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Review

Resting beta-cells – A functional reserve?

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Abstract

Pancreatic beta-cells play a pivotal role to synthesize and secrete insulin, as the solo source of the body. Physical as well as functional loss of beta-cells over a certain threshold result in diabetes. While the mechanisms underlying beta-cell loss in various types of diabetes have been extensively studied, less is known about residual beta-cells, found even in autoimmune type 1 diabetes and type 2 diabetes with a substantial amount. Why have these beta-cells been spared? Some patients with neonatal diabetes have demonstrated the life-changing restoration of functional beta-cells that were inactive for decades but awakened in several weeks following specific treatment. The recent striking outcomes of bariatric surgery in many obese diabetic patients indicate that their beta-cells are likely "preserved" rather than irreversibly lost even in the multifactorial polygenic state that is type 2 diabetes. Collectively, the preservation of residual beta-cells in various diabetic conditions challenges us regarding our understanding of beta-cell death and survival, where their sustenance may stem from the existence of resting beta-cells under physiological conditions. We posit that beta-cells rest and that studies of this normal feature of beta-cells could lead to new approaches for potentially reactivating and preserving beta-cell mass in order to treat diabetes.

Keywords: Beta-cells; Islet; Pancreas; Resting beta-cells

1. Lazy ants

Hard work is a good thing. One may suffer during the course, but it will pay off in the future. As the famous Aesop fable "The Ant and the Grasshopper" describes, ants represent "the hard workers" that teach us the value of dedication. They always work hard for their colony all day long. *How true is it?* A study on ants in real life, monomorphic ants, *Myrmica kotokui*, conducted by Ishii and Hasegawa has revealed intriguing observations [1]. Ants are social insects. Members of a colony are organized into groups, which are functional units with high levels of cooperation among members. Their tasks consist in a wide range from attending their queen and brood, foraging, transporting food to fixing the nest. The group-level optimization is crucial in their colonial life that directly affects efficiency and survival of the colony. *Do they all work hard day and night?* The answer is no. As many as 70% of ants are "lazy" and do not participate in any task. They are indulged in resting, self-grooming, eating and strolling. Moreover, 10% of ants never work in their lifetime. It is indeed a way of clever risk management strategy to maintain a colony through disastrous events, having an excess reserve of resting workers that can immediately be recruited. The authors found that after an experimental demographic change by removing hard workers out of a colony, some previously inactive workers started to work. Interestingly, when lazy ants were removed, some previously active workers became inactive. Such shifts resulted in the constant restoration of a substantial amount of variation in the working degree, from hardworking to lazy ones. This homeostatic recolonization appeared to be regulated by an altered "response threshold" of each ant to various tasks, which is unrelated to intrinsic factors such as reproductive potential or age. Molecular mechanisms of this group-level optimization of work-related behaviours are still unknown, however, importantly, it implies that a dynamic spatial signal transduction does exist and is efficiently utilized in the colonial life of eusocial organisms.

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2. Sleepy neurons

Sleep is essential for normal physical and mental health. The sleep–wake cycle of the brain can be measured as electroencephalography (EEG) slow-wave activity (SWA) in the cortex. During SWA, neurons oscillate in a synchronized pattern between ON (electrically active) and OFF (electrically silent) states and animals are still and unresponsive to external stimuli with their eyes closed. Vyazovskiy et al. examined the electrical activity of cortical neurons in sleep-deprived rats [2]. The animals were kept awake for an additional 4 hours from light onset by stimulating with new objects to play with. Their wakefulness was confirmed by a detailed video analysis. While the animal was awake, with increasing sleepiness, a subset of neurons started to opt themselves out, entering the OFF state, most likely at a single neuron level. This switching-off occurs in one cortical area but not in another, and even within the same cortical area, some neurons are off while others remain on. The authors suggest that local sleep periods in the awake state may serve functional roles from energy saving to the initiation of a local restorative process. In fact, other amazing adaptations are found in cetaceans and birds demonstrating the example of active sleep: one hemisphere of the brain remains awake, while the other is in slow-wave sleep so that animals can continue moving [3,4].

