REVIEW ARTICLE

The Use of Organoid Models of Endocrine Diseases: Research Progress and Potential

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Abstract

The absence of robust and reliable *in vitro* models that can accurately recapitulate the biological characteristics of many mammalian tissues and disease states represents a major barrier to both basic and translational research, owing to limited sample availability and ethical concerns. Stem cell-derived self-assembling three-dimensional (3D) organoids can replicate key structural and functional aspects of organs in a more physiologically relevant manner than traditional 2D models, thus providing a superior platform for simulating human physiology and pathology. To date, researchers have developed organoid models for a variety of endocrine tissues and their associated diseases (including pancreatic, pituitary, thyroid, adrenal tumors, etc.), offering invaluable tools for studying complex endocrine disorders. Such organoid models have significantly enhanced the accuracy and translational potential of research in disease modeling, drug screening, and regenerative medicine. Looking forward, the integration of bioengineering and multi-omics analyses with next-generation organoid models holds great promise for unraveling disease mechanisms and advancing precision medicine.

Keywords: organoids, 3D culture, endocrine diseases, translational applications, disease modeling, tumor.

1 Introduction

Organoids are a relatively new and innovative scientific tool first reported in the 1970s by Rheinwald and Green [1], who co-cultured 3T3 fibroblasts with primitive human keratin-forming cells to yield an epidermis-like lamellar squamous epithelial system. However, achieving the complex 3D organization of cells into tissue- and organ-like structures remained a challenge for decades.

The reliable establishment of 3D organoid culture systems depends on an in-depth understanding of the extracellular matrix (ECM) [2, 3] and advances in suspension culture techniques [4–6]. Early work demonstrated morphogenesis within 3D laminin-rich matrices, producing alveolar-like structures with polarized epithelial cells [6, 7]. Seminal studies by Sato et al. [8] and Eiraku et al. [9] later showed that adult stem cells (ASCs) and pluripotent stem cells (PSCs) could self-organize into intestinal organoids and optic-cup structures, respectively. These findings established the core principle of organoid research: the intrinsic capacity of stem cells to self-organize into

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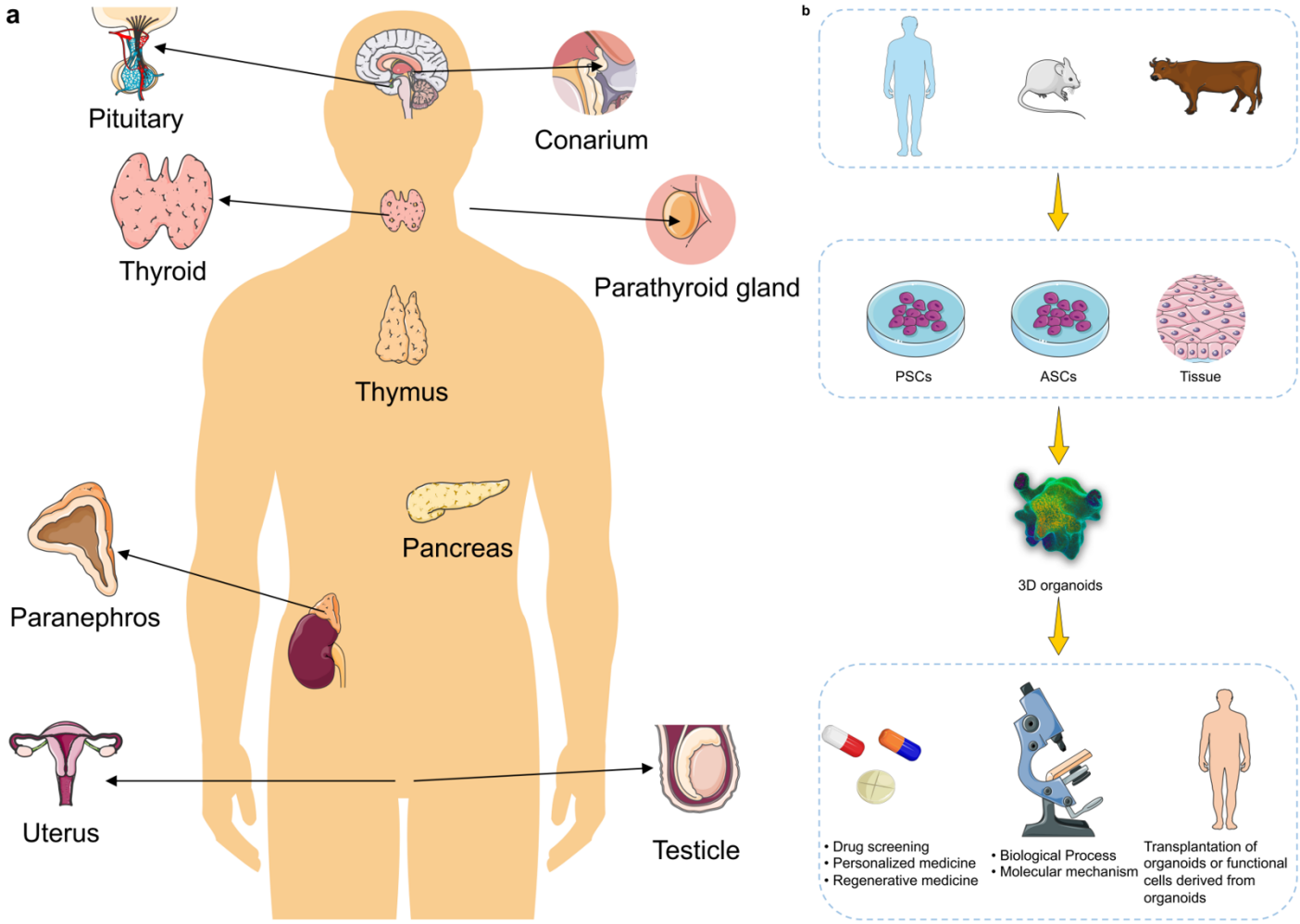

