CHAPTER #

Islet of Langerhans
Cellular Structure and Physiology

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Abstract

Islets of Langerhans, named after their discoverer Paul Langerhans, constitute a unique endocrine organ of critical importance in the metabolism of nutrients and energy homeostasis. Individual islets consist of three major types of electrically excitable cells, namely β-cells that secrete insulin, α-cells that secrete glucagon and δ-cells that secrete somatostatin. Islets develop from the gut endoderm and a set of transcription factors including PDX1, PAX4 and PAX6, play important roles in determination of the cell types and their functions. These microorgans are coordinated by neural and hormonal networks and secret hormones in an oscillatory manner. Nutrient metabolism and incretin hormones trigger insulin secretion. Important cellular components and messengers that determine insulin secretion include glucose transporters, glucokinase, ATP/ADP-ratio, mitochondrial metabolism, ATP-sensitive potassium channels, cAMP and Ca^{2+}. Because of their importance in the pathogenesis of diabetes and increased interest in islet transplantation during recent years, islets of Langerhans continue to be a field of extensive research throughout the world.

Introduction

The islets of Langerhans, named after the German pathologist Paul Langerhans, constitute a critical organ unique in that it is split into about a million units hidden in the pancreas, thus contributing to the enormous difficulty in harvesting them. It was in 1869 that Paul Langerhans, then a 22-year old physician, studied anatomy and histology of the pancreas in great details. In his dissertation he described small, clearer areas in the pancreas which stained differently from the rest of the pancreas. Langerhans' speculation was that these structures were lymphatic tissue. Others thought that these structures could be embryonic remnants. It was not earlier than 24 years later that the structures were named "islets of Langerhans" by the French histologist Edouard Laguesse, who also suggested that the structures constituted the endocrine part of the pancreas with a possibility to produce a hormone with glucose-lowering effect.[1] It is unclear why nature has chosen to locate islets in the pancreas. The location is however advantageous, since the hormones are secreted directly into the portal vein enabling direct control of the hepatic function. Furthermore, it is speculated that a vascular system that allows the exocrine pancreas tissue to be nourished by endocrine hormones may have had importance during some stages of evolution explaining location of islets amidst the acinar lobules.[2] The islets have a pivotal role in regulation of glucose homeostasis in the body. The blood glucose-lowering hormone insulin is antagonized by glucagon and together they make a fine-tuning system that ensures that the glucose levels in the blood are kept in a narrow interval irrespective of food intake or starving situation. Impaired function or destruction of the insulin secreting cells in the islets underlies pathogenesis of different forms of diabetes, which is a major health problem throughout the world. Islet transplantation for the cure of type 1 diabetes appears more and more a reality and extensive research is going on in this field at the moment. The goal of this chapter is to give a bird's eye view of anatomy and physiology of the islets of Langerhans with an emphasis on clinical implications.

Histological Features of the Islets of Langerhans

In humans, islets of Langerhans constitute spherical or ellipsoid clusters of cells with a diameter between ~50-250 μm (Fig. 1).[3] The number of islets in a given pancreas increases with a decreasing diameter of the islets.[4] Most of the islets in the pancreas are of small diameter, i.e., ~50-100 μm. However, medium sized islets with a diameter of ~100-200 μm contribute most to the total islet volume at all ages with the only exception of the newborn, where it is the opposite.[4] Some islets in diabetics can be very large, up to ~350 μm in diameter, because of oedema and deposition of amyloid.[3]

