Revisiting The Concept of Incretin and Enteroendocrine L-cells as Type 2 Diabetes Mellitus Treatment

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Abstract

The significant growth in type 2 diabetes mellitus (T2DM) prevalence strikes a common threat to the healthcare and economic systems globally. Despite the availability of several anti-hyperglycaemic agents in the market, none can offer T2DM remission. These agents include the prominent incretin-based therapy such as glucagon-like peptide-1 receptor (GLP-1R) agonists and dipeptidyl peptidase-4 inhibitors that are designed primarily to promote GLP-1R activation. Recent interest in various therapeutically useful gastrointestinal hormones in T2DM and obesity has surged with the realisation that enteroendocrine L-cells modulate the different incretins secretion and glucose homeostasis, reflecting the original incretin definition. Targeting L-cells offers promising opportunities to mimic the benefits of bariatric surgery on glucose homeostasis, bodyweight management, and T2DM remission. Revising the fundamental incretin theory is an essential step for therapeutic development in this area. Therefore, the present review explores enteroendocrine L-cell hormone expression, the associated nutrient-sensing mechanisms, and other physiological characteristics. Subsequently, enteroendocrine L-cell line models and the latest associated L-cell targeted therapies are reviewed critically in this paper. Bariatric surgery, pharmacotherapy and new paradigm of L-cell targeted pharmaceutical formulation are discussed here, offering both clinician and scientist communities a new common interest to push the scientific boundary in T2DM therapy.

Keywords: Bariatric Surgery, Enteroendocrine L-cell, Incretin, Pharmaceutical Formulation, Pharmacotherapy

Abbreviations: AA, amino acids; BS, bariatric surgery; CaSR, calcium-sensing receptor; CCK, cholecystokinin; DPP4-i, dipeptidyl peptidase-4 inhibitor; DSPE-PEG2000, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy (polyethylene glycol)2000]; EECs, enteroendocrine cells; FFAR, free fatty acid receptors; GIP, glucose-dependent insulinotropic polypeptide; GIT, gastrointestinal tract; GLP, glucagon-like peptide; GLP-1, glucagon-like peptide-1; GLUT-2, glucose transporter 2; GPBAR1/TGR5, G_s-coupled bile acid receptors; GPCRs, G-protein coupled receptors; GPRC6A, G-protein coupled receptor family C group 6 subtype A; HbA1c, haemoglobin A1c; HRQoL, patients health-related quality of life; INSL5, insulin-like peptide 5; K_{ATP}, ATP-sensitive K^+ channels; LNC, lipid

nanocapsules; mGluR1/4, metabotropic glutamate receptors 1/4; NLC, nanostructured lipid carriers; NT, neurotensin; OXM, oxyntomodulin; PPARδ, peroxisome proliferator-activated receptor δ; PEPT1, proton-dependent intestinal peptide transporter 1; PYY, peptide YY; RYGB, roux-en-Y gastric bypass; SCFAs, short-chain fatty acids; SG, sleeve gastrectomy; SGLT-1, sodium-glucose cotransporter 1; STR, sweet taste receptor; T1R1/3, type 1 taste receptor subunit 1/3; T2DM, type 2 diabetes mellitus; TPH1, tryptophan hydroxylase 1; TRPA1, Transient Receptor Potential Ankyrin 1

1. Introduction

Incretins, namely enteroendocrine K-cells-secreted glucose-dependent insulinotropic polypeptide (GIP) and enteroendocrine L-cells-secreted glucagon-like peptide-1 (GLP-1) mediate the insulin secretion in response to oral glucose administration. This experimental-based definition [1, 2] that emphasised the association between gastrointestinal incretin hormones and glucose-dependent insulin secretion effect has subsequently attracted tremendous drug development and market enthusiasm among researchers. In particular, GLP-1 receptor agonist and dipeptidyl peptidase-4 inhibitor (DPP4-i) are widely studied for their quality glucose management in type 2 diabetes mellitus (T2DM) [3], thanks to the low hypoglycaemia risk [4] and other associated clinical benefits [4-7]. Recently, efforts in advancing oral peptide GLP-1 delivery had led to the successful listing of semaglutide (Rybelsus®) in the market [8].

The current incretin concept may be too rigid, superficial, and more importantly, skewed from the original meaning that defines incretin as any gastrointestinal hormone that elicits secretion of pancreatic hormones under physiological circumstances [9]. This perception may result in overfocus of GIP and GLP-1, and subsequent underestimation of its true therapeutic development potential by researchers and health practitioners. Rehfeld [9] highlighted three main issues that arise from this concept in his recent review. Firstly, GIP and GLP-1 are not the only gastrointestinal hormones that trigger insulin secretion; secondly, incretins can target multiple sites synergistically, and the mechanism is not ‘one-hormone-one-target’; and finally, high dose glucose used in experiments does not reflect normal physiological circumstances where an everyday diet contains substantial amounts of lipid, protein, simple and complex carbohydrate. Hence, there is need for a broader perspective ‘revision’ in appreciating the fundamental gastrointestinal endocrinology concept for future T2DM therapeutic development.

Intestinal-expressed enteroendocrine cells (EECs) are gaining popularity as alternative treatment targets for obesity and T2DM [10]. These treatments centre around exploiting the ability of L-cells to secrete GLP-1 and other incretins [11, 12]. In fact, this notion is far from new and may arguably represent the cores of the original incretin concept. This review revisits the fundamental incretin theory and provides an overview of enteroendocrine L-cell and its potential to advance T2DM treatment development.

2. Incretin Secreting Enteroendocrine L-Cells

The gastrointestinal tract (GIT) that functions principally for digestion and nutrient absorption is notably the largest endocrine organ in the body. Approximately 1% of the intestinal epithelium cells scattered along the GIT are identified as EECs. These cells are derived from local intestinal stem cells and are generally believed to migrate from the crypt towards the tip of the villus under constant replacement every 4-5 days [13]. However, a recent study suggests that some EECs may survive longer than 60 days [14]. EECs are open-type intestinal cells in nature with spindle or flask-shaped morphology to allow direct contact with nutrients and other luminal stimuli that subsequently trigger various hormones secretion for endocrine, paracrine and neuronal actions [13].

L-cells are primarily located along the GIT, and the density increases towards the colon [15], with more L-cells present in the crypts than in the villi [16]. However, L-cell number does not correlate to the total GLP-1 content and secretion in the intestine, where the upper small intestine contains more GLP-1 followed by the lower small intestine and colon. Moreover, another study observed that ileal and colonic L-cells exhibited differential genes expression and stimulus-response, suggesting that they may have different physiological roles [17]. Similarly, recent clinical studies reported that healthy and T2DM participants possess significant differences in L-cells product expression [12] but not the density and turnover rate [16]. Overall, current findings may imply that the therapeutic development process should also consider the associated anatomically dependent and cellular physiological characteristics of L-cells at different regions of the intestine.

