Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Enteroendocrine cells as druggable gut sensors: a bibliometric and pharmacological target mapping analysis (1980–2025)

Kemal Yüce

yuce2020@hotmail.com

Ağrı İbrahim Çeçen University

Seçil Nazife Parlak

Ağrı İbrahim Çeçen University

Hakan Ocak

Ağrı İbrahim Çeçen University

Research Article

Keywords: Enteroendocrine cells, Enterochromaffin cells, Glucagon-like peptide-1, Nutrient-sensing receptors, Gut–brain axis, Bibliometrics

Posted Date: November 12th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11552801/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Enteroendocrine cells as druggable gut sensors: a bibliometric and pharmacological target mapping analysis (1980–2025)

Kemal Yüce[1*], Seçil Nazife Parlak[2], Hakan Ocak[3]

[1] Department of Physiology, Faculty of Medicine, Ağrı İbrahim Çeçen University, 04100 Ağrı, Türkiye, ORCID: https://doi.org/0000-0001-8915-4900.

[2] Department of Histology and Embryology, Faculty of Medicine, Ağrı İbrahim Çeçen University, 04100 Ağrı, Türkiye, ORCID: https://doi.org/0000-0001-9577-986X.

[3] Department of Anatomy, Faculty of Medicine, Ağrı İbrahim Çeçen University, 04100 Ağrı, Türkiye, ORCID: https://doi.org/0000-0002-0288-4167

*Corresponding author: Kemal Yüce, Department of Physiology, Faculty of Medicine, Ağrı İbrahim Çeçen University, 04100 Ağrı, Türkiye, ORCID: https://doi.org/0000-0001-8915-4900,

e-mail: yuce2020@hotmail.com

Running title: Bibliometric mapping of enteroendocrine cell research

Abstract

Enteroendocrine cells (EECs) are the sensory interface of the gut epithelium and the cellular source of hormones targeted by several established drug classes, yet no quantitative map of this research field is available. We analysed 3,652 original articles published between 1980 and 2025 and indexed in the Web of Science Core Collection. Performance analysis, collaboration and co-word networks, Kleinberg burst detection, co-citation analysis and dictionary-based mapping of 31 pharmacological targets and drug classes were combined. Annual output rose from 10 to 201 articles (compound annual growth rate 6.9%), and the corpus accumulated 206,196 citations (h-index 190). The United States contributed 30.9% of the articles, whereas China showed the steepest recent growth, rising from 7.8% to 20.4% of articles between 2010–2017 and 2018–2025. Reimann F, Gribble FM and Holst JJ were the most influential authors. Co-word analysis resolved three domains: incretin and metabolic signalling, serotonin and gut–brain/disease signalling, and EEC development studied with stem cells and organoids. Bursts for gut microbiota, organoids, the gut–brain axis and single-cell RNA sequencing remained active in 2025. Overall, 34.6% of the articles addressed at least one pharmacological target. The GLP-1 receptor, taste receptors and 5-HT3/5-HT4 receptors were the most frequent targets, whereas Piezo2, the farnesoid X receptor, Toll-like receptors, TRPM5/TRPV1, the GIP receptor and FFAR2/FFAR3 emerged fastest and classic serotonergic agents declined. These findings position EECs as a druggable sensory platform that extends beyond incretin therapy and identify mechanosensory, microbial metabolite and bile acid pathways as priorities for pharmacological research.

Keywords Enteroendocrine cells; Enterochromaffin cells; Glucagon-like peptide-1; Nutrient-sensing receptors; Gut–brain axis; Bibliometrics

Introduction

Enteroendocrine cells (EECs) are scattered throughout the gastrointestinal epithelium and constitute only about 1% of epithelial cells, yet collectively they form the largest endocrine system of the body (Gribble and Reimann 2016; Gribble and Reimann 2019). EECs sense luminal nutrients, microbial metabolites, bile acids, irritants and mechanical forces, and translate these signals into the release of more than 20 hormones and transmitters, including glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), peptide YY (PYY), cholecystokinin (CCK), ghrelin and serotonin (5-hydroxytryptamine, 5-HT) (Date et al. 2000; Holst 2007; Gribble and Reimann 2019). Through endocrine, paracrine and neural routes, these signals regulate glucose homeostasis, appetite, gastrointestinal motility, epithelial barrier function and visceral sensation (Mawe and Hoffman 2013; Gribble and Reimann 2016).

