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Pancreatic and Islet Development and Function: The Role of Thyroid Hormone

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Abstract

A gradually expanding body of literature suggests that Thyroid Hormone (TH) and Thyroid Hormone Receptors (TRs) play a contributing role in pancreatic and islet cell development, maturation, and function. Studies using a variety of model systems capable of exploiting species-specific developmental paradigms have revealed the contribution of TH to cellular differentiation, lineage decisions, and endocrine cell specification. Moreover, *in vitro* and *in vivo* evidence suggests that TH is involved in islet β cell proliferation and maturation; however, the signaling pathway(s) connected with this function of TH/TR are not well understood. The purpose of this review is to discuss the current literature that has defined the effects of TH and TRs on pancreatic and islet cell development and function, describe the impact of hyper- and hypothyroidism on whole body metabolism, and highlight future and potential applications of TH in novel therapeutic strategies for diabetes.

Keywords

Thyroid hormone; Thyroid hormone receptor; Pancreatic islet; β cell; Insulin secretion

INTRODUCTION

The pancreas is a compound digestive gland, comprised of an exocrine and an endocrine compartment that secrete digestive enzymes and hormones, respectively. The exocrine pancreas is comprised of duct and acinar cells, whereas the endocrine pancreas is organized into structures known as the islets of Langerhans [1]. While endocrine mass comprises only

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~2% of the total pancreas mass, the contribution of hormone-producing endocrine cells to whole body metabolism is significant. Decades of studies focused on development of the pancreas in the mouse (*Mus musculus*) have uncovered the structural organization of this organ from the fetal and perinatal stages through to the adult. As these studies demonstrate, understanding structure often lends great insight into function.

In the mouse, pancreas development begins around embryonic day (E) 8.5 when cells of the foregut endoderm begin to express markers that instruct pancreas formation. The dorsal and ventral pancreatic buds evaginate from the primitive gut tube due to signals from the adjacent mesoderm [2]; the progenitor cells that comprise the buds co-express Pdx1 (pancreatic and duodenal homeobox 1) and Ptf1a (pancreatic transcription factor 1a) [3]. The stage of embryonic pancreas development from E9.5 to E12.5 is known as the *primary transition* (reviewed in [4]) during which progenitor cells in the dorsal and ventral epithelial buds organize into an epithelial arbor structure with both “tip” and “trunk” domains, as well as a few early differentiated “first wave” endocrine cells (composed mostly of glucagon-expressing α cells [5]). The *secondary transition*[6] is characterized mainly by the differentiation and expansion of the endocrine and exocrine cell populations. In particular, multipotent progenitor cells in the “tip” domain (Cpa1+ (carboxypeptidase A1), Ptf1a+, Cmyc+ (myelocytomatosis oncogene)) give rise to acinar cells, whereas progenitor cells in the “trunk” domain (Neurog3+) delaminate from the epithelial cords and differentiate into the hormoneexpressing endocrine cells, including β (insulin), α (glucagon), δ (somatostatin), PP (pancreatic polypeptide), and ε (ghrelin) cells [7]. The existence of distinct domains of progenitor cells, which give rise to the differentiated cell populations in the developing pancreas, suggests that fate decisions may be decided in these early progenitor cells [8,9]; however, recent studies have also begun to shed light on the plasticity of differentiated pancreatic cells [10-13]. While the current body of work is quite limited, Thyroid Hormone (TH) and the Thyroid Hormone Receptors (TRs) may be factors of significance to pancreatic and islet cell development, maturation, and function.

PANCREAS AND ISLET DEVELOPMENT

The deiodination of the precursor thyroxine (T4) permits the synthesis of thyroid hormone (3,5,3′-triiodo-L-thyronine; T3; TH). The subsequent action of T3 is mediated by two Thyroid Hormone Receptors (TRs). The genes that encode TRα (*Thra*; *Nr1a1*) and TRβ (*Thrb*; *Nr1a2*) contain alternative promoters and splice variants ultimately resulting in the production of four mRNAs and the synthesis of four nuclear receptors – TRα1, TRβ1, TRβ2, TRβ3 [14]. The action and antagonism of the receptors is quite complex, and numerous mouse models have been generated to dissect the function of TH and the various TR isoforms. With regard to gene expression, TRα and TRβ are differentially expressed, resulting in distinct protein expression patterns. Certain TRα isoforms are ubiquitous, whereas others are specifically expressed in the intestine [15]. While also widely expressed, TRβ isoforms are found in liver, pituitary, hypothalamus, inner ear, retina, kidney, lung, skeletal muscle, heart, spleen and brain [14]. With respect to the pancreas, the expression of TR isoforms is noted in rat pancreas [16,17] and mouse islets [18]; however, the expression pattern of TH and the TRs has not been carefully examined at the cellular level in the embryonic pancreas. Aiello and colleagues [19] assessed the abundance of TRα and TRβ mRNA transcript in whole embryonic pancreas from E12.5 through postnatal day (P) 0 (birth). Specifically, TRα is expressed at E12.5 and steadily increases as pancreas development proceeds until reaching a maximum at birth (P0). In contrast, expression of TRβ is nearly undetectable from E12.5 to E15.5 and then rises dramatically in late development (E17.5) and at birth [19]. While the expression of TH or the TRs within specific cell populations in the embryonic pancreas still remains unknown, the identification of mRNA transcript suggests that TH signaling may occur during mouse pancreas development.

