

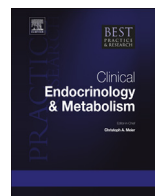


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Human pluripotent stem cell based islet models for diabetes research



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Although similar, mouse and human pancreatic development and beta cell physiology have significant differences. For this reason, mouse models present shortcomings that can obscure the understanding of human diabetes pathology. Progress in the field of human pluripotent stem cell (hPSC) differentiation now makes it possible to derive unlimited numbers of human beta cells *in vitro*. This constitutes an invaluable approach to gain insight into human beta cell development and physiology and to generate improved disease models. Here we summarize the main differences in terms of development and physiology of the pancreatic endocrine cells between mouse and human, and describe the recent progress in modeling diabetes using hPSC. We highlight the need of developing more physiological hPSC-derived beta cell models and anticipate the future prospects of these approaches.

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Introduction

Diabetes mellitus is a major healthcare problem affecting 382 million people globally in 2013, a number that is expected to increase up to the 592 million by 2035 as estimated by the International Diabetes Federation [1]. Diabetes is characterized by high levels of glucose in blood due to insufficient

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insulin secretion by the beta cell [2]. In type 1 diabetes (T1D) the beta cells are destroyed through a targeted autoimmune attack, generally during childhood or early adulthood. T1D accounts for around 5–10% of all diabetes cases, more in the industrialized countries with a high incidence. Type 2 diabetes (T2D) is the most common form and it presents in adulthood. It is a multifaceted metabolic disorder associated with sedentary lifestyle and obesity, with a strong genetic component. In many instances, initial peripheral insulin resistance develops until beta cells cannot efficiently compensate for the increased insulin demand [3], which leads to their dedifferentiation [4] and apoptosis, resulting in beta cell loss and impaired glycemic control [5].

Animal models have been extensively used to study the intricacies of pancreas development [6], beta cell physiology and diabetes [7]. In particular, transgenic mouse models have been key to unveil the detailed mechanism of pancreatic anlage specification and segregation of the three pancreatic lineages: ductal, exocrine and endocrine cells [8]. On the other hand, the studies on human pancreatic development are limited by the scarcity of the research material available, mostly based on aborted embryos donated to research.

After the derivation of the first human embryonic stem cell (hESC) lines, it soon became apparent that a better understanding of early human development is needed in order to replicate it *in vitro*. The pioneering efforts in generating pancreatic progenitors and endocrine cells from hESC followed the strategy of mimicking *in vitro* the early developmental signals, mainly learned from mouse development. This approach proved to be efficient for the specification of definitive endoderm [9]. However, a deeper and more detailed understanding of the signals and mechanisms controlling further differentiation steps, together with years of empirical testing, was needed to develop protocols that would result in bona fide islet cell precursors.

In this review, we summarize the characteristics of mouse and human beta cells and highlight the differences that limit the use of mouse models to study human diabetes. We also illustrate the possibilities of using human pluripotent stem cell-derived beta cells as a better model.

Differences between mouse and human beta cell development and physiology

Development

Most of the knowledge about pancreas development has been obtained from studies in mouse, starting by pioneering studies in the 1960's [10]. Upon gastrulation of the embryo, the three germinal layers are specified and they give rise to all the different tissues in the organism. The endodermal lineage forms the gut tube structure early in development. Specific domains along the gut tube become specified and grow into one of the endodermal organs: thymus, lungs, liver, pancreas, and small and large intestine. Signals from the nearby developing aorta and notochord specify the endodermal epithelium into pancreatic endoderm, identified by the expression of Pdx1, the master transcription factor for pancreas development [6]. The pancreatic endoderm forms a thickened stratified epithelium that becomes polarized in a process of microlumen formation [11]. These microlumens expand and coalesce, forming a plexus that will further organize and branch, giving rise to the pancreatic ductal tree formed by multipotent pancreatic progenitors (MPCs). MPCs organize in two domains and restrict their differentiation potential: tip-domain cells give rise to exocrine cells and trunk-domain cells to ductal and endocrine cells. During mouse pancreas development there are two distinct waves of endocrine formation, a primary transition which occurs around day E8.5–E9 and gives rise to insulin-expressing and glucagon-expressing cells, and a secondary transition around E12–E13 which generates all the endocrine cells forming the islets [12]. The transcription factor Neurogenin 3 (Neurog3) plays a key role in this specification process. Upon its expression it generates a competence window in which the progenitor cells become specified to endocrine lineage and will be allocated to one of the 5 distinct endocrine subtypes: glucagon-secreting alpha cells, insulin-secreting beta cells, pancreatic polypeptide-secreting gamma cells, somatostatin-secreting delta cells and ghrelin-secreting epsilon cells [13,14]. For a more exhaustive review on mouse pancreatic development see Pan et al. [6].

Human and mouse are separated by 65 million years of evolutionary history [15]. Thus it is not surprising that the different physiological needs have impacted also developmental processes [16]. Development of human pancreas starts at day 26 post conception (dpc) when the ventral bud followed

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