Figure 1. (a) General distribution of major endocrine organs in the human body. (b) Overview of organoid derivation methods. Organoids can be generated from pluripotent stem cells (PSCs) recapitulating development, or from adult tissue stem cells (ASCs) and patient-derived tissues for disease modeling.

3D organ-like structures. Building on this, numerous organoid models have been generated from various tissues and species.

The endocrine system, a network of glands including the pituitary, thyroid, adrenal, and parathyroid (Figure 1), secretes hormones crucial for systemic homeostasis. Its function is tightly regulated by feedback loops, notably the hypothalamus-pituitary axis (HPA). Dysfunction in these glands or secondary endocrine tissues (e.g., pancreas, gonads) leads to a spectrum of disorders, from diabetes to endocrine tumors. Endocrine diseases can also significantly impact liver function through altered hormone metabolism and signaling, highlighting the hepato-endocrine interplay [10]. The intricate and systemic nature of endocrine regulation makes it challenging to study *in vitro*. Organoid technology, by recapitulating native tissue microenvironments in 3D, offers an unprecedented opportunity to model endocrine physiology and disease with high fidelity. Significant progress has been made in generating endocrine organoids from diverse species and cellular sources (Table 1).

This review focuses on the application of organoid technology in modeling endocrine diseases. We discuss the generation methods and translational applications of organoids for major endocrine glands, highlighting their use in studying both benign and malignant conditions (Figure 1). We also examine the current challenges—such as achieving vascularization and long-term functional stability—and propose future directions for developing more robust, clinically relevant next-generation models. While we acknowledge advancements in tissue engineering that enhance organoid culture, detailed discussion of field-specific applications is beyond our scope, and readers are directed to recent specialized reviews.

ASCs, adult stem cells; PSCs, pluripotent stem

Table 1. An overview of primary endocrine organoid types and associated characteristics.