Another established physiological notion is that EECs exceedingly overlap each other, expressing multiple gastrointestinal hormones and enzyme on the same site [18]. For example, Glass and colleagues [19] discovered three primary preproglucagon-expressing cells subgroups from the upper small intestine, one with high levels of *Gcg* and *Pyy* (encoding GLP-1 and Peptide YY, respectively), another high in *Tph1* (tryptophan hydroxylase-1), and another high in *K-cells*-contained *Gip*, implicating that L-cells overlap with enterochromaffin and K-cells. On the other hand, four L-cell subgroups in the colon identified by another group

[20] are also multi-hormonal and overlapping. Collectively, these pieces of evidence not only challenge the traditional ‘one-cell, one-hormone’ belief, but also indicate great potential for therapeutic development in T2DM and obesity. Consequently, more researchers are trying to uncover the complex physiology and pharmacology of L-cells using various L-cell study models to ‘hijack’ the secretory machinery. Fig. 1 summarises the different enteroendocrine L-cell subpopulations along the GIT that co-express different peptides with various metabolic functions.

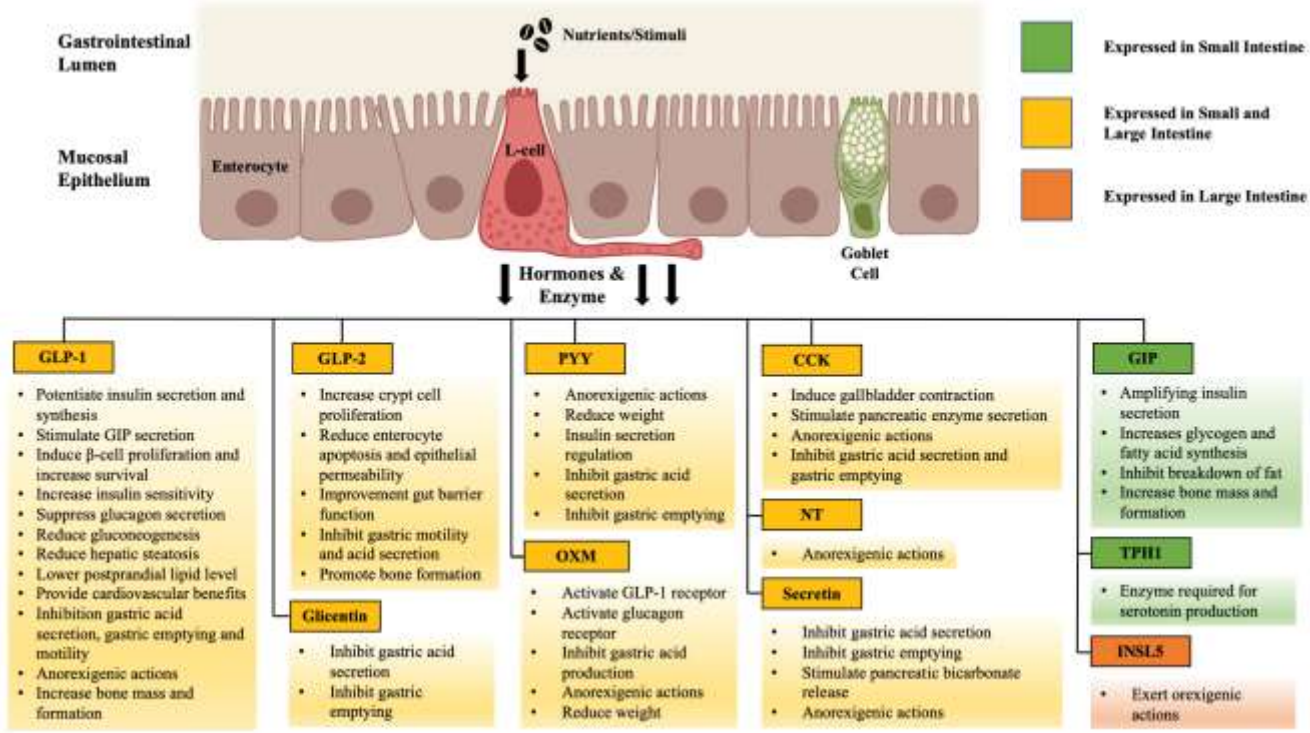

Fig. 1: Overview of Enteroendocrine L-cells With Overlapping Gastrointestinal Peptides Expression. A simplifying schematic representation of the multiple co-localised gastrointestinal hormones and enzyme in different L-cell subpopulations along the intestinal tract, which respond to luminal nutrients or other stimuli by secreting these peptides for various metabolic functions.

GLP: glucagon-like peptide; PYY: peptide YY; OXM: oxyntomodulin; CCK: cholecystokinin; NT: neurotensin; GIP: glucose-dependent insulinotropic polypeptide; TPH1: tryptophan hydroxylase 1; INSL5: insulin-like peptide 5

3. In Vitro L-cells cell line models

The abundance of literature on the complex L-cells physiology and nutrient-sensing mechanism are attributed to the vast combination of study models. Among all, mammalian carcinoma-derived cell lines are the earliest employed models due to isolation difficulty of native L-cells that is low in number, randomly distributed, and co-localised with other enterocytes [21]. To study incretin secretion and its correspondent stimuli, STC-1, GLUTag,

and NCI-H716 cell lines are routinely used as they are well-established and easily cultured; while HuTu-80 is least frequently employed. Nonetheless, the clinical relevance of carcinoma-derived cell models remains questionable despite sharing many similarities with native L-cells at the transcriptomic level. In reality, genetic and morphological discrepancies exist between cell line models and native L-cell; and even within the model itself [22, 23]. For instance, Kuhre et al. [23] reported that STC-1, GLUTag, and NCI-H716 do not contain PYY, but some researchers [21, 24] reported otherwise. Furthermore, the simplified cell line model can never provide cell-cell or cell-microbiota interaction that mimics the in vivo environment. A comparison chart between all the cell lines are presented in Table 1.

Table 1: Enteroendocrine L-cells line models.