Knock-out and knock-in mouse models used to investigate the function of TR isoforms demonstrate no gross morphological changes in the pancreas; however, it should be noted that the pancreas is not the specific focus of the investigations that prompted the generation of the deletion mutants. Additionally, given the complex nature of the TR gene loci it is not surprising that multiple phenotypes are observed in various mouse models. Highlighting only a few of the mouse models of TRα, these studies have identified that loss of TRα1 alters thermogenesis, lipogenesis and maturation of the neonatal brain [20]. Homozygous loss of both TRα1 and TRα2 results in hypothyroidic mice that also display growth arrest, a delay in maturation of the small intestine and bones, and death by five weeks of life [21]. The mutation of TRα that also affects the naturally truncated TRΔα isoform (transcribed from an internal promoter located in intron 7), demonstrates that TRα is important for intestinal maturation as well as transcriptional activation of the intestine-specific genes *Cdx1* (caudal type homeobox transcription factor 1) and *Cdx2* (Caudal type homeobox transcription factor 2) [15]. With respect to loss of the TRβ isoform, deletion of TRβ alone alters the hypothalamic-pituitary-thyroid axis, the retina, and impairs hearing [22]. The generation of mice with a homozygous TRβ mutation that is also found in humans (TRβPV) results in severe dysfunction of the pituitary-thyroid axis, impaired weight gain and abnormal bone development, which is a distinct phenotype compared with the TRβ null mutant [23]. Interestingly, when the TRα and TRβ mutations are combined, mice are viable but display severe growth reduction, hypothermia and hearing impairment [24]. Overall, these studies point to loss of TRs having a profound effect on the normal development and function of many organs; however, the necessity and function of TRs for pancreas development and/or pancreatic and islet cell function remains a fairly understudied area of research. As will be discussed in the following section, there is mounting evidence that TH plays a functional role in pancreatic cell fate decisions, as well as structural organization of the pancreatic organ proper.

CELLULAR DIFFERENTIATION

The process of cellular differentiation is critical to the development of all organs, and various model organisms have been used to understand the stages or processes involved in how the pancreas develops. The mouse (*Mus musculus*) is the most widely used model system for studies investigating mammalian physiology and metabolism; however, this model has also been used to decipher key factors that instruct or influence pancreatic organogenesis. Additionally, zebrafish (*Danio rerio*), the African clawed frog (*Xenopus laevis*), and the chicken (*Gallus gallus*) exhibit species-specific experimental advantages for pancreatic studies. For example, given the complicated models/genetics required to study pancreas regeneration in the mouse [10], tools generated using the zebrafish model system have greatly enlightened our understanding of pancreas and β cell regeneration [25].

A unique aspect of *Xenopus*/amphibian development is the requirement of TH for the process of organ development to proceed. Specifically, the formation of the skin, brain, intestine, liver and pancreas in the tadpole/frog requires the transformation or remodeling of these tissues in order for the mature organ to be formed; a process known as "metamorphosis" [26,27]. At metamorphosis, TH levels increase and after the metamorphic climax, TH levels revert to baseline [26]. The simultaneous effect on pancreas development is quite dramatic, such that mRNAs that encode terminally differentiated enzymes decline in response to increased TH, and the pancreas dramatically loses ~80% of its volume by the middle of the metamorphic climax [28]. This process of exocrine pancreas "regression" includes the dedifferentiation of acinar cells, which is controlled by TH, and subsequent re-differentiation after metamorphic climax resulting in the formation of the adult exocrine pancreas as well as a ductal tree [28]. Interestingly during the eight days of metamorphic climax, pre-existing β cells scattered throughout the pancreas cluster into islet structures due to both the increase in TH as well as the interaction with the surrounding dedifferentiated acinar cells [29]. By two months following completion of metamorphosis, the exocrine pancreas reforms and contains acinar cells, a structured ductal network, and cell clusters that have replicated and expanded (reviewed in [27]). These studies demonstrate the specific influence of TH on pancreatic organogenesis in *Xenopus*.

The influence of TH on mammalian pancreas development is gradually being resolved. Aiello and colleagues utilized the tissue explant culture system to treat E12.5 mouse pancreas explants with T3 (3,5,3′-triiodo-L-thyronine) for 7 days, and demonstrate an increase in pancreatic ductal markers [19]. Moreover, when T3 is removed from the culture, the ductal cells in the T3-treated explants possess the ability to differentiate into endocrine cells, first up-regulating the pro-endocrine gene *Neurog3* and then completing differentiation into endocrine cells, including those expressing insulin or glucagon [19]. Interestingly, T3 treatment also induces pro-endocrine gene expression in the mouse acinar cell line 266-6 [19], and β cell-specific gene expression in the ductal human pancreatic cell line hPANC1 [30]. Furthermore, Furuya and colleagues demonstrate that acinar cells infected with an adenovirus vector expressing TRα driven by the *Amylase2* promoter could be reprogrammed into insulin-producing β cells [31]. This work adds to the increasing number of reports identifying cellular plasticity in the pancreas, such that pancreatic cells are capable of both trans-differentiation and regeneration [10-13].

Islet (β cell) maturation, growth, and function

An elegant study by Aguayo-Mazzucato and colleagues describes the role of TH and TRs in postnatal rat islet maturation [16]. Specifically, T3 supplementation from birth through the first week of life (P7) results in an increase in body weight, pancreatic weight and β cell proliferation, while T3 treatment of rat islets isolated at P7 causes increased glucose-stimulated insulin secretion. Interestingly, the authors also demonstrate that TR directly binds and activates the *MafA* gene promoter, providing evidence that T3 supplementation coordinately increases expression of *MafA*. Furthermore, T3-induced increases in GSIS could be blocked with the use of a dominant negative form of MafA [16], ultimately identifying a role for TH in early postnatal islet cell function.

Additional evidence of the role for TH in pancreatic islet function comes from *in vitro* culture systems where T3 treatment of insulinoma cells or cultured islets results in preserved viability and β cell proliferation under basal and stress conditions. These results are attributed to activation of phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signaling through the non-genomic effects of TRβ [32-34]. *In vivo*, administration of T3 attenuates β cell death and improves glucose intolerance in mice treated with streptozotocin, and these effects are likewise associated with increased activation of AKT [35].

A direct relationship between TH and glucose tolerance?

Despite the positive effects of T3 on β cell function observed using *in vitro* and *ex vivo* model systems, hyperthyroidism is associated with impaired glucose tolerance, which has been attributed to several different mechanisms including impaired insulin action, increased gluconeogenesis, excess lipolysis, increased serum free fatty acid levels, and decreased insulin secretion. In aggregate, this body of literature suggests a combination of peripheral insulin resistance and impaired β cell function [36-39]. However, older studies demonstrate that an increase in intestinal absorption of carbohydrates also contributes to the hyperthyroid state [40]. Mechanistic studies have also begun to investigate the association between autoimmune hyperthyroidism and increased levels of proinflammatory cytokines, such as IL-18, that may contribute to metabolic derangements in concert with elevated thyroid hormone levels [41].

Hypothyroidism can lead to alterations in glucose tolerance. The pharmacological induction of hypothyroidism in dogs results in reduced insulin sensitivity with a concomitant increase in the acute insulin response to glucose [42]. In rats made acutely hypothyroid, with either surgery or anti-thyroid drugs, glucose tolerance is also impaired; however studies in humans identify that the resolution of even mild or subclinical hypothyroidism leads to an improvement in insulin sensitivity as assessed by hyperinsulinemic-euglycemic clamp [43]. Clearly the precise effects of hypothyroidism on islet function have not been completely resolved given that the *ex vivo* and *in vivo* assessment of islet function in response to alterations in thyroid hormone status have yielded varying results.

CONCLUSION

While the current body of literature examining the role of TH and TRs in the β cell is limited, several key studies have identified an important role for TH in pancreatic development, islet cell growth and β cell function. Continued research in these areas is needed to: (1) determine whether TH could be included as a potential molecule in *in vitro* differentiation protocols to assist in the differentiation of insulin-producing β cells, (2) understand the benefit of TH as a novel therapeutic in paradigms such as islet transplantation, and (3) resolve the relationship between hyperand hypothyroidism and altered β cell function. These areas of inquiry are ripe for further exploration and many unanswered questions await investigation.

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ABBREVIATIONS

E	Embryonic day
Pdx1	Pancreatic and Duodenal Homeobox 1
Ptf1a	Pancreatic Transcription Factor 1a
Cpa1	Carboxypeptidase A1
Cmyc	Myelocytomatosis oncogene
TH	Thyroid Hormone
T4	Thyroxine (T4)
T3	3,5,3′-Triiodo-L-Thyronine
TR	Thyroid Hormone Receptors
P	Postnatal day
Cdx1	Caudal Type Homeobox Transcription Factor 1
Cdx2	Caudal Type Homeobox Transcription Factor 2
PI3K	Phosphoinositide 3-Kinase
AKT	Protein Kinase B

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