Endocrine organ	Source	Translational applications
Pituitary	Mouse PSCs [11]	Ectopic transplantation in hypophysectomized mice; modeling developmental disorders
	hiPSCs [12–15]	hiPSC-derived pituitary organoids to model the disease of congenital pituitary disorders [12]
		hiPSC-derived pituitary organoids for autoimmune pituitary disease and anti-PIT-1 antibody syndrome [13–15]
Thyroid	Mouse PSCs [16, 17]	-
	Human dissociated tissue [18, 19]	Exceptional preclinical *in vitro* simulation
Parathyroid	Human dissociated tissue [20, 21]	Explore the mechanisms governing hyperparathyroidism
	bovine parathyroid cells [22, 23]	
	Rat ADSCs [24]	Differentiating ADSC-derived pituitary organoids for the treatment of hypoparathyroidism
Thymus	Human HSPCs [25, 26]	Generation of mature T cells from human HSPCs in artificial thymic organoids
	Mouse HSPCs [26]	
	Murine HSCs [27–30]	Experimental platform for the interrogation of clonal thymopoiesis from HSCs
Adrenal	Human dissociated tissue [31]	-
Pancreas	Mouse ASCs [32]	-
	Mouse dissociated tissue [32]	-
	Human dissociated tissue [33, 34]	Comparison between mouse pancreatic organoids generated from normal, early neoplastic and tumoural cells has revealed new insights on genes involved in the progression of pancreatic ductal adenocarcinoma
	hPSCs [35]	Interrogate pathways involved in pancreatic tumorigenesis
	Mouse dissociated embryonic tissue [36]	-
	hESCs [37–39]	A therapeutic approach in diabetes mellitus
Gonad Ovary	hESCs [40]	-
	Human dissociated tissue [41, 42]	Xenograft and drug-sensitivity assays
	Mouse dissociated tissue [43]	
Testicle	hSSCs [44]	-
	Rat SSCs [44, 45]	-
	mouse iPSCs [46]	Induce spermatogenesis in azoospermic testis

cells; hiPSCs, human induced PSCs; ADSCs, Adipose-Derived Stem Cells; HSPCs, hematopoietic stem and progenitor cells; hESCs, human embryonic stem cells.

2 The Pituitary

The pituitary gland is a master regulator of systemic homeostasis. Its development from oral ectoderm is tightly regulated by signaling factors like FGF (fibroblast growth factor). Disruptions lead to congenital hypopituitarism. Human pituitary research has been hampered by tissue scarcity and species differences [12].

Efforts to overcome these limitations have largely focused on the use of different types of human PSCs (hPSCs) such as embryonic stem cells (ESCs) and induced PSCs (iPSCs), as they offer valuable opportunities to assess organ development and the dysfunction thereof [47, 48]. While hPSCs have been used to generate a range of tissue and organ types to date for use in a range of applications [49], these cells have yet to be successfully used for pituitary organoid generation as *in vitro* pituitary cell induction remains challenging. However, approaches to the *in vitro* differentiation of hPSC-derived anterior and posterior pituitary cells have recently been described [50–52], enabling researchers to better study the complex biology of this important primary endocrine organ.

In experimental contexts, iPSCs are commonly used to model disease-related processes by inducing these cells to differentiate into the tissue type of interest, with such approaches being of particular value in the context of diseases arising as a consequence of germline mutations [53]. Congenital hypopituitarism is a complex, multifactorial disease that is partially driven by genetic factors. Owing to the lack of a reliable human model of this disease and to differences between human and animal systems, however, the precise mechanistic basis for this condition remains to be fully clarified. The use of 3D culture methods to model fetal pituitary differentiation during the fetal period offers an opportunity to maintain interactions between the oral ectoderm and hypothalamus, making them potentially promising

for use in modeling congenital pituitary disorders. In one recent study, iPSCs from a patient with an $OTX2$ missense mutation were successfully used to model congenital hypopituitarism. Prior work has highlighted $OTX2$ as a key transcription factor that regulates the development of the pituitary [12], with multiple $OTX2$ mutations having been linked to various forms of congenital hypopituitarism. During development, the expression of $OTX2$ is evident in the hypothalamus and oral ectoderm [54], but the specific mechanistic role that it plays in controlling pituitary tissue development in these two tissue compartments remains controversial [55, 56]. Researchers found that the ability of these patient-derived iPSCs to differentiate into pituitary progenitor cells was impaired in the context of $OTX2$ mutation, and further leveraged this model to demonstrate that the expression of this transcription factor in the hypothalamus, rather than that oral ectoderm, is of particular importance in the induction of pituitary progenitor cell development, controlling hypothalamic FGF(fibroblast growth factor) expression. Such iPSC-based organoid models thus offer clear value as tools that can be leveraged to clarify the mechanisms governing a range of pituitary disorders.