Cell Lines	Origin	Hormones	Advantages	Disadvantages
STC-1	Derived from duodenum enteroendocrine tumour of double transgenic mice (proinsulin-SV40 Large T antigen/proinsulin-polyoma x Small T antigen)	GLP-1, GLP-2, GIP, CCK glicentin, OXY, NT, glucagon, vasoactive intestinal peptide, pancreatic polypeptide and somatostatin Secretion of PYY showed conflicting results	Similar to GLUTag which possesses and secretes more diverse peptide than NCI-H716 Responses appropriately towards low concentration acetate and propionate that induces GLP-1 secretion in murine primary colonic cultures	Resembles human L-cells the least, such as storing and secreting high GIP level, but low GLP-1 upon activation. Stores and secretes non-L-cells containing glucagon Low NT and somatostatin storage and inconsistency secretion result upon stimulation Cell population shows high heterogeneity and significant test result variability for the same stimuli. Poorly differentiated and slow-growing cell line with reportedly low transfection efficiencies
GLUTag	Derived from colonic tumour of	GLP-1, GLP-2,	Most commonly used, specific and	May not represent human L-cells fully,

	proglucagon-SV40 Large T antigen transgenic mice	CCK, glicentin, OXY, NT, glucagon, vasoactive intestinal peptide and somatostatin	best murine L-cell model Responses appropriately toward the same stimuli that induces in vivo GLP-1 secretion High resemblance to non-immortalised L-cells genetic and protein expression profile Similar to STC-1 which possesses and secretes more diverse peptide than NCI-H716 Shows better stability in proglucagon gene expression pattern and differentiates better than STC-1 High homogeneity and secretes GLPs in a highly regulated manner Easy to transfect	such as storing and secreting glucagon but not PYY Low NT and somatostatin storage and inconsistency secretion result upon stimulation Not suitable to study short-chain fatty acid stimulus effect Requires matrix to support and attach to well plates
NCI-H716	Derived from cecum adenocarcinoma (ascites) originated from a 33 year old Caucasian male	GLP-1, GLP-2, glicentin, OXY, NT, glucagon and somatostatin Secretion of PYY shows conflicting results	Human originated cell line Expresses short-chain fatty acid receptors GLP-1 expressed mostly homogenously and secreted in a regulated manner, producing low test result variability (~10% standard error)	Not fully mirroring native human L-cell with its carcinoma-derived feature Secretes glucagon and does not express CCK Low NT and somatostatin storage and inconsistency secretion result upon stimulation Contains a very

			Easy to transfect	restricted peptide pattern Proglucagon gene transcription aberrantly regulated with its mechanism deviated from human and rat. Heterogeneous cell line Requires matrix to support and attach to well plates
HuTu-80	Derived from duodenum adenocarcinoma originated from a 53 year old Caucasian male	GLP-1, PYY, GIP, CCK, secretin	Human originated cell line and expressed *Gcg* and *Pyy* Less variability in siRNA transfection efficiency Easy to transfect Widely available cell line	Carcinoma-derived cell line and may not resemble fully native L-cells Demonstrated lesser or no response to same stimuli used for STC-1

The multiple limitations of conventional L-cells models have led to the emergence of more advanced in vitro and ex vivo models for L-cells research such as fetal rat intestinal culture model, intestinal organoids, intestine-on-a-chip and the use of Ussing chamber. Nevertheless, immortalised cell lines remain an important asset and serve as a primary screening model for potential incretin secretion inducer prior to in vivo studies, and is particularly useful in high throughput screening. Details of cell culture protocols and advanced L-cells research models are discussed in these studies [21-25].

4. L-Cells Nutrient Sensing

4.1 Carbohydrates

Due to the incretin effect, oral glucose administration results in greater insulin secretion compared to intravenous administration. This effect is not limited to glucose, where high-sucrose feeding has also been shown to induce postprandial GLP-1 secretion [26]. These

together consolidate the fundamental blood sugar homeostasis. Clinical study in the past observed a rapid (five minutes) GLP-1 surge after liquid glucose ingestion [27]. Hence, it was generally believed that the distal intestine region is not involved in glucose sensing. Moreover, previous studies have shown that proximal region does not contain L-cell [28]. These had led Roberge and Brubaker [29] to explore the possibility of proximal-distal loop neuronal or hormonal systems in mediating the rapid rise in GLP-1 secretion. Another study using canine L-cells has also reported that glucose was unable to induce GLP-1 secretion [30]. On the other hand, Sun et al. [31] demonstrated that direct activation of proximal L-cells is accountable for the rapid GLP-1 secretion phase and others have observed glucose concentration-dependent GLP-1 secretion in GLUTag cell line [32, 33]. Similarly, it was revealed that rapid-phase secretion of GLP-1 is preserved in ileal resection patients, which further confirmed the role of proximal intestine in glucose sensing [34]. Overall, more evidence favours the theory of proximal intestinal L-cells being responsible for glucose-induced GLP-1 rapid phase secretion, and does not involve proximal-distal indirect signalling.

ATP-sensitive K^+ channels (K_{ATP}) have gained much interest given that glucose- and fructose-induced GLP-1, CCK and NT secretion pathways involve K_{ATP} closure, cell depolarisation and subsequently opening of voltage-gated calcium channel [32, 33, 35]. The proposed monosaccharide-dependent secretion mechanism is enhanced by the administration of K_{ATP} blocker, tolbutamide, and diminished by K_{ATP} opener, diazoxide [32]. However, the relative importance of K_{ATP}-mediated incretin release is not supported by the available in vivo studies [36, 37]. Likewise, results from a recent study using human gut tissue specimens did not support the involvement of K_{ATP} and showed that instead, sodium-glucose cotransporter 1 (SGLT-1) dominates the pathway [31].

SGLT-1 is an essential cotransporter that employs two Na^+ for every glucose or galactose apical crossing. Its subsequent concentration equilibrium between plasma and enterocyte is mediated further by Glucose Transporter 2 (GLUT-2) at the basolateral site [38]. GLUT-2 translocates to the apical side and supports glucose and galactose absorption when a high concentration of glucose is present in the small intestine [38]. Intriguingly, recent studies [39, 40] found similarities between β-cells insulin secretion and L-cells GLP-1 secretion, where both follow a biphasic secretion pattern. The SGLT-1-mediated depolarisation is propagated via voltage-dependent Ca^{2+} and Na^+ channels that lead to the first phase GLP-1 secretion; while the second phase is exemplified by GLUT-2-mediated glucose absorption that causes

metabolic ATP-driven K_{ATP} closure. This is further substantiated by the report of a well-known diabetes complication contributor, 3-deoxyglucosone that can attenuate GLUT-2 expression and impair GLP-1 secretion [41]. Nonetheless, the degree of K_{ATP} involvement in incretin secretion remains a topic of debate.

Another sensing mechanism worth noting is the sweet taste receptor (STR), a heterodimer comprising T1R2/T1R3. Studies from GLUTag [42], NCI-H716 [43], and HuTu-80 [44] cells have collectively demonstrated that sucralose activates GLP-1 secretion through STR, but comparable results were not replicated to replicate in studies using murine primary intestinal cultures [45] and in vivo rat models [46]. On the contrary, *Polygonatum cyrtonema* polysaccharide administration in NCI-H716 cells and rat studies appear to induce GLP-1 secretion via STR activation [47]. Hence, this receptor requires further investigation for therapeutic usage.