The pharmacological relevance of EECs is unusually broad. Incretin hormones secreted by L and K cells provided the biological basis for GLP-1 receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, two drug classes that have reshaped the treatment of type 2 diabetes and obesity (Drucker and Nauck 2006; Baggio and Drucker 2007; Drucker 2018). Enterochromaffin (EC) cells produce most of the body's serotonin, and the serotonergic signalling system has long been targeted by 5-HT3 and 5-HT4 receptor ligands in functional gastrointestinal disorders (Gershon and Tack 2007; Mawe and Hoffman 2013). In parallel, EECs express a repertoire of nutrient-sensing G protein-coupled receptors (GPCRs), transporters and ion channels, including free fatty acid receptors, GPR119, the bile acid receptor TGR5, taste receptors, transient receptor potential channels and the mechanosensitive channel Piezo2, many of which are pursued as drug targets (Jang et al. 2007; Edfalk et al. 2008; Lauffer et al. 2009; Thomas et al. 2009; Tolhurst et al. 2012; Alcaino et al. 2018). The discovery that some EECs form synapse-like contacts with enteric and vagal neurons, the so-called neuropod cells, further positioned these cells as fast sensory transducers of the gut–brain axis (Bohorquez et al. 2015; Bellono et al. 2017; Kaelberer et al. 2018).

Methodological advances have also transformed the field. Lgr5-based stem cell biology and intestinal organoids enabled the generation of human EECs in vitro (Barker et al. 2007; Sato et al. 2009; Petersen et al. 2014), and single-cell transcriptomics resolved EEC subtypes and their differentiation trajectories at unprecedented resolution (Grün et al. 2015; Haber et al. 2017; Gehart et al. 2019; Hickey et al. 2023). Together with the growing recognition that the gut microbiota modulates EEC output (Yano et al. 2015; Ye et al. 2021; Yoon et al. 2021),

these developments have produced a large, fragmented and rapidly expanding literature that spans endocrinology, gastroenterology, cell biology, neuroscience and pharmacology.

Bibliometric analysis provides a reproducible way to quantify such literatures, identify influential contributors and knowledge structures, and detect emerging research fronts (Small 1973; Zupic and Čater 2015; Donthu et al. 2021). Bibliometric studies are increasingly used to map pharmacological research areas, and recent assessments of this literature have recommended the use of multiple author performance indicators, separate co-word analyses of titles, abstracts and keywords, and citation burst detection (Abdelwahab et al. 2025; Kumar 2026). Bibliometric analyses in pharmacology have generally focused on individual drugs, drug classes or diseases (Abdelwahab et al. 2025), but the EEC itself, as the common cellular platform from which several therapeutic targets originate, has not been mapped. Moreover, no study has quantified how pharmacological targets expressed by or acting on EECs have been distributed across time and disease contexts.

The aim of this study was therefore to provide a comprehensive bibliometric analysis of EEC research published between 1980 and 2025. Specifically, we (i) characterised publication and citation dynamics, (ii) identified the leading countries, institutions, journals and authors and their collaboration patterns, (iii) mapped the conceptual structure, thematic trends and research bursts of the field, (iv) delineated its intellectual base through co-citation analysis and (v) developed a pharmacological target map to identify established, declining and emerging druggable mechanisms in EEC biology.

Materials and methods

Data source and search strategy

Bibliographic data were retrieved from the Web of Science Core Collection (WoS; Clarivate), which provides standardised metadata and complete cited-reference fields required for citation and co-citation analyses (Mongeon and Paul-Hus 2016; Donthu et al. 2021). The search was performed on 26 October 2026 using the topic field (TS), which covers titles, abstracts, author keywords and Keywords Plus. The search string combined the cell-type terms “enteroendocrine cell*”, “enterochromaffin cell*” and “neuropod cell*” with L-cell terms (“L cell*” OR “L-cell*”) restricted by GLP-1-related or intestinal terms. The complete query was: TS=("enteroendocrine cell*" OR "enterochromaffin cell*" OR "neuropod cell*" OR (("L cell*" OR "L-cell*") AND ("glucagon-like peptide" OR GLP-1 OR intestin*))). Results were limited to original articles written in English; review articles and early access

records were excluded at the database level. To avoid bias from repeated retrieval, the search was completed and exported on a single day.