A growing body of evidence has identified autoimmunity as an important driver of certain forms of hypopituitarism, including lymphocytic hypophysitis [57], IgG4-related hypophysitis [58], and immune checkpoint inhibitor-induced hypophysitis [59]. Appropriately modeling such immune-mediated diseases, however, necessitates the matching of HLA (human leukocyte antigen) types between hiPSC-derived tissues and patients. In previous studies, hiPSC-derived pituitary cells have successfully been used to model autoimmune anti-PIT-1 antibody syndrome [13–15], underscoring the potential value of these systems as tools for modeling autoimmunity, although further work is needed to more fully model disease based on patient iPSCs and donor matched cytotoxic T lymphocytes (CTLs).

During the early stages of mammalian development, the glandular epithelium originates from the on-neural head ectoderm adjacent to the anterior neural plate [60, 61], with the ectoderm and rostral hypothalamic tissues thus interacting with one another [62]. To better mimic these microenvironmental interactions, 3D ES-based culture methods have been employed, with researchers having successfully utilized aggregate murine ES cells to efficiently generate self-assembling 3D adenohypophysis tissues. To achieve this outcome, ES cells in adjacent layers of the culture system were induced to undergo differentiation into non-neural head ectodermal and hypothalamic neuroectodermal tissues, with hedgehog signaling treatment being employed. At the interface between these layers, the self-assembly of 3D Rathke's pouch-like structures was evident consistent with the biological characteristics observed in vivo, facilitating the subsequent production of a range of endocrine cell types such as corticotrophs and somatotrophs. The resultant corticotrophs were able to secrete adrenocorticotropic hormone when stimulated with corticotrophin-releasing hormone, and the in vivo grafting of these cells improved glucocorticoid levels in a murine model of hypopituitarism. As such, these ES cell culture-based tissues can effectively recapitulate local tissue interactions [11].

Current Limitations and Future Directions: While promising, current pituitary organoids often lack the complete vascular network and long-range feedback loops (e.g., HPA axis) of the native gland. Future models integrating endothelial cells and microfluidic systems ("organ-on-a-chip") are needed to study systemic hormone regulation and complex disorders like Cushing's disease.

3 The Thyroid Gland

The thyroid gland, a butterfly-shaped gland in the neck, is responsible for the synthesis, secretion and storage of thyroid hormones, which perform four major functions: controlling the rate at which the body uses energy, promoting the breakdown of proteins, fats and carbohydrates, promoting growth and development and regulating the body's sensitivity to other hormones, making it one of the most important endocrine organs in the body. PSC culture and differentiation techniques have been conducive to the *in vitro* self-assembly of 3D organoids [63, 64]. As engineered cells commonly exhibit poor engraftment that constrains their amenability to in vivo functionality and transplantation, organoid model systems offer a more robust opportunity to recapitulate in vivo endocrine tissue function without the need for orthotopic transplantation, as the engraftment of these organoids in any tissue compartment with access to systemic circulation has the potential to rescue clinical hormone deficiency. PSC-derived thyroid organoids offer potential for regenerative therapy. Mouse PSC-derived thyroid progenitors matured into follicular organoids that secreted hormones and

reversed hypothyroidism in mice [17, 65]. Patient iPSCs with NKX2-1 haploinsufficiency have been differentiated into thyroid cells, modeling genetic hypothyroidism [17]. These results offer insight into the mechanistic basis for the regulation of thyroid organogenesis and highlight promising avenues towards the development of cell-based regenerative treatments for hypothyroidism.