4.2 Proteins

While it is clear that the complex incretin secretion mediates postprandial carbohydrate metabolism and glycaemic homeostasis, proteins on the other hand, trigger postprandial incretin secretion in humans such as GLP-1 and PPY [48]. Unlike carbohydrates, proteins break down into 20 different amino acids (AA), as well as about 400 dipeptides and 8000 tripeptides, making it more challenging to study of its absorption and sensory mechanisms. Similar biophysical AA can be absorbed through their respective transporters [49]; while the transport of dipeptides, tripeptides and oligopeptides depend on the proton-dependent intestinal peptide transporter 1 (PEPT1) [50, 51]. Subsequently, these absorption processes are accompanied by different protein hydrolysate-sensing mechanisms to induce incretins secretion. A study using STC-1 cells suggests that PEPT1 can additionally function as ‘sensors’ for the peptides, as its activation causes membrane depolarisation and releases incretin hormones [52]. This finding is underpinned by a recent in vivo study that shows the co-administration of casein and PEPT1 non-translocated competitive inhibitor 4-aminomethylbenzoic acid diminished the GLP-1-mediated glucoregulatory role of PEPT1 [53].

In addition, numerous apically absorbed protein fragments can activate a second sensor on the basolateral side, namely calcium-sensing receptor (CaSR) [54]. This homodimeric receptor couples to multiple G_{α} proteins (G_s, G_q, G_i, and $G_{12/13}$) [55], where the predominant

G_q-coupling activates phosphatidylinositol-specific phospholipase C and intracellular Ca^{2+} mobilisation [56, 57]. CaSR is shown to induce GIP, GLP-1 and PYY secretion when aromatic, polar and charged AA bind to it allosterically [58-61]. Furthermore, the CaSR-dependent pathway is involved in sensing peptones [54, 62], but results from in vitro [63] and human studies [64] did not show a contribution from branched-chain AA.

This leads to the possibility that these diverse protein fragments may additionally bind elsewhere, with overlapping sensing mechanisms. In fact, aromatic AA L-phenylalanine and L-tryptophan, and oligopeptides with N-terminal tryptophan are some of the noticeable natural ligands that purportedly activate G_q-coupled GPR142 receptors in the GIT [65-67]. However, aromatic AA [66] and whey protein [65] administration in GPR142-deficient mice did not attenuate incretin secretion. Similarly, when studying L-tryptophan-induced GPR142-mediated glucose-stimulated insulin secretion (GSIS) from pancreatic β-cells, Ueda et al. [67] did not observe complete blockage despite administering CaSR antagonist to diet-induced obesity GPR142KO mice. Taken together, more studies are required to understand these receptors, their expression locations, and other potential overlapping signalling pathways for a better understanding of their T2DM therapeutic potential.

G-protein coupled receptor family C group 6 subtype A (GPRC6A) is another broad-spectrum receptor that senses a considerable amount of AA and co-localises with GLP-1 expressing cells in the small intestine [68]. It resembles CaSR in its response to AA with basic structure, coupling with G_q protein and possessing a calcium-binding site [69-71]. A recent study using GLUTag cells demonstrated that a low-molecular fraction of wheat gluten hydrolysate activates GLP-1 secretion in a dose- and time-dependent manner through the GPRC6A-mediated Ca^{2+}/calmodulin-dependent kinase II pathway [72]. Although this resemblance may suggest potential overlapping mechanisms, GPRC6A responds mainly to basic AA but not aromatic AA [73]. Furthermore, Oya and colleagues [74] showed that L-ornithine is able to elicit GLP-1 secretion in GLUTag cell models, but not in primary intestine culture model. Alternative receptors such as the metabotropic glutamate receptors 1/4 (mGluR1/4) and type 1 taste receptor subunit 1/3 (T1R1/3), which reportedly co-expressed with GPRC6A and CaSR in SCT-1 cell model may be potential candidates to be explored [75].

4.3 Lipids

In the ‘90s, literature has documented the involvement of lipid components in eliciting incretin secretion from human studies [76, 77]. This effect is supported by more recent studies in NCI-H716 cells [78] and Sprague-Dawley rats [79]; and human, where it was proven that the lipid component is a more potent inducer than protein and glucose [80]. However, incretin secretion stimulatory effects are highly associated with different carbon chain lengths and saturation that confer distinct affinities towards their respective G-Protein Coupled Receptors (GPCRs), also referred to as the Free Fatty Acid Receptors (FFAR) [81]. For instance, long-chain fatty acids reportedly possess higher binding affinities toward G_q-coupled receptors GPR40/FFAR1 and GPR120/FFAR4 than medium-chain fatty acids [81]. Several studies have demonstrated that activation of these receptors using natural lipid ligands or synthetic agonists can elicit the release of incretins such as GLP-1 [82], GLP-2 [83] and PPY [84], but other studies showed that GPR40/FFAR1 activation further involves G_s [85] and $G_{i/o}$ [86] proteins in the downstream signalling. Therefore, targeting these receptors should exploit the incretin metabolic benefits in enhancing satiety and insulin release. Li et al. [87] reported that orexigenic effect of mercaptoacetate is mediated by GPR40/FFAR1 and possibly GPR120/FFAR4. Besides, these activatable pathways also appeared to be PYY-stimulated Y_1 receptor-mediated and glucose-sensitive [84]. Overall, GPR40/FFAR1 and GPR120/FFAR4 appear to be promising therapeutic targets and theoretically should not cause any hypoglycaemic side effect.

The predominantly G_q-coupled GPR43/FFAR2 [88] and G_s-coupled GPR119 [56] signalling activities are PYY-mediated and glucose-dependent [89, 90]. However, the $G_{i/o}$-coupled GPR41/FFAR3 expressed on L-cells and enteric neurons is both glucose- and PYY-independent [90]. Colonic bacteria-produced short-chain fatty acids (SCFAs) from indigestible fibre were shown to activate both GPR43/FFAR2 and GPR41/FFAR3 [81]. These SCFAs and microbiome have attracted great attention due to their distinct physiological roles and their ability to directly modulate the metabolic health of the host. Growing evidence suggests the close association between microbiome and the pathophysiology of obesity and T2DM [91]. Gut microbes are viewed as a virtual external organ that physiologically participates in nutrient absorption, energy utilisation, feeding behaviour, gut homeostasis and development of immune and nervous systems of the host [92-94]. They can communicate with the EECs and regulate the host system through their metabolic products by fermentation and other enzymatic pathways. For instance, SCFAs

induce GLP-1 secretion through the GCPRs expressed on the L-cells and selectively increase the differentiation of L-cells [88, 95]. Likewise, Brooks et al. [96] have demonstrated that SCFAs could expand PYY-positive cell density within the proximal colon through GPR43/FFAR2, leading to increased circulating PYY level.

