispersed cells, but their secretion at low glucose levels is still clamped off, putatively by a juxtacrine mechanism. Mice lacking β cell gap junctions have near-normal average insulin levels, but are glucose intolerant due to reduced first-phase and pulsatile insulin secretion, illustrating the importance of temporal dynamics. Here, we review the quantitative data on islet synchronization and the current mathematical models that have been developed to explain these behaviors and generate greater understanding of the underlying mechanisms.

The unique properties of the pancreatic islet are important for blood glucose homeostasis

The islet of Langerhans (see Glossary) is a pancreatic micro-organ comprising mainly β cells, which have a central role in blood glucose homeostasis through dose-dependent and regulated insulin secretion [1]. There are several important properties of insulin secretion that are unique to the intact islet: (i) near-zero insulin secretion at glucose levels <3 mM; (ii) a steep sigmoidal secretory response to glucose; (iii) a peaked first phase of insulin secretion; (iv) coordinated secretory pulses during second-phase insulin secretion; and (v) increased insulin secretion at glucose levels >11 mM. All of these behaviors are lost upon dispersion of the islet into individual β cells, which exhibit significant heterogeneities [2,3].

In normal physiology of humans and rodents, a first peaked phase of insulin secretion (approximately 5–10 min) is followed by a sustained second phase, during which pulses of insulin are secreted with a 3–8-min period [4,5]. The full implications of the two secretory phases and insulin pulsatility are poorly understood, but increasing evidence points to major roles in blood glucose homeostasis [6–10]. First-phase insulin secretion and insulin pulsatility are both reduced and eventually lost as type 2 diabetes mellitus (T2DM) progresses [11], and these losses correlate with long-term complications of diabetes. Pulsatile insulin secretion leads to enhanced suppression of hepatic glucose production [10], and therapeutic insulin pulses have been postulated as an improved diabetes treatment [6,7]. Insulin pulsatility depends on oscillations in membrane potential, intracellular free calcium ($[Ca^{2+}]_i$) [12], and cAMP [13], and

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Glossary

Connexin 36 (Cx36): belongs to a family of structurally related transmembrane proteins that assemble to form gap junctions between cells. These are four-pass transmembrane proteins with two extracellular loops and both the C and N termini in the cytoplasm.
EphA-(ephrin-A): a subfamily of receptor tyrosine kinases that are activated in response to binding ephrin ligands. Both Eph receptors and their ephrin ligands are membrane-bound proteins that require direct cell–cell interactions for receptor activation.
Kir6.2: the pore-forming subunit of the ATP-sensitive K^+ channel, an integral membrane protein that allows potassium to flow into a cell. Kir6.2 is found associated with the sulfonylurea receptor. Mutations in the gene encoding Kir6.2 are associated with congenital hyperinsulinism.
Hodgkin–Huxley model: a mathematical model that describes how action potentials in neurons are initiated and propagated. It is based on a set of equations that approximate the electrical characteristics of excitable cells.
Islets of Langerhans: clusters of hormone-producing cells of different types that comprise the endocrine part of the pancreas. Each islet contains 1000–10 000 β cells and there are approximately 1 million islets in the human pancreas.
Insulin oscillation: the insulin concentration in blood rises after meals and gradually returns to basal levels, during the following 1–2 h. However, the level of postprandial insulin level is not stable but oscillates with a period of 3–6 min. Although the amplitude of these oscillations increases after a meal, the periodicity remains constant. Insulin oscillations are generated in part by pulsatile release of the hormone, which is driven by oscillation of the calcium concentration in the β cells. Pulsatile secretion requires exquisite synchronization between β cells. Insulin oscillations become synchronized by electrical coupling between closely located β cells, which are connected by gap junctions. β cells lacking gap junctions exhibit variable periodicity in insulin oscillations.
Insulin secretion: insulin release from β cells occurs in a rapid, first-phase release followed by a second, slow phase, sustained release, of newly formed vesicles. During the first phase, glucose enters the β cells through the glucose transporter, GLUT2. Glucose is then metabolized, leading to an increase in the intracellular ATP:ADP ratio that in turn closes the ATP-sensitive SUR1/Kir6.2 potassium channel. The increased potassium concentration leads to depolarization of the cell membrane, whereby voltage-gated Ca^{2+} channels open, allowing calcium to move into the cell. The increased intracellular calcium activates phospholipase C and downstream signaling pathways that further raise the calcium, ultimately causing the release of previously synthesized insulin stored in secretory vesicles.