For thyroid cancer, patient-derived papillary thyroid cancer organoids retain the histopathological and genomic features of the original tumor, enabling personalized drug sensitivity testing [18]. Although their use in studying tumorigenesis is still emerging, thyroid cancer organoids represent a powerful preclinical model for drug screening [19]. A key challenge is achieving stable, long-term hormone secretion regulated by physiological stimuli (e.g., TSH). Incorporating vasculature to enable systemic hormone delivery in transplantation scenarios is also crucial for therapeutic applications.

4 The Parathyroid Glands

Hyperparathyroidism, characterized by excessive parathyroid hormone (PTH) secretion, leads to hypercalcemia and bone disease. In vitro studies of parathyroid cells are challenging due to loss of function. Early organoid systems using bovine cells maintained calcium-responsive PTH secretion for weeks [22, 23]. Human parathyroid cells from hyperplastic glands (secondary hyperparathyroidism) have been cultured long-term in organoid form, preserving CaSR expression and function [20].

When cultured *in vitro*, parathyroid cells often lose their physiological characteristics, leading Ridgeway et al. [22] to pioneer the production of multicellular organoid aggregates derived from bovine parathyroid cells in a rotating centrifuge tube. The resultant organoids exhibited consistent responsiveness to extracellular calcium stimulation *in vitro* for a minimum of two weeks. Ritter et al. [23] further developed a prosthetic parathyroid gland system by combining bovine parathyroid cells and type I collagen such that 1-2 mm artificial glands were evident within two weeks. Importantly, these glands retained expected parathyroid gland-related functional properties for extended culture periods.

Roussanne et al. [20] isolated parathyroid cells from hyperplastic gland samples from human SHPT patient hyperplastic gland tissue samples, isolating a mixed population of clustered cells capable of maintaining calcium-induced PTH secreting activity for 5 months in part owing to the lack of use of a filter to generate a single-cell suspension during initial tissue digestion. The prolonged integrity of these parathyroid organoids may be attributable to the initial isolation of cellular aggregates, to the properties of the hyperplastic tissue from which they were derived, or the utilization of phosphate-rich media by the authors. Owing to the long-term functionality of this model system, it is well-suited to assessing the characteristics of parathyroid cell development and PTH production *in vitro*.

For hypoparathyroidism, cell therapy is being explored. Rat adipose-derived stem cells (ADSCs) differentiated into parathyroid-like cells that secreted PTH in response to calcium, offering a potential autologous cell source [24]. thus sought to generate rat ADSC-derived parathyroid-like cells as a tool for the treatment of hypoparathyroidism. When treated with activin A and SHH, these ADSCs secreted PTH and upregulated PTH, calcium-sensing receptor (CaSR), and GCM2 (glial cells missing homolog 2) in a dose- and time-dependent fashion,Primary human parathyroid organoids, especially from adenomas, are difficult to establish and expand. Developing robust protocols and understanding the niche factors that maintain parathyroid chief cell identity *in vitro* are key goals.

5 The Thymus

Early thymic organoid studies relied upon the utilization of 3D murine systems [27-29] or engineered human thymic microenvironment models [25] derived from thymic stroma capable of promoting *in vitro* human T cell maturation and positive selection. As they rely on primary thymic tissue samples, however, these experiments are difficult to perform and exhibit highly variable results, underscoring the need for serum-free approaches to efficiently and reliably promoting HSPC-derived human T cells positive selection and maturation.

To appropriately study human T cell development, model systems must be capable of recapitulating all stages of the thymopoiesis from the HSPC stage to the production of mature T cells. While current *in vitro* models can drive HSPCs to undergo T cell lineage commitment, the ultimate yield of single-positive CD4+ or CD8+ CD3+TCRab+ T cells via this approach remains poor. The thymus is essential for T-cell development. Artificial thymic organoids (ATOs) have been developed to study thymopoiesis

and generate T cells. Serum-free ATOs using human HSPCs efficiently produce diverse, functional T cells [26]. The T cells generated using these ATO-based systems were found to exhibit a diverse TCR repertoire, a range of naïve phenotypes, and TCR-mediated functionality, giving rise to antigen-specific cytotoxic activity and a near total absence of endogenous TCR Vβ expression, consistent with Vβ allelic exclusion. These ATOs thus represent a valuable tool for studying human T cell development and utilizing stem cells in the production of engineered T cell therapeutics.