However, a recent study [97] observed that FFAR2- or FFAR3-selective agonist and antagonist failed to elicit expected effects from the isolated perfused rat colon. This had led to the suggestion that, either some less investigated Olfr78 [98] and GPR109A [99] receptors might be involved, or incretin secretion requires FFAR2 and FFAR3 coactivation, in which the latter opinion is supported by Tough et al. [90]. Furthermore, in isolated rat colons model, vascular infusion (basolateral side) of SCFAs acetate and butyrate induced stronger GLP-1 secretion than that given luminally (apical side) [97]. This result is supported by a human study [100] which showed that circulating SCFAs concentration (basolateral) is strongly correlated to the GLP-1 level, but not faecal SCFAs (apical). On the other hand, another lipid sensing GPCR, GPR119 binds to endogenous lipid components, oleoylethanolamide [101, 102] and 2-monoacylglycerols [102], which are likely to act synergistically with GPR40/FFAR1 in mediating incretin secretion [103]. It was later found that that GPR119 is located on both apical and basolateral sides [89].

The need for metabolism and absorption of lipid in incretin secretion has attracted interest after incretin secretion was found to be impaired by orlistat lipase inhibitor [104-107]. Pancreatic lipase participates heavily in dietary triglycerides lipolysis, and can affect enterocyte uptake process after emulsification by bile acids. Moreover, triglyceride re-synthesis process [108] and its transported chylomicron [109] can also affect incretin secretion. The importance of packaging process was revealed when the secretions of GLP-1 and GIP are attenuated after administration of pluronic L-81 surfactant that inhibits chylomicron synthesis [110]. Some studies support the presence of lipid sensors on the basolateral site to receive the absorbed lipid components (stimuli) and subsequently induce incretin secretion [89, 111]. On the other hand, the emulsifying bile acids can trigger L-cells secretion in cell lines and primary murine culture models [112, 113] through G_s-coupled bile acid receptors (GPBAR1/TGR5) interaction, and inhibited by bile acid sequestrant Sevelamer in T2DM patients [114]. GPBAR1/TGR5 are located basolaterally on the L-cells [115]. As such, microbiome exert another great influence on incretin secretion because they can modify the bile acids to become more hydrophobic, allowing the secondary bile acids to permeate

across epithelium cells [116]. Overall, these nutrient associated sensing mechanisms show that incretin concept is not merely about GLP-1, GIP and oral glucose, but involves other nutrient compounds, and chemical digestion and absorption processes.

5. L-Cells-Based Therapeutic Approaches

5.1 Bariatric surgery

In the early 1940s, anecdotal evidence recorded remarkable hypoglycaemia as a complication of post subtotal gastrectomy for peptic ulcer, which later presented the first connecting point between bariatric surgery (BS) and T2DM [117]. Subsequently, more evidence emerged and underpinned the clinical surgery values in improving body weight, glycemia, haemoglobin A1c (HbA1c), and T2DM remission rate [118, 119]. Sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB) and gastric banding are the three most commonly performed BS for obesity treatment [120]. However, only SG [121] and RYGB [122, 123] are reportedly able to go beyond obesity treatment and amplify incretin secretion for clinically meaningful T2DM treatment, yet their underlying mechanism remains debatable and likely multifactorial. The anatomical rearrangement involving either SG or RYGB surgical procedures [120] could increase nutrient delivery to the distal enteroendocrine L-cells. This is by far the most acceptable mechanism to explain the postprandial incretins surge after surgery [124].

The considerable luminal and serum bile acid elevation after BS could lead to a positive metabolic impact [125]. It was proposed that the relative contribution of different gastrointestinal anatomical rearrangements modifies bile acid enterohepatic circulation, thereby increasing GPBAR1/TGR5 activation to secrete incretins [125]. On the other hand, some researchers tried to investigate the postprandial incretin surge post-surgery by elucidating BS fundamental physiological changes associated with density and gene expression of L-cells. A higher number of L-cells is reported in rats and humans following RYGB [126], but the SG outcome remains inconclusive [126, 127]. The transcriptomics and peptidomics modification were not observed in mice and humans after SG and gastrectomy with RYGB respectively [17, 128], but post-surgery preprohormone gene expression alteration was reported [129].

Nevertheless, the clinical evidence of BS for obese patients with T2DM remains solid and further supported by cost-effectiveness evidence in a recent meta-analysis [130]. It is noteworthy that data from this study [130] focused only on high-income countries. Further investigation on low- and middle-income countries is required to justify the effectiveness against financial feasibility. The accessibility to such services and the availability of bariatric surgeons will unquestionably be the barrier for the T2DM community from lower economic classes. Moreover, T2DM patients might worry about BS-associated surgical risk and complications, such as gastric pouch dilatation, gastroesophageal reflux and excess skin around the area of upper leg and arm, inguinal and abdominal areas [120, 131]. Recently, Jiang et al. [131] suggested body contouring surgery as an aesthetic supplement for improving excess skin issues, but extra cost factors and lack of reimbursement have again imposed financial barriers among the patients. Thus, BS is recommended only for selected obese patients with T2DM, taking into consideration the associated risk and cost factors.

5.2 Pharmacotherapy

The substantial clinical evidence of postprandial incretin hormone surge associated with BS has paved the way for new development in T2DM treatments. Currently, scientists are attempting to eradicate the disadvantages of BS and 'compress' only the metabolic benefits that arise from incretins surge into a 'BS pill'. On the one hand, some prefer to explore molecular analogues that target the incretin receptors directly. These include the previously discussed GLP-1 receptors targeting Rybelsus® [8] as well as novel ligands that target GIP receptors and GIP/GLP-1 receptors. Although GIP was thought to have no clinical benefit in lowering glucose in the early days, Eli Lilly has recently presented their novel dual GIP/GLP-1 receptors agonist, Tirzepatide (LY3298176), with promising results in glucose control, weight loss and safety profile among the poorly controlled T2DM patients in phase 2 trial [132]. Furthermore, Lazzaroni and colleagues [133] reported that Tirzepatide (LY3298176) possess stronger weight loss effect than commonly used anti-obesity drugs, such as exenatide and dulaglutide. Similarly, an anti-GIP receptor antagonistic monoclonal antibody developed by Amgen has demonstrated substantial inhibition of weight gain in a preclinical study [134]. However, while the clinical benefits of targeting GIP receptors are indisputable, controversy exists whether it is therapeutically best to activate or inhibit these receptors for obesity and T2DM [135, 136]. On the other hand, other researchers prefer to mimic post BS effects by targeting the multi hormones secreting enteroendocrine L-cells. A wide array of sensors expressed on L-cells as discussed earlier have opened up avenues to develop new drugs for

T2DM. For instance, TAK-875, a GPR40/FFAR1 agonist developed by Takeda, has demonstrated its promising anti-diabetic properties in phase I and phase II clinical trials. However, it was terminated later in phase III trials due to hepatotoxicity induced mainly by its acyl glucuronide metabolites [137]. Nevertheless, the quest to synthesise new targeting agonists and uncover potential natural substances for these receptors remains and are summarised in Table 2 by highlighting the relevant studies and results for the interest of this review.