Eligibility and data cleaning

The export comprised 3,891 records with full records and cited references (Fig. 1). Records were de-duplicated by WoS accession number. Retracted publications and publications carrying an expression of concern (n = 5) were removed. Because the analysis focused on complete calendar years, records with a publication year of 2026 or 2027 (n = 179) were excluded. Records that did not contain an EEC-related term in the title, abstract, author keywords or Keywords Plus were then screened manually at the title and abstract level, and off-topic records retrieved through homonyms (for example, the murine fibroblast "L cell" line) were excluded (n = 55). The final dataset contained 3,652 articles published between 1980 and 2025.

Data processing and keyword normalisation

Data were processed in Python 3 (pandas, NumPy and NetworkX; figures in Matplotlib). Indicator definitions followed the bibliometrix framework (Aria and Cuccurullo 2017), which was also used through its biblioshiny interface for initial data inspection. Country affiliations were extracted from all author addresses; England, Scotland, Wales and Northern Ireland were merged as the United Kingdom. Author keywords and Keywords Plus were normalised using a thesaurus that merged spelling variants, abbreviations and singular/plural forms (for example, "glucagon-like peptide-1", "GLP-1" and "GLP1"; "5-HT" and "serotonin"). Search terms and non-informative general terms (for example, "expression", "mice" and "secretion") were removed from the mapping analyses.

Performance analysis

Annual scientific production was summarised by the number of articles per year and the compound annual growth rate (CAGR) between 1980 and 2025; the growth pattern was evaluated by exponential regression. Citation impact was expressed as total citations, mean citations per article and mean citations per article per citable year. To describe the development of the field, the study period was divided into four intervals: 1980–1999, 2000–2009, 2010–2017 and 2018–2025. Country productivity was assessed by all-author affiliation counts and, for the collaboration pattern, by the corresponding-author country, distinguishing single-country publications (SCP) from multiple-country publications (MCP). Journal concentration was evaluated with Bradford's law (Bradford 1934) and author productivity

with Lotka's law (Lotka 1926). Author impact was assessed with the h-index, g-index and m-index calculated within the dataset (Hirsch 2005; Egghe 2006). Influential articles were ranked by local citation score, that is, the number of citations received from other articles in the dataset, which reflects influence within the field more specifically than global citation counts.

Science mapping

Co-word analysis was performed on author keywords. The 70 most frequent normalised keywords were retained, links with at least three co-occurrences were kept and isolated nodes were removed. Clusters were identified with the Louvain modularity algorithm (Blondel et al. 2008). In line with recent methodological recommendations (Abdelwahab et al. 2025), the most frequent terms were also extracted separately from author keywords, Keywords Plus, titles and abstracts, including bigrams and trigrams (Online Resource 1). Thematic evolution was described by trend topics, defined by the median and interquartile range of the publication years of keywords occurring at least 12 times (Cobo et al. 2011; Aria and Cuccurullo 2017). Research bursts were detected with Kleinberg's two-state algorithm (scaling parameter $s = 2$, transition cost $\gamma = 1$) applied to yearly keyword counts between 1991 and 2025 for keywords occurring at least 15 times (Kleinberg 2003; Chen 2006). International collaboration was visualised for the 20 most productive countries with links of at least five co-authored articles. For co-citation analysis (Small 1973), the 60 most frequently cited references were identified from the cited-reference fields; pairs co-cited at least ten times were linked and clustered with the Louvain algorithm.

Pharmacological target mapping

To quantify the pharmacological dimension of EEC research, a dictionary of 31 targets and drug classes grouped into seven classes was constructed from the established EEC literature (Mawe and Hoffman 2013; Gribble and Reimann 2016; Gribble and Reimann 2019): nutrient-sensing GPCRs, ion channels and mechanosensors, nutrient transporters, serotonergic machinery, hormone receptors and degrading enzymes, nuclear and innate immune receptors, and drugs or drug classes. Each entry was defined by regular expressions that captured gene symbols, receptor names, synonyms and drug names in titles, abstracts, author keywords and Keywords Plus. For each target, the number of articles, first year of appearance, median publication year and the proportion of articles published in 2018–2025 were calculated, and its share of all articles was computed for each period. Co-occurrence with eight disease or biological contexts (obesity and energy balance; type 2 diabetes, glycaemia and incretin

effects; bariatric surgery; irritable bowel syndrome, motility and visceral pain; inflammatory bowel disease and colitis; neuroendocrine tumours; gut–brain axis and behaviour; microbiota and microbial metabolites) was expressed as the percentage of target articles that also mentioned each context. Because WoS abstracts are available mainly from 1991 onwards, target shares for 1980–1999 are based predominantly on titles and keywords.