In an effort to overcome the challenges associated with artificially replicating the distinct thymic ECM when generating thymic organoids, Decellularized thymic scaffolds repopulated with thymic epithelial cells can also support lymphocyte development [66]. As thymic transplantation in athymic patients with rare medical conditions is hampered by aberrant T cell education and immunological dysfunction following transplantation, Valente et al. [67] posited that organoids may represent a valuable tool for restoring normal thymic functionality in a more appropriately regulated manner. consistently, the implantation of a microporous annealed particle scaffold that had been seeded using thymic stromal cells into athymic mice was sufficient to facilitate T cell repopulation within two weeks. Future extensions of these regenerative medicine approaches thus have the potential to modulate adaptive T cell responses in clinically relevant contexts.

These systems have applications in immunotherapy and modeling immune disorders. ATOs can generate antigen-specific T cells for therapy and model T-cell development defects [30]. In an RNA-seq analysis of their prepared M-ATO T cell populations, the authors confirmed them to be phenotypically identical to normal thymocyte populations. When generated using bone marrow derived from Rag-/- mice, these M-ATOs were able to recapitulate normal thymopoiesis. When generated using defined HSC and lymphoid progenitor populations from the bone marrow and thymus, M-ATO systems could further be utilized to track the differentiation of T cells in a longitudinal manner. The deposition of individual HSCs into these M-ATOs was sufficient to give rise to a full repertoire of T cell clones largely recapitulating endogenous thymic biology. As such, these M-ATO platform-based systems represent promising tools for the reproducible study of clonal thymopoiesis. Moreover, human HSPCs can potentially be employed together with ATO systems to produce naïve antigen-specific engineered T cells in a simple, scalable, and reproducible manner, thus allowing researchers to readily study human T cell development and engineered T cell therapeutic tools.Reconstituting the full complexity of the thymic stroma, including its spatial organization and role in central tolerance, remains a challenge. ATOs also need to support the complete spectrum of T-cell maturation more consistently.

6 The Adrenal Glands

The adrenal gland produces steroids and catecholamines. Organoids derived from human fetal adrenal tissue recapitulate the gland's dual cortical and medullary compartments and maintain age-specific steroidogenic programs [31]. This model is valuable for studying adrenal development and diseases like congenital adrenal hyperplasia.Modeling the adult adrenal cortex and its zonation, as well as adrenal tumors (e.g., pheochromocytoma, adrenocortical carcinoma), is an unmet need. Incorporating chronic stress hormone regulation *in vitro* is also a significant challenge.

7 The Pancreas

The primary endocrine functions of the pancreas are the regulation of blood glucose levels and digestive enzyme production. A wide range of pathological conditions, including diabetes mellitus and pancreatic cancer, can disrupt this normal tissue functionality, thereby seriously adversely affecting patient well-being. At present, there is a dearth of reliable approaches to the *in vitro* expansion of pancreatic samples in a manner that retains the characteristics of native tissue, thus limiting efforts to treat these debilitating diseases.

Normally in adult pancreatic tissue, Lgr5 is not expressed and Wnt signaling activity is inactive. Partial duct ligation (PDL), however, reportedly stimulates injury-induced Wnt signaling activation and Lgr5 upregulation, which promotes pancreatic duct regeneration [32]. Duct fragments derived from the murine pancreas can promote the expression of Lgr5 in RSPO1 culture systems, resulting in the production of budding organoids capable of undergoing five-fold weekly expansion for up to 440 weeks. Pancreatic organoids can also be generated from individual isolated duct cells, allowing for the clonal expansion of Lgr5-expressing progenitor cell populations. The resultant clonal pancreatic organoids can then be induced to undergo differentiation into ductal or endocrine cells following transplantation,

enhancing their potential utility.

For pancreatic cancer (PDAC), organoids derived from patient tumors preserve genomic alterations and tumor heterogeneity, serving as excellent platforms for drug screening and personalized medicine [33–35]. They have revealed insights into chemoresistance and tumor-stroma interactions.