Table 2: Recent findings (2016-2021) on synthetic and natural compounds that induce incretin secretion from enteroendocrine L-cells.

Synthetic/Natural Compounds	Target Sites	Study Models/Subjects	Outcomes	References
Synthetic Compounds				
AgoPAMs	Activates GPR40/FFAR1	Diabetic Goto-Kakizaki rats	Increased GLP-1, GIP, PYY and insulin secretion; reduced glucose level, food intake and body weight	[138]
		GLP-1R$^{-/-}$ mice and wild type mice	Reduced glucose level in both mice types; induced higher insulin secretion in wild type than GLP-1R$^{-/-}$ mice	
SCO-267	Activates GPR40/FFAR1	GLUTag cells	Induced GLP-1 secretion	[139]
		Wild-type mice and GPR40-knockout (*Ffar1*$^{-/-}$) mice	Increased GLP-1 secretion; reduced food intake and body weight reduction in wild-type mice, but not *Ffar1*$^{-/-}$ mice	
		Normal rats	Increased GLP-1, GIP, PYY, insulin and glucagon secretions	
		Neonatal streptozotocin-treated rats	Increased insulin and GLP-1 level; improved glucose	

			tolerance; no changes in food intake and body weight	
		Diet-induced obese rats	Increased GLP-1 and PYY plasma levels; reduced food intake, cholesterol, fat mass and body weight; no changes in lean mass and glucose and triglycerides plasma level	
GSK137647 and Compound-A	Activate GPR120/FFAR 4	High-fat-fed Swiss TO mice	Both agents increased GLP-1 and insulin level; improved glucose tolerance; synergistically increased glucose lowering effect is observed when given together with sitagliptin (DPP4-i); GSK137647 increased GIP level, but not Compound-A; AH-7614 (FFAR4 antagonist) impaired both agents' insulinotropic and glucose lowering properties	[140]
		Lean Swiss TO mice	Both agents improved glucose excursion; satiation effect was observed when agents given alone, but	

			sitagliptin (DPP4-i) impaired the satiation effect of Compound A at 60 min and GSK137647 from 60 min to 180 min	
AZ13581837 and Metabolex-36	Activate GPR120/FFAR 4	STC-1	Both agents increased GLP-1 secretion	[141]
		Lean wild-type mice	Both increased GLP-1 and insulin secretion; reduced glucose level; exendin 9–39 (GLP-1 receptor antagonist) abolished insulin secretion and glucose lowering effect of both agents	
		GPR120 *null* mice	Glucose tolerance effect of Metabolex-36 was not observed; AZ13581837 did not induce acute insulin secretion and it impaired glucose elimination	
AS1269574	Activates GPR119 and Transient Receptor Potential Ankyrin 1 (TRPA1) channel	STC-1	Stimulated GLP-1 release and increased $[Ca^{2+}]_i$	[142]
		GLUTag	Stimulated proglucagon gene promoter activity	
DS-8500a	Activates GPR119	Zucker fatty rats	Increased plasma GLP-1 concentration and reduced glucose level	[143]
		Fasted Sprague-	Did not change	

		Dawley rats	plasma glucose concentration; stimulated insulin secretion in the presence of glucose	
		Neonatal streptozotocin-treated rats	Induced glucose-stimulated insulin secretion; reduced glucose level	
ZB-16	Activates GPR119	Streptozotocin–nicotinamide-treated rats	Increased GLP-1, insulin, insulin-positive pancreatic endocrine cells and glucose utilisation.	[144]
YH18421	Activates GPR119	GLUTag	Increased GLP-1 secretion	[145]
		Normal C57BL/6J male mices	Single YH18421 oral administration improved glucose tolerance and GLP-1 level; synergistically increased glucose lowering effect and GLP-1 levels are observed when YH18421 given together with Linagliptin (DPP4-i)	
		Diet induced obese mice model	Four weeks repeated YH18421 administration lower blood glucose level and showed dose-dependently inhibited weight gain; synergistically increased glucose lowering effect is	

			observed when YH18421 given together with sitagliptin (DPP4-i)	
HBK001	Activates GPR119 and inhibits DPP4	ICR mice	Increased GLP-1 and GIP level; inhibited DPP4 activity; reduced blood glucose level	[146]
		Diabetic KKAy mice	Reduced plasma glucose level and food intake; increased insulin secretion; no effect on body weight	
		db/db (BKS.Cg-m+/+ *Lepr*db/J) mice	Reduced plasma glucose level	
L3740	Activates GPBAR1/TGR5	Mouse intestinal organoids	Increased L-cell density and GLP-1 secretory capacity; elevated expression of *Gcg* and *Cck* and transcription factors *Ngn3* and *NeuroD1;* no increment effect on L-cells and no GLP-1 secretion was observed from organoids lacking GPBAR1	[147]
		Human intestinal organoids	Increased L-cell density; elevated expression of *Gcg* and transcription factors *NeuroD1*	
		GLU-Venus mice in vivo model	Increased basal GLP-1 plasma level, L-cell density and expression of	

			Gcg and *Ngn3* and GLP-1 levels; improved glucose tolerance; no differences in food intake and body weight	
Compound 24 (BDM72881)	Activates GPBAR1/TGR5	Diet-induced obesity and insulin resistance C57Bl6 mice	Increased GLP-1 secretion and improved glucose homeostasis	[148]
LX2761	Inhibits SGLT-1 and SGLT-2	Healthy mice	Reduced glucose level; increased plasma GLP-1 when administered alone and synergistic increased GLP-1 level is observed when given together with sitagliptin (DPP4-i); no significant changes in food intake and body weights	[149]
		Healthy rats	Reduced glucose excursions; increased plasma GLP-1; no significant changes in food intake and body weights	
		Streptozotocin-treated mice	Early-onset diabetes: Reduced fasting and postprandial glucose level; slowing of the rise in HbA1c levels; no effect on food intake, body weight and GLP-1 level on the final study	

			day Late-onset diabetes: Reduced fasting and postprandial glucose level and HbA1c; increased GLP-1 level, survival rate, food intake and body weight	
CPU025	Activates GPR40/FFAR1 and peroxisome proliferator-activated receptor δ (PPARδ)	FLIPR assay (Chinese hamster ovary (CHO, RRID:CVCL_0213) cells)	EC_{50} value of 38.7 nM for GPR40/FFAR1	[150]
		AutoDock vina1.1.2	Molecular docking simulations showed multiple hydrogen bonding formed between carboxylic acid of CPU025 and key binding residues of GPR40/FFAR1 (Arg2258, Tyr2240, Arg183 and Tyr91)	
		Male ICR mice	Could not induce GLP-1 secretion	
		Diabetic *ob/ob* mice and C57BL/6 mice	Exhibited better reduction in blood glucose, HbA1c, triglyceride and consumption of food and water than TAK-875, GPR40/FFAR1 partial agonist; no body weight changes; improved β-cell function; displayed relatively dense	

			arrangement of insulin-positive cells; alleviated fatty liver	
ZLY032	Activates GPR40/FFAR1 and PPARδ	Male *ob/ob* mice and male C57BL/6 mice	Improved fasting glucose level, HbA1c, glucose tolerance and pancreatic β-cell function; decreased plasma total cholesterol, triglyceride, LDL, adipocytes area, liver steatosis and ballooning; showed stronger insulin sensitive and lipid improvement compared to TAK-875; no changes in body weight	[151]
DKS26	Unidentified/ unreported receptors	NCI-H716 cells	Echanced GLP-1 release and expression	[152]
		Streptozotocin-treated and *db/db* diabetic mice	Increased plasma insulin level; enhanced GLP-1 release and expression; reduced glucose level, plasma glycosylated serum protein; no significant changes in body weight A reduction of food intake was observed in Streptozotocin-treated mice, but no effect on *db/db* diabetic mice	

Natural Compounds				
Polygonatum cyrtonema polysaccharide	Activates sweet taste receptor T1R2/T1R3	NCI-H716 and male Sprague-Dawley rats	Increased GLP-1 secretion	[47]
Matrine	Activates CaSR	STC-1 cells	Increased GLP-1 secretion	[153]
		Type 2 diabetic C57BL/6 mice	Improved glucose metabolism; reduced fasting serum insulin level; increased GLP-1 level and oral-induce insulin level; high-dose Matrine increase body weight in the third week of study	
Curcumin	Activates GPR 40/120	GLUTag	Increased GLP-1 secretion; reduced GLP-1 secretion when pre-treated with GW1100 (GPR40/120 antagonist) and neomycin (PLC inhibitor - a downstream molecule of GPR40/120 pathway)	[154]
		Male Sprague-Dawley rats	Increased GLP-1 and insulin secretion; improved glucose tolerance; reduced glucose-lowering effect when pre-treated with GW1100 (GPR40/120 antagonist)	
Phytosphingosine	Activates GPR120/FFAR 4	Transforming Growth Factor α-shedding assay	IC50 value of 33.4 μM; the activation is significantly	[155]

			inhibited by AH7614 (GPR120/FFAR 4 antagonist)	
Angelica dahurica extract (phellopterin)	Activates GPR119	GLUTag Normal C57BL6 mice Diabetic *db/db* mice	Increased GLP-1 secretion Increased insulin and reduced glucose level Reduced glucose level	[156]
Costus pictus D. Don	Unidentified/ unreported receptors	GLUTag	Increased acute GLP-1 secretion; improved GLUTag viable cells when given in low concentration (1.56, 3.125 and 6.25 μg/ml); no changes on prohormone convertase 1 and 2 protein expression; reduced proglucagon and prohormone convertase 1 gene expression	[157]
Delphinidin 3-rutinoside-rich blackcurrant extract	Unidentified/ unreported receptors	Male Sprague-Dawley rats	Increased GLP-1 and insulin secretion, and reduced glucose level	[158]

Traditionally, drug design is driven by minimising unwanted drug distribution and targeting a single biological entity to avoid adverse effects. However, this concept is now considered obsolete in diseases involving complex aetiology like T2DM [159]. The idea of targeting GPCRs on the L-cells received considerable attention, not only because it can induce metabolic beneficial incretins secretion from L-cells, but the same receptors expressed on other targets can offer synergistic or additional clinical benefits. GPR40/FFAR1 [139], GPR120/FFAR4 [140, 141] and GPR119 [143, 145, 146] are some of the receptors found on L-cells and pancreatic islets which induce GLP-1 secretion and GSIS after activation at the respective expression sites. Furthermore, Satapati et al. [160] demonstrated that combined

exposure to L-cells' GPR40/FFAR1 and GPR120/FFAR4 synergistically provides superior blood glucose control compared with either agonist alone. It is also worth mentioning that activated GPR120/FFAR4 on osteoclasts and osteoblasts may provide additional modulating effects for metabolic bone diseases [161], but activation of CaSR on the heart can contribute to cardiac injury [162]. Therefore, the overall landscape of optimising drug design for L-cells should consider both target receptor-associated adverse effects and its beneficial signalling pathways.

Some currently available non-L-cells targeting T2DM pharmacotherapy compounds are found to associate with L-cells sensing mechanisms and increase GLP-1 secretion. Alpha-glucosidase inhibitor is one of the orally prescribed T2DM medications that competitively inhibits carbohydrate digestion participating enzymes, leading to prolonged digestion time and greater delivery of monosaccharides to the distal intestine. Seifarth et al. [163] believed this mechanism of drug action explains their study's result, where patients were given 100g of oral sucrose and 100mg of an alpha-glucosidase inhibitor (acarbose), enhanced and extended GLP-1 secretion was observed. However, increment in GLP-1 secretion was not seen when acarbose was given with mixed meals [163]. Other T2DM medicines that are able to slow glucose absorption in the proximal intestine include canagliflozin and sotagliflozin [165]. They reportedly inhibit SGLT1/2 and lower glucose absorption at the respective intestine and proximal tubule expression sites. Nonetheless, some disagreement remains on the proposed mechanism because L-cells cannot utilise SGLT-1 as the glucose sensor to induce GLP-1 secretion. Lastly, the well-known first-line T2DM medicine metformin has been shown to increase plasma GLP-1. The proposed underlying mechanisms include a similar reduction in SGLT-1 activity, increased intestinal exposure of bile acid, reduced DPP4 activity [166], and direct activation of L-cells via the AMPK pathway [167].

5.3 Pharmaceutical Formulation

Conventionally, the strategy for targeted therapy drug design revolves around uncovering new chemical entities and exploring existing compounds that can bind to the targeted sensors. However, researchers [168-171] have recently proposed a novel approach to produce the L-cell therapeutic targeting effect from an unusual perspective. The strategy that Beloqui et al. [168] first proposed was based on L-cells lipid-sensing mechanism, hypothesising that lipid-based nanoparticle formulation can mimic endogenous ligands to trigger GLP-1 secretion. Rather than using the usual ligand grafting approach, they formulated different polymeric and

lipid-based nanoparticles in their study. Among all, only nanostructured lipid carriers (NLC) can induce significant GLP-1 secretion from GLUTag and NCI-H716 cells through GPR41/FFAR3 and GPR84 receptors. Unfortunately, the nanoparticles were shown to be trapped at the mucus layer in human intestinal ex vivo model [169]. Subsequently, the same group of researchers [170, 171] modified the lipid nanocapsules (LNC) surface with 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy (polyethylene glycol)2000] (DSPE-PEG2000) to enhance mucus diffusion capacity, which later demonstrated promising results both in vitro and in vivo.