3. Resting beta-cells

Olsson and Carlsson found a markedly heterogeneous oxygenation of endogenous islets and examined islet oxygenation in normal rats *in vivo* [5]. In their experiments, pimonidazole, a small molecule hypoxia marker, was injected into the tail vein of awake animals. This drug binds to thiol-containing proteins specifically in hypoxic cells at oxygen concentrations less than 14 μM, equivalent to an oxygen tension of 10 mmHg at 37 °C. The authors observed that 20–25% of islets had low oxygen utilization (p)O_2 < 10 mmHg and suggest these may represent "dormant" islets that achieve this state by turning off metabolism. Islets normally have been reported to have an oxygen tension of ∼40 mmHg, which is higher than in other visceral organs and closer to that of neurons. Whole pancreas transplantation into rats doubled the fraction of low-oxygenated islets in the endogenous pancreas of the recipients by shifting active beta-cells into the resting state. By contrast, these low-oxygenated cells nearly disappeared after a 60% partial pancreatectomy, implying that resting islets were "on call".

4. Critical mass of beta-cells and normoglycaemia

It appears that beta-cells can rest when "a visitor" takes over their task (i.e. pancreas transplantation). They can also take a rest when the default system is working fine as it is supposed to be (i.e. dormant islets). How can these phenomena be interpreted in diabetic conditions? In other words, what is the critical mass of beta-cells out of the entire pool needed to maintain normoglycaemia? Then vice versa, how many beta-cells can be lost, before the onset of impaired glucose tolerance and diabetes?

Non-obese diabetic (NOD) mice are a widely used model of type 1 diabetes (T1D). This inbred animal strain sharing the same genetic background and the laboratory environment exhibits marked heterogeneity in progression and onset of T1D among littermates. It has been documented that while insulitis is penetrant, overt diabetes is not. In our recent studies on NOD mice [6,7], we took advantage of the existence of "non-progressors" within NOD mouse littermates, and followed up all the mice in our colony from birth to > 40-week of age with both sexes to identify "progressors" and "non-progressors". Using transgenic NOD mice expressing green fluorescent protein (GFP) under the control of mouse insulin I promoter (MIP), the relationship between the residual beta-cell mass and the progression of overt diabetes was examined [6]. While both progressor and non-progressor animals underwent autoimmune destruction of beta-cells as evidenced by lymphocyte infiltration in islets and endoplasmic reticulum stress in beta-cells shown by electron microscopy, overt T1D did not develop until animals lost ∼70% of the total beta-cell mass. A similar threshold of critical beta-cell mass to maintain normoglycaemia has been reported in other animal models as well as humans [8–17].

The contribution of beta-cell loss to development of T2D has also been demonstrated and characterized as from "moderate" (20–30%) [18–21] to "marked" (40–60%) [22–27]. While it is evident that a physical loss of insulin-producing beta-cells occurs in patients with T2D, reduced beta-cell mass does not solely explain the development of chronic hyperglycaemia in T2D. It may be reasonable to assume that "dysfunctional" beta-cells that synthesize insulin but are deficient in secretion are spared for relatively a long period of time in some individuals. This should explain clinical deteriorations in the setting of increased insulin resistance and reduced beta-cell function associated with T2D, obesity and aging, which may not be directly reflected in a physical beta-cell loss.

5. Wake-up call for non-functional beta-cells

The preservation of non-functional beta-cells over years has been most clearly demonstrated in cases of neonatal diabetes due to activating mutations in the genes encoding the two subunits of the ATP-sensitive potassium channel (K_{ATP}), *KCNJ11* and *ABCC8* encoding Kir6.2 and sulfonylurea receptor 1, respectively [28]. High-dose sulfonylureas efficiently block some mutated K_{ATP} channels and therefore this medication can replace insulin injection in many patients [29]. After the first clinical studies in subjects with activating Kir6.2 mutations demonstrated a response to intravenous tolbutamide [30], a number of cases have been reported including the treatment with oral medications [31,32]. What is amazing is that non-functional quiescent beta-cells survived for decades and woke up in a matter of several weeks (or less) following sulfonylurea treatments.

6. Death of beta-cells

Non-functional beta-cells, such as those found in patients with neonatal diabetes due to activating mutations in Kir6.2 and SUR1, can synthesize insulin but cannot secrete it and are spared