is recapitulated in isolated islets. Cell interactions between β cells have a key role in islet function, because dissociated β cells exhibit different insulin secretion profiles compared with those within intact islets [14,15]. Functional coordination among β cells was first observed by using electrophysiology [16], with further evidence from measurements of $[Ca^{2+}]_i$ [17], interstitial K^+ [18,19], and insulin secretion [20].

Despite a preponderance of evidence regarding its multicellular nature, many of the current paradigms underlying islet biology are based on single cell studies and concepts, which includes many mathematical models. We are now beginning to understand quantitatively how these properties of islet behavior arise from multicellular interactions, and how cellular heterogeneity forms an important basis for islet behavior. Here, we describe key experimental data that reveal various aspects of cellular communication between β cells in the islet, and present mathematical models that have been used to describe and predict islet function, with an emphasis on models based on its specific multicellular structure

β cell heterogeneity and gap junctions

All of the coordinated events described above are lost upon dispersion of the islet into individual β cells, which exhibit significant heterogeneities [2,3]. Dispersed β cells show heterogeneous glucose transport [21], insulin biosynthesis [2], glucose sensitivity of metabolism [22], $[Ca^{2+}]$ response and dynamics [23], and insulin secretion [24–26], but most manifestations of these cellular heterogeneities are lost within the intact islet. Deletion of the glucose sensor, glucokinase (GK), in approximately 30% of β cells leads to a heterogeneous distribution of metabolic responses within the islet [27]. However, the overall islet electrical activity and insulin secretion profiles from these islets was unchanged from wild type islets, which shows the importance of cell coupling in creating a homogeneous response from the heterogeneous population of β cells. Recently, incretin action was shown to have a role in maintaining coordinated islet activity during lipotoxicity in mice and humans, although the molecular determinants of this effect remain to be defined [28,29].

Gap junctions are intercellular channels that allow the direct transfer of ions and second messengers between adjacent cells. β cell gap junctions were initially detected by using electron microscopy (EM) [30] and functionally characterized by using dye coupling [31] and electrophysiology [32]. After 20 years of research (reviewed in [33]), the biophysical properties of β cell gap junctions pointed to connexin 36 (Cx36) as the pore-forming unit in the islet [34], and this was quickly confirmed using mice lacking the *Cx36* gene ($Cx36^{-/-}$), whose islets do not show synchronous oscillations in $[Ca^{2+}]_i$ and insulin release [35]. β cells within $Cx36^{-/-}$ islets exhibit random $[Ca^{2+}]_i$ oscillations similar to those measured in dispersed β cells from either

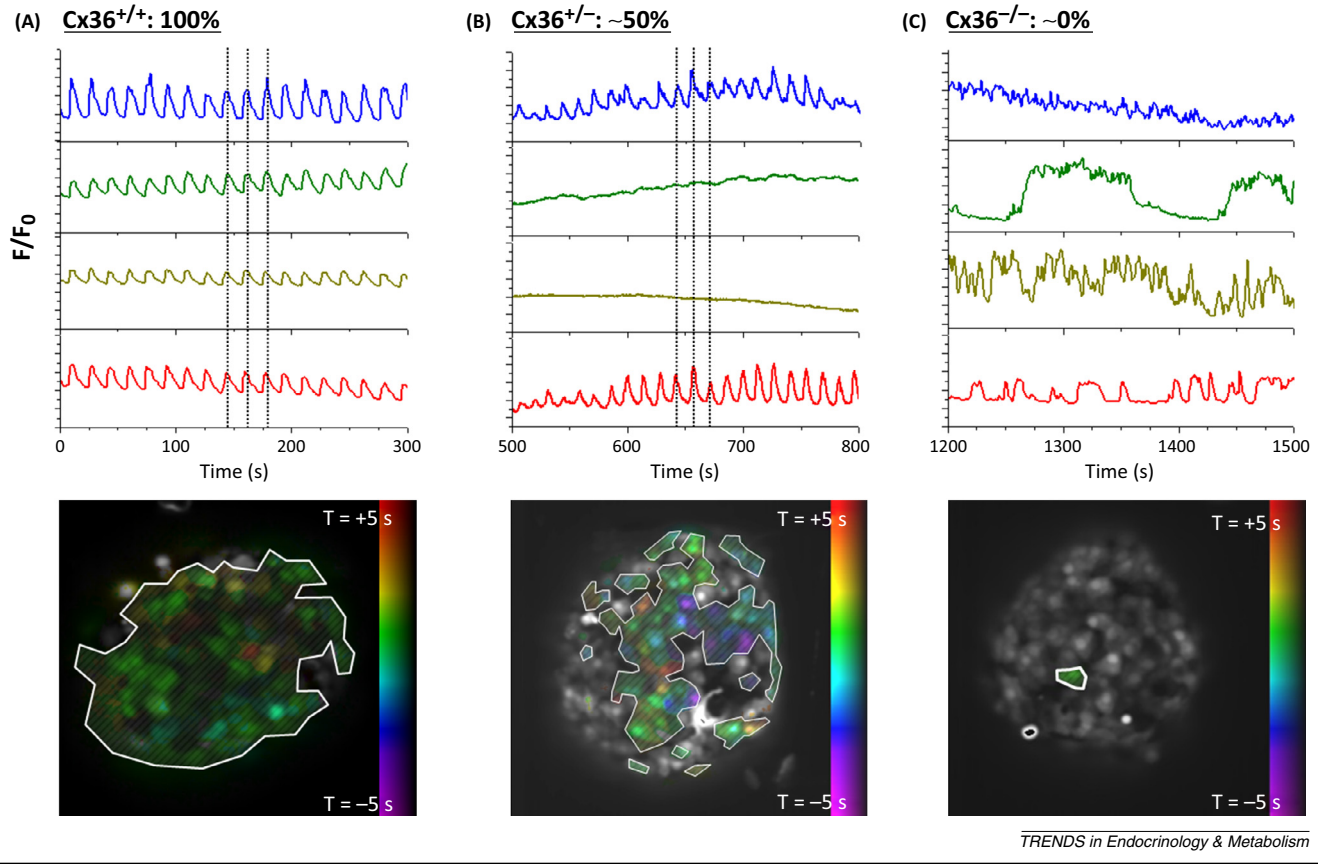

Figure 1. Experimental dependence of intracellular free calcium ($[Ca^{2+}]_i$) dynamics of gap junction coupling. Representative oscillations of $[Ca^{2+}]_i$ in four cells of an islet, together with a phase map of $[Ca^{2+}]_i$ oscillations, where colored cells show oscillations that are synchronized with other colored cells, whereas uncolored (gray) cells show poorly synchronized oscillations or absence of oscillations. Oscillations and phase map are displayed for a wild type islet with normal gap junction coupling **(A)** [connexin 36 (Cx36), 100%]; an islet from a mouse with a heterozygous knockout of Cx36 that has approximately 50% gap junction conductance **(B)** ($Cx36^{+/-}$, 50%); and an islet from a mouse with a homozygous knockout of Cx36 that has approximately 0% gap junction conductance **(C)** ($Cx36^{-/-}$, 50%). Note the transition between regular, near-fully synchronized oscillations, and heterogeneous irregular, uncoordinated oscillations as Cx36 is reduced. Adapted from [37].

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