Resected tumor tissues and biopsy samples can be used to readily generate pancreatic organoids which exhibit disease-related and ductal characteristics while being well-suited to surviving cryopreservation. When grown in defined media on a gel-based artificial ECM, these pancreatic cells can self-assemble into self-renewing organoids that exhibit genomic stability, properties consistent with those of the cells from which they were derived, in addition to differentiating into functional endocrine cells in vivo. The ability to modulate the genetic characteristics of these organoids has the potential to enable the reliable *in vitro* manipulation of adult stem cells in a manner conducive to regenerative medicine-based treatment strategies. In proteomic and transcriptional analyses of murine pancreatic organoids, researchers were able to identify key pathways and gene expression patterns that were dysregulated in the context of disease progression, underscoring the value of these organoids as an accessible model system for discovery research.

Approaches to promoting the expansion of pancreatic progenitor cells and the differentiation thereof into β cells capable of secreting insulin would be of clear clinical value. Greggio et al. [36] utilized Matrigel to establish a 3D culture system enabling the reliable expansion of dissociated murine embryonic pancreatic progenitor cells. Pancreatic organoids model both endocrine (islets) and exocrine (ductal) diseases. For diabetes, hPSC-derived islet-like organoids can secrete insulin in response to glucose and ameliorate diabetes in mice [37–39]. These "pancreatoids" hold promise for cell therapy and disease modeling. A major hurdle is creating fully functional islets with correct alpha, beta, delta, and PP cell proportions and coordinated hormone release. For cancer models, incorporating the dense fibrotic stroma characteristic of PDAC is critical for accurate drug response prediction.

8 The Ovaries

Ovarian organoids are used to study development and cancer. hESC-derived ovarian follicle-like structures model early oogenesis [40]. By focusing on two germ cell-specific RNA-binding proteins that regulate meiotic entry and a loss of pluripotency (BOULE and DAZL), authors were able to utilize recombinant human GDF9 and BMP15 to upregulate these proteins, generating meiotic germ cells that could be further induced to produce ovarian FLCs consisting of a central oocyte like cell population and an outer granulosa-like cell layer. These characteristics are indicative of the ability of these cells to undergo self-assembly into an organized organoid amenable to use for studying the mechanisms shaping hPSC differentiation into late primordial germ cells, meiotic germ cells, and ovarian follicles.

For ovarian cancer (OC), a lethal malignancy often diagnosed late, patient-derived organoid biobanks encompassing all subtypes have been established [41]. These OC organoids exhibited the genomic and histological characteristics from their parental lesions, presenting with both inter- and intra-donor heterogeneity that was amenable to genetic modification. The authors utilized these OC organoids for drug screening, assessing the responses of different subtypes to platinum-based chemotherapy. This approach served as a means to study the development of chemoresistance upon disease recurrence. Prepared OC organoids were also amenable to xenografting such that they can be used to assess drug sensitivity in vivo. Together, these findings demonstrate the promise of these tumor-derived organoids as tools for individualized treatment.

These recapitulate tumor heterogeneity and enable high-throughput drug screening. Studies using resistant OC organoids have identified pathways like Aurora-A/SOX8/FOXK1 driving chemoresistance [42]. These authors determined that Aurora-A was able to promote resistance to cisplatin treatment by modulating glucose metabolism and cellular senescence via the SOX8/FOXK1 axis in OC. These results underscore a potential avenue to reversing chemoresistance in this deadly cancer type. Genetic editing in fallopian tube organoids has modeled the origin of high-grade serous ovarian cancer. [43] utilized a CRISPR-Cas9 genetic editing strategy to introduce mutations into genes frequently found to be mutated in HG-SOC including PTEN, NF1, BRCA1, and TP53. The results of this analysis supported the potential for both the OSE and fallopian tubes to give rise to these high-grade malignancies. The resultant mutated oviductal organoids underwent more rapid *in vitro* expansion and in vivo malignant tumor formation following transplantation. Modeling

the complex ovarian follicle maturation cycle and the hormone-responsive tumor microenvironment (e.g., involving ovarian stroma) *in vitro* remains difficult. Long-term culture of normal ovarian epithelial organoids is also challenging.