It is generally stated in textbooks that the islets of Langerhans constitute 2-3% of the pancreas and that the pancreas has one million islets. However, the total number of islets, in the pancreas, depends on age, BMI, size of the pancreas and conditions such as pregnancy.[5] The distribution of the islets in the pancreas also varies to some extent. Thus the concentration of islets in the tail is significantly higher than in the head and body of the pancreas.[6] Experience with islet transplantation during recent years has yielded information about the number of islets that can be recovered from one human pancreas. For clinical transplantation recovery of more than 300 000 islets per human pancreas is considered to be successful. However only 50-60% of the isolations are successful at the best isolating centers.[7] By using improved protocols for isolation of islets, on the average 349 000 islet equivalents can be recovered from one pancreas.[8] Each islet is surrounded by a collagen capsule. Characterization of different collagens in the islet-exocrine interface shows that collagen I, IV, V and VI are present and that collagen VI is the major component in the extracellular matrix.[7]

The islets consist of cords of polyhedral cells that are in close proximity to fenestrated capillaries and are lined by basement membrane on their free sides. Each islet contains from a few number of cells to several thousands cells. By using immunohistochemical techniques and specialized staining procedures, one can identify three major types of cells, namely the α-, β- and δ-cells that are irregularly mixed and

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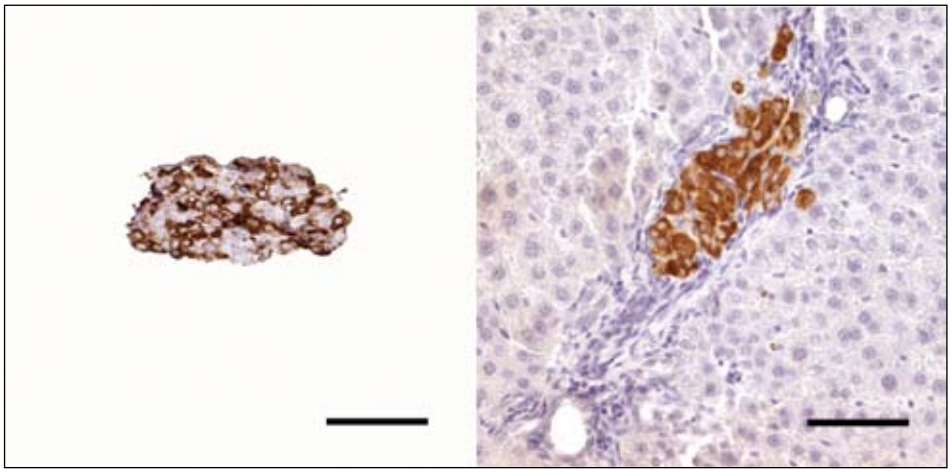

Figure 1. The figure shows a single human islet isolated for transplantation (left) and a rat islet syngeneically transplanted intraportally into the liver (right). The islets were stained for insulin (brown) and counterstained with hematoxylin. Scale bars represent 100 micrometer. Courtesy of Joey Lau, Uppsala University, Sweden. A color version of this figure is available online at www.Eurekah.com.

scattered throughout the islet.[9] In addition there are other minor cell types, namely the pancreatic polypeptide-secreting (PP)-cells and the dendritic cells. Most of the cells in the human islet are insulin-secreting β-cells (64%). Among the remaining are 26% glucagon-secreting α-cells, 8% δ-cells and 0.3% PP-cells. δ-cells secrete somatostatin and possibly gastrin. In each islet there are 5-20 dendritic cells which express class II antigen with phagocytosis capacity.[10] The β-cells secrete islet amyloid polypeptide (IAPP) in addition to insulin. However all β-cells probably do not secrete IAPP since only 54% of β-cells stain for IAPP.[3]

Different islet cells also have their characteristic appearances of the granules as seen under electron microscope. The α-cells possess granules that are 200-250 nm in diameter, have an inner rounded core and a less dense peripheral halo. The secretory granules in the β-cells have a diameter of 300-350 nm, are mainly found in the cell pole facing the blood capillaries and consist of a dense polymorphous core, sometimes several, surrounded with a spherical membranous sac. The granules in δ-cells are numerous with a diameter around 300 nm and are gathered at the vascular side of the cell. The PP-cells have granules that are irregularly shaped, oval or round and much smaller, 150 nm in diameter, than granules of α- and β-cells.[11]

In spite of the fact that the islets are structurally separated, they seem to have a mechanism to coordinate their work. Individual β-cells in an islet are able to communicate with each other through paracrine mechanisms via secretory products or via a local vascular system within the islet. Electrophysiological studies show electrical synchronization between different β-cells through gap junctions. β-cells also communicate with non β-cells via gap junctions. The gap junctions are made of connexin36 and permit passages of small molecules of up to 900 D between cells.[2] The functional importance of connexin36 of β-cells is evident from the fact that in connexin36 knockout mice, there is impaired oscillation of insulin secretion.[12]

Development and Regeneration of Islet Cells

Islets of Langerhans arise from gut tube endoderm.[13] A hierarchy of transcription factors such as PDX1, FoxM1, Ngn3, IA1 and a MafB-MafA switch and many growth factors, such as activins, TGF-βs, fibroblast growth factors, epidermal growth factors, hedgehogs and wnts play important roles in pancreas development.[14-16] Activin and bone morphogenic factors induce progenitor cells that express the transcription factor PDX1 to develop endocrine cells from pancreatic duct epithelial cells.[17] Coordination of specific transcription and growth factors is essential for generation of the different cell types in the islets during embryonic development. Notch signalling controls differentiation of progenitor cells to mature endocrine cells.[18] Identification of important transcription factors for the islet cells during their different stages of development has given important information about pancreas development as well as about several types of diabetes.[13] PDX1 is crucial for the development of the pancreas and for the function of differentiated β-cells. It controls transcription of several genes involved in glucose sensing and insulin synthesis. Among other transcription factors that are important for development of islet cells are PAX4 and PAX6. Deletion of Pax4 causes complete loss of β- and δ-cells, but increase of the number of α-cells.[19] Pax6 knockout causes decrease of all endocrine cell types and total absence of α-cells. Knockout of Pax4 and Pax6 leads to total loss of endocrine cells in the pancreas. Disruption of the Pdx1 gene in human results in agenesis of the pancreas. In human, mutations of Pdx1 gene are associated with development of maturity onset diabetes of the young type 4 (MODY4) and also predispose to the development of type 2 diabetes.[20]

Mature β-cells have a slow turnover process which involves replication of already existing β-cells, differentiation from precursor cells in the ductal epithelium and neogenesis. The individual β-cell mass can also increase by hypertrophy.[21] Remarkable examples of increase of the β-cell mass include pregnancy and obesity. Reduction of β-cells takes place through apoptosis.

Vasculature and Innervation

The islets are richly vascularized by a capillary network connected with the exocrine pancreas and receive at least 10% of the pancreatic blood flow. The endothelial cells contain more fenestrae compared with corresponding acinar capillaries.[22] One to three arterioles enter the core of the islet and form fenestrated capillaries that reassemble again into venules either before or after leaving the islet. In this way a serial connected insulo-acinar portal system is formed with capacity to carry insulin in high concentrations.[2] The intra-islet blood flow is thought to provide a mechanism for paracrine interactions, although the structural basis for such interactions is poorly understood.

The islets are mainly innervated by the parasympathetic system, but are also innervated by sympathetic, peptidergic and non-peptidergic nerves.[2] The parasympathetic preganglionic origins are the dorsal motor nucleus of the vagus nerve and nucleus ambiguus. The nerve branches reach their ganglia in the pancreas tissue and demyelinated nerve fibres innervate the islet cells. It has been suggested that there is a close relationship between innervation of the islets and innervation of the

acinar cells in the pancreas. The main part of the fibres enters the islets with the arterioles.[23] The parasympathetic ganglia form neuroinsular complexes with both α- and β-cells. Autonomic transmitters such as acetylcholine and noradrenalin affect the secretion of hormones from the islet cells. The parasympathetic system mainly increases insulin secretion, but glucagon and polypeptide secretion is also stimulated by acetylcholine. The sympathetic system inhibits glucose-induced insulin release and stimulates glucagon release in order to maintain or increase glycemia.

