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HIGHLIGHT ARTICLE

Pancreatic Stem Cells: A Glimmer of Hope for Diabetes?

Po Man Suen, Po Sing Leung

Department of Physiology, Faculty of Medicine, The Chinese University of Hong Kong.
Shatin, New Territories, Hong Kong

Diabetes mellitus (DM) is a devastating disease afflicting over 200 million people in the world. While type 1 diabetes mellitus (T1DM) is characterized by autoimmune destruction of islets, it is now well-recognized that reduced pancreatic beta cell mass and insulin secretory failure play a pivotal role in the development and progression of type 2 diabetes mellitus (T2DM). Routine exogenous insulin treatment seems to have been dominant over the past decades, notwithstanding episodes of inadequate control of chronic hyperglycemia leading to microvascular complications or increased incidences of hypoglycemia [1]. Recent success in islet transplantation protocol has been proven to restore the physiological secretion of insulin in patients with T1DM and in some patients with severe forms of T2DM. However, beta-cell replacement therapy is significantly hampered by an acutely limited source of transplantable human islets from cadaveric donors [2]. Of great interest in this context is the possible exploitation of cellular medicine for providing alternative sources of functional islet cells [3]. Notably, the possibility of using stem cells and pluripotent or multipotent cells which can self-renew and differentiate into multiple cell lineages, either embryo-derived or fetal/adult tissue-derived, in treating diabetic patients is now gaining credibility [4].

Insulin-secreting cells have been shown to develop from stem/progenitor cells isolated from a variety of tissues, such as recently reported in bone marrow, liver and intestinal epithelium. However, no clearly identifiable pancreatic stem cells (PSCs) have been found until now, despite considerable evidence that such cells are present in the islet or ductal cells of the pancreas [5]. While the mechanism for beta-cell mass expansion either from existing beta-cell expansion [6] or from stem cell activation, is still under debate, a conceptual mechanism regarding beta-cell differentiation occurs; to this end, epithelial to mesenchymal transition (EMT) was suggested to take place in the pancreas. It thus proposes the dedifferentiation of fully differentiated epithelial cells into stem cells of a “mesenchymal” phenotype which, in turn, redifferentiate back into epithelial cells in a new location [7]. An established neuroepithelial protein nestin, which was reported as a marker for endocrine progenitor cells in the early 2000s, is controversial. These nestin-positive putative PSCs when exposed to different growth factors or microenvironments give rise to islet-like cell clusters (ICCs) which temporarily express multiple endocrine hormones [8]. In addition to the minimal response from such PSCs to glucose challenge, it has been shown that those PSC-derived-beta-cells acquired only an immature beta-cell phenotype. Taken together, these results represent the inability of the existing cocktail of growth factors such as nicotinamide, betacellulin, glucagon-like peptide, or activin A to induce full differentiation of PSCs into functional

insulin-secreting cells. To this end, the exploration of novel growth factors is of paramount importance [9].

In this respect, our preliminary data have demonstrated that PSCs with stem cell markers, such as nestin, ATP-binding cassette transporter (ABCG2) and c-kit, can be isolated and cultured from human fetal pancreases. Such PSCs, which can be extensively expanded and passaged, also possess the receptors of certain growth factors including hepatocyte growth factor (c-met), glucagon-like peptide (GLP-1R) and epidermal growth factor (erbB1). Intriguingly, a novel factor called PDZ-domain containing 2 (PDZD2) for growth and insulin gene expression was richly localized in the nucleus and perinuclear membrane of these PSCs [10]. This protein is of highly homologous with interleukin 16 (IL-16) which has the function of growth and differentiation in various tissues [11]. While their functional similarities remain unknown, our recent findings suggest that a 37 kDa peptide secreted from PDZD2 may exert a mitogenic effect on the PSCs (unpublished data).

PSCs are definitely a potential approach to islet cell replacement therapy; however, much more work is essential for full maturation of the *in vitro* growth of insulin-secreting cells. The identification of 1) a specific marker for the lineage-tracing studies, 2) temporal gene expressions during the developmental stages of PSC-derived islets, and 3) appropriate cocktails of growth factors or microenvironments essential for beta-cell differentiation will represent a major breakthrough for the therapeutic intervention for T1DM in the near future.

Keywords Diabetes Mellitus; Insulin; Intermediate Filament Proteins; Nerve Tissue Proteins; Pancreas; Stem Cells

Abbreviations ABCG2: ATP-binding cassette transporter; DM: diabetes mellitus; EMT: epithelial to mesenchymal transition; GLP: glucagon-like peptide; ICCs: islet-like cell clusters; IL-16: interlukin 16; PDZD2: PDZ-domain containing 2; PSCs: pancreatic stem cells; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus

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Correspondence
Po Sing Leung
Department of Physiology
Faculty of Medicine
The Chinese University of Hong Kong
Shatin, New Territories
Hong Kong
Phone: +852-2609.6879
Fax: +852-2603.5022
E-mail: psleung@cuhk.edu.hk

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