9 The Testes

A variety of strategies have been developed for the *in vitro* modeling of the testicular microenvironment, with these models having been employed for studies of the development and physiology of the testicular compartment. However, further work is needed to generate an *in vitro* system capable of reliably assessing testicular organogenesis and the spermatogonial stem-cell (SSC) niche. Testicular organoids offer a robust tool to study the underlying biology of these systems, and a few have been described to date for use in the context of reproductive biology and medicine.

Testicular organoids model spermatogenesis and the spermatogonial stem cell (SSC) niche. Co-culture systems with Sertoli and Leydig cells support germ cell differentiation and can be used for toxicity testing [44, 45]. iPSCs transplanted into an azoospermic testis niche can differentiate into SSC-like cells [46]. These results indicate that iPSCs can home to the testicular niche, with the local microenvironment playing an essential role in inducing their differentiation into SSCLCs.

Achieving complete, sustained spermatogenesis leading to haploid sperm production *in vitro* is the ultimate but unrealized goal. Reproducing the intricate cytoarchitecture of the seminiferous tubule is a major technical hurdle.

10 Current Challenges and Future Directions

Despite rapid progress, significant challenges impede the full potential of endocrine organoids.

1. Lack of Vascularization and Innervation: Most endocrine organoids lack functional blood vessels and nerves. This is a critical limitation because endocrine organs rely on vasculature for systemic hormone delivery and on neural inputs for regulation (e.g., adrenal medulla). Integrating endothelial and neural cells, or using microfluidic devices to provide perfusion, is a top priority.
2. Recapitulating Systemic Feedback Loops: Endocrine function is governed by body-wide feedback axes (e.g., HPA, HPT). Isolated organoids cannot replicate this. Connecting multiple endocrine organoids on a chip to mimic inter-gland communication is a promising future direction.
3. Maturity and Long-Term Stability: Many PSC-derived organoids resemble fetal rather than adult tissues. Achieving full functional maturation and maintaining hormone secretion stability over months in culture is challenging. Optimizing differentiation protocols and niche factors is essential.
4. Tumor Microenvironment Complexity: Cancer organoids often lack the native tumor microenvironment (TME), including immune cells, cancer-associated fibroblasts, and vasculature. Co-culture systems incorporating these elements are needed for more predictive drug testing.
5. Standardization and Scalability: Protocol variability between labs hinders comparison. Automated, high-throughput production and characterization platforms will be crucial for drug discovery and biobanking.
6. Ethical and Regulatory Pathways: For therapeutic applications (e.g., islet organoids), clear regulatory frameworks for safety, efficacy, and standardization need to be developed alongside the technology.

11 Conclusions

Organoid technology has revolutionized the modeling of endocrine diseases, offering unprecedented insights into human physiology and pathology that are not achievable with traditional 2D cultures or animal models. From elucidating the developmental origins of congenital hypopituitarism to enabling personalized drug screening for thyroid and ovarian cancers, endocrine organoids are proving to be indispensable tools. They bridge the gap between simplistic cell cultures and complex in vivo systems, providing a patient-relevant platform for mechanistic studies, drug discovery, and regenerative medicine strategies.

The field is now moving beyond descriptive modeling towards solving fundamental biological questions and addressing clinical needs. The integration of bioengineering, such as organ-on-a-chip technology and 3D bioprinting, with advanced molecular profiling, will drive the development of next-generation organoids that are more

vascularized, functional, and physiologically integrated. Overcoming the current challenges of standardization, scalability, and recapitulation of systemic interactions will be key to translating organoid research into tangible clinical benefits, such as personalized treatment predictions and novel cell therapies for endocrine disorders. In conclusion, endocrine disease organoids represent a dynamic and powerful paradigm, poised to accelerate our understanding and treatment of a wide spectrum of endocrine conditions.

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Conflicts of Interest

The authors declare no conflicts of interest.

AI Use Statement

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Ethical Approval and Consent to Participate

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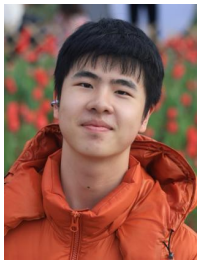

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