Regulation of Insulin Secretion

In vitro studies of islets by electrophysiology or imaging techniques assume that β-cells have a resting state when they do not secrete insulin and a stimulated state when they do. However, in vivo under physiological conditions, large insulin secretion occurs even under fasting states and secretion increases after food intake. About 75% of total insulin secretion into the portal vein in human occurs in the form of dramatic oscillations with an interpulse interval of about five minutes.[24,25] The pulsatile pattern of insulin secretion which has many physiological advantages is lost in individuals with type 2 diabetes and their first degree relatives. Liver extracts about 80% of the insulin during the first passage. In the systemic circulation the pulsatile nature of insulin secretion is evidenced by small oscillations in insulin concentration. Regulation of insulin secretion occurs by regulation of the amplitude rather than frequency of insulin oscillation. Even islets transplanted into the liver secrete insulin in a pulsatile manner. It is unclear what signals synchronize insulin secretion from a large number of islets but neural networks are thought to play a role in this process.

After a mixed meal, there is an increase in the concentrations of nutrients including glucose, amino acids and free fatty acids in the plasma and the amplitude of insulin pulses increases. Molecular mechanisms that couple glucose stimulation to insulin secretion have been extensively studied. Glucose must be metabolized to be able to trigger insulin secretion and in this respect the enzyme glucokinase works as a glucose sensor. Several mutations in the glucokinase gene can lead to maturity onset diabetes of the young (MODY).[26] Metabolism of pyruvate in the mitochondria and mitochondrial ATP production are essential for glucose-stimulated insulin secretion. In addition to ATP, several other factors generated from mitochondria potentiate insulin secretion. Mutations or deletions in mitochondrial DNA result in some uncommon forms of diabetes.

Cytoplasmic ATP/ADP ratio acts as intracellular messenger that couples nutrient metabolism to electrical activity of β-cells. In this respect, the ATP-sensitive potassium channels (K_{ATP} channels) act as sensors of cellular metabolism. These channels are the targets for sulfonylurea drugs. K_{ATP} channels of β-cells consist of two subunits, the channel subunit KIR6.2 and the sulfonylurea receptor SUR1. Activating mutations in the genes that encode KIR6.2 and SUR1 cause permanent neonatal diabetes. Inactivating mutations usually of genes that encode SUR1 cause familial hyperinsulinemic hypoglycaemia of infancy.

An increase in the cytoplasmic ATP/ADP ratio leads to closure of K_{ATP} channels which leads to depolarization of the plasma membrane. This in turn leads to activation of the L-type voltage gated Ca^{2+} channels and influx of Ca^{2+}. This leads to Ca^{2+} induced Ca^{2+} release from the endoplasmic reticulum.[27] An increase in the cytoplasmic free Ca^{2+} concentration is an essential trigger for insulin exocytosis. In addition to nutrients, insulin secretion is also regulated by neurotransmitters and incretin hormones secreted from the gut. Glucagon like peptide 1 (GLP-1) is an important incretin hormone that not only increases insulin secretion, but also increases somatostatin secretion and inhibits glucagon secretion. Furthermore, it promotes β-cell survival and proliferation. These actions of GLP-1 are mediated by cAMP as well as Ca^{2+} and other signalling pathways. Incretin and incretin mimetics are already being used as drugs for treatment of type 2 diabetes.[28,29]

Future Perspectives

In spite of enormous importance of islets in health and disease, there are so far no imaging or isotopic techniques available for visualization or quantification of islets in living individuals. In this regard recent attempts to image islets by positron emission tomography or magnetic resonance imaging using magnetic nanoparticles are interesting approaches.[30,31] Future research should be directed to enable novel discoveries in this aspect.

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