The selection of lipid-based excipients selection and the design of NLC in the above studies [168, 169] were indicated to improve Saquinavir bioavailability [172], and mainly contain long (palmitic acid and stearic acid) and medium-chain (caprylic acid and capric acid) saturated acid. The lipid components of LNC were mainly caprylic acid, capric acid, phosphatidylcholine and phosphatidylethanolamine [170, 171]. Although these lipid components may induce GLP-1 secretion through their respective GPCRs/FFAR, their affinity and potency are likely to vary significantly due to the saturability and length of their carbon chains [81]. Therefore, there is room for exploration with different lipid-based excipients, such as using the more potent unsaturated fatty acid [81]. Besides, lipidic excipients are generally considered a safer and cheaper option than drug compounds. Other lipid-based formulations include solid lipid nanoparticles, lipid-drug conjugates, and self-emulsifying drug delivery systems may also impart the same clinical functionality. Thus, it is worth exploring these dual-action drug delivery systems holds great potential in targeting enteroendocrine L-cells and improving drugs' pharmacokinetic profile for T2DM treatment.

6. Perspectives and Commentary

Incretin history and the use of incretin-based therapies reflect the progression and advancement in many lines of sciences. This has led to the emergence of GLP-1 analogues and DPP4-i as T2DM therapies in the market. However, the therapeutic outcomes and some concerning side effects [3] indicate that peripheral hijacking of GLP-1 alone is not adequate to replicate the remission seen in BS. Indeed, the dramatic surge of various beneficial metabolic hormones observed post-GIT rearrangement by BS is associated with higher exposure of nutrients and stimuli to the intestinal distal segment. As a matter of fact, this

phenomenon touches the enteroendocrine physiological system and mirrors the original incretin definition. Continued effort in advocating for original incretin definition in practice allows different science disciplines and healthcare practitioners to take part in advancing new treatment development that can mimic BS clinical outcomes better through a broader perspective. Therefore, targeting enteroendocrine L-cells is a renewed enthusiasm in this area for its multiple potential therapeutical hormone secretion.

There have been aggressive efforts to develop new molecular entities based on the structure-activity relationship from current literature. However, a thorough understanding of receptor localisation is essential for further advancement. Specifically, whether the targeted receptor(s) are located on the intestinal apical or basolateral site; and whether or not they are present in other organs. This aspect is crucial as a nonabsorbable agonist should be designed for apically expressed receptors to minimise systemic exposure and off-target effects, whereas basolaterally expressed receptors require the molecular structure to adapt for crossing the epithelial layer. Therefore, having nonabsorbable apically targeted drugs for receptors like GPR40/FFAR1, GPR120/FFAR4, and GPR119 may ultimately sacrifice their additional GSIS effects from the pancreatic islets. However, the development of such ligands is necessary to ascertain L-cells receptors expression sites. Furthermore, present works suggest the existence of L-cell subpopulations and may be responsible for different physiological roles. Hence, understanding the anatomical and physiological aspects of these subpopulations can lead to a better drug targeting design, and further improve drug formulation strategies to target the selected intestinal segment.

Current evidence of nutrient sensing mechanism clearly suggests that manipulation of diet through specific foods, or their by-products intake should promote interaction with the L-cells and induce incretin secretion. While seeking a balance between total calorie and nutritious diet is essential in influencing glycaemic outcomes, nutritional modulation of incretin appear to be another factor of consideration in future practice or guideline in modifying T2DM daily diet. Diabetes educators from different healthcare disciplines are the most suitable facilitators to empower this dietary concept to bedside and play a significant role in advancing diabetes management. Nonetheless, the establishment of such dietary guidelines for practice still requires a considerable amount of research translation and careful consideration from different perspectives. This may be the case for T2DM patients that are at risk for other diabetes-associated complications such as cardiovascular diseases.

Similarly, the emerging idea of using lipid-based nanoparticle formulation to induce L-cells incretin secretion through FFARs sensing mechanisms appears promising. However, this approach alone is unlikely to replace synthetic agonists due to its lower efficacy. In this regard, incorporation of active pharmaceutical ingredients in lipid-based nanoparticles provides dual-function and is expected to elicit a greater response than either approach on its own. This area is still largely unexplored and is worthy of investigation. Future ongoing attempts might focus on synthesising potent L-cells expressing receptors agonist or direct multi-targeting incretin receptors agonist. L-cells targeted pharmacotherapy is likely to emerge in the foreseeable future, attributable to the vast sensing mechanisms by L-cells and valuable pharmacokinetics insight from TAK-875 phase III clinical trial. This gives rise to more opportunities and strategies to develop novel therapeutic agonists for incretin secretion. Nevertheless, the reality of drug discovery and development from bench to bedside remains complex, time-consuming and relies heavily on private and public resources. Hence, empowering T2DM patients to adopt dietary modification and developing L-cells targeted drug carriers such as lipid-based nanoparticles may provide a faster and more economical solution for enhancing incretin secretion. These strategies are expected to be used in synergy with synthetic agonists in future T2DM treatments. Overall, a multidisciplinary approach would be the way forward to push the boundary of science in T2DM therapy.

7. Conclusion

In summary, the incretin concept has attracted considerable interest for T2DM therapy development for many years. However, past incretin-based therapy development has caused today's treatments to overly focus on GLP-1 alone, leading to a loss of characteristic in the fundamental incretin concept and underestimation of its therapeutic value. Thus, targeting enteroendocrine L-cells that encompasses GLP-1 and other gastrointestinal hormones represents a novel and promising approach to provide direct and indirect synergistic therapeutic effect for T2DM. In fact, this may go beyond improving plasma glucose level and body weight with the multiple incretin secretion, and provide a breakthrough T2DM remission through non-surgical approaches. Nevertheless, the continued effort to deorphanise

receptors and study the associated synthetic ligands and nutrients' secretory mechanism remains crucial in this niche area. A thorough understanding of these mechanisms would enable the translation of research findings to drug development and clinical practice that could reshape the current gastrointestinal endocrinology landscape in T2DM treatment.

Declaration of Competing Interest

The authors declare no conflict of interest.

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CRediT authorship contribution statement

Kok-Hou Lok: Conceptualization, Writing – Original Draft;Nicholas J Wareham: Validation, Writing – Review & Editing. Rajesh Sreedharan Nair: Writing – Review & Editing. Chee Wun How: Writing – Review & Editing . Lay-Hong Chuah: Funding Acquisition, Project Administration, Writing – Review & Editing, Supervision, Visualization

Declaration of Competing Interest

The authors declare no conflict of interest.

Graphical abstract