Ethical considerations

This study analysed publicly available bibliographic metadata and did not involve human participants or animals; ethical approval was therefore not required.

Results

Overview of the dataset

The final dataset comprised 3,652 articles published in 984 sources by 16,093 authors (Table 1). The articles accumulated 206,196 citations, corresponding to a mean of 56.5 citations per article and an h-index of 190 for the whole corpus. On average, articles had 6.70 co-authors, only 142 articles (3.9%) were single-authored, and 25.8% involved international co-authorship. The articles cited 93,777 distinct references and contained 5,453 distinct author keywords.

Publication and citation trends

Annual output increased from 10 articles in 1980 to 201 in 2025, corresponding to a CAGR of 6.9% (Fig. 2a). Growth followed an exponential pattern ($R^2 = 0.94$). Output was relatively low and stable until 1999 (534 articles), increased moderately in 2000–2009 (597 articles), and accelerated sharply after 2010; 2010–2017 and 2018–2025 together accounted for 69.0% of all articles (1,170 and 1,351 articles, respectively). Mean citations per article per citable year increased from below 2 in the 1980s to approximately 4–9 after 2005 (Fig. 2b). The peak in 2021 reflected a single highly cited article showing that central and peripheral GLP-1 systems suppress eating independently (Brierley et al. 2021).

Countries, institutions and collaboration

Authors from 89 countries contributed to the field. The United States was the most productive country, with 1,129 articles (30.9%) and 94,673 citations, followed by Japan (428), the United Kingdom (404), China (386) and Canada (290) (Table 2; Fig. 3a). Among countries with at least 90 articles, Switzerland (165.5), the Netherlands (99.1) and the United Kingdom (94.6) had the highest mean citations per article. Among the ten most productive countries, the

proportion of internationally co-authored articles among corresponding-author publications was highest for Denmark (42.6%), France (36.0%) and the United Kingdom (34.0%), and lowest for Japan (11.7%) and China (16.1%). The geographic distribution changed markedly over time: articles with Chinese affiliations rose from 19 in 2000–2009 to 91 in 2010–2017 and 275 in 2018–2025, increasing China's share from 7.8% to 20.4% between the last two periods. The collaboration network was centred on the United States, whose strongest links were with China (68 co-authored articles), Canada and the United Kingdom (58 each), Germany (52) and Japan (50); a dense European axis connected Denmark, the United Kingdom, Germany and Sweden (Fig. 3b). At the institutional level, the University of Copenhagen (177 articles), the University of Toronto (116) and the University of Cambridge (74) led the field, with the University of Cambridge and the affiliated Addenbrooke's Hospital showing the highest mean citations per article among the leading institutions (Table 2).

Journals and authors

The 3,652 articles were distributed across 984 sources. According to Bradford's law, 31 core journals (3.2% of all sources) published 1,208 articles (33.1%). The American Journal of Physiology-Gastrointestinal and Liver Physiology (124 articles), Endocrinology (97), PLOS ONE (83), Gastroenterology (71) and Neurogastroenterology and Motility (54) were the most productive journals, while Gastroenterology had the highest h-index within the dataset (54) (Table 3). The leading journals represented physiology, endocrinology, gastroenterology and multidisciplinary science, reflecting the interdisciplinary nature of the field; Naunyn-Schmiedeberg's Archives of Pharmacology contributed 16 articles, mainly on the receptor-mediated modulation of serotonin release from EC cells. Author productivity followed Lotka's law, with 78.3% of authors contributing a single article. Holst JJ (112 articles), Reimann F (101) and Gribble FM (89) were the most productive authors. Reimann F had the highest h-index (53), g-index (101) and m-index (2.21), followed by Gribble FM (h = 50) and Holst JJ (h = 49) (Table 4).

Most influential articles

The ten articles with the highest local citation scores are presented in Table 5. The most locally cited article was the primary culture study of glucose sensing in L cells by Reimann et al. (2008) (250 local citations), followed by the demonstration that short-chain fatty acids stimulate GLP-1 secretion through FFAR2 (Tolhurst et al. 2012) and the identification of gut-expressed gustducin and taste receptors as regulators of GLP-1 secretion (Jang et al. 2007). The list also included studies that redefined EEC identity through transcriptional profiling and

hormone co-expression (Egerod et al. 2012; Habib et al. 2012), early morphological and cell line studies (Sjolund et al. 1983; Eissele et al. 1992; Drucker et al. 1994), the description of altered mucosal serotonin signalling in irritable bowel syndrome (Coates et al. 2004) and the characterisation of EC cells as chemosensors coupled to sensory nerves (Bellono et al. 2017). By global citations, the most cited articles were Brierley et al. (2021) (5,359 citations), Yano et al. (2015) (2,931) and Tolhurst et al. (2012) (2,043).

Conceptual structure, trend topics and research bursts

GLP-1 (518 occurrences), serotonin (304), incretins (114), obesity (110), diabetes (102), PYY (100) and gut microbiota (100) were the most frequent author keywords. The co-word network of 67 author keywords comprised 255 links and resolved into three clusters (Fig. 4). The incretin and metabolic cluster (32 keywords) linked GLP-1, GIP, PYY, CCK, incretins, type 2 diabetes, obesity, bariatric surgery and nutrient-sensing receptors such as TGR5, FFAR1, FFAR4 and GPR119. The serotonin, gut–brain and disease cluster (25 keywords) connected serotonin with the enteric nervous system, motility, irritable bowel syndrome, inflammatory bowel disease, neuroendocrine tumours, chromogranin A, gut microbiota, short-chain fatty acids and the gut–brain axis. The development, stem cell and organoid cluster (10 keywords) grouped stem cells, organoids, differentiation, NEUROG3, the intestinal epithelium and Drosophila midgut models. Separate analyses of Keywords Plus, titles and abstracts reproduced the same dominant themes and highlighted multi-word terms such as “glucagon-like peptide-1 secretion”, “intestinal stem cells”, “enteroendocrine cell line” and “short-chain fatty acids” (Online Resource 1).

Trend topic analysis showed a clear thematic progression (Fig. 5a). Immunoreactivity, the glucagon gene, islet cells, enteroglucagon and transgenic mice characterised the late 1990s and the turn of the millennium; peristaltic reflex, gastric acid secretion, mast cells and the enteric nervous system the late 2000s; and irritable bowel syndrome, serotonin, GIP, GLP-1 and food intake the early-to-mid 2010s. Obesity, insulin resistance, bariatric surgery, short-chain fatty acids and stem cells peaked around 2017–2019, whereas gut microbiota, organoids, the gut–brain axis and epithelial barrier were the most recent topics. Burst detection supported this progression (Fig. 5b). Early bursts involved transgenic mice (strength 21.7; 1991–2007), pancreas (17.6; 1992–2006) and guinea pig models (16.8; 1991–2004). Irritable bowel syndrome (18.7; 2006–2010), taste receptors (10.1; 2009–2013), GPCRs (9.7; 2010–2018), bariatric surgery (7.9; 2015–2021) and GLP-1 secretion (9.4; 2017–2021) marked the following decades. The strongest burst of the entire period was that of gut

microbiota (38.5; 2018–2025). Together with organoids (18.2; 2019–2025), inflammation (12.1; 2019–2025), stem cells (10.7; 2020–2025), the gut–brain axis (8.5; 2019–2025) and single-cell RNA sequencing (7.2; 2021–2025), this burst remained active at the end of the study period.

Pharmacological target landscape

Overall, 1,265 articles (34.6%) addressed at least one of the 31 targets or drug classes. This proportion increased from 31.7% in 2000–2009 to 45.5% in 2010–2017 and remained high in 2018–2025 (36.0%) (Fig. 6a; Table 6). The GLP-1 receptor was the most frequently studied target (201 articles; 8.0% of articles in 2010–2017), followed by taste receptors (151), 5-HT3/5-HT4 receptors (139), GLP-1 receptor agonists (126), tryptophan hydroxylase (121) and DPP-4 (113). Nutrient-sensing GPCRs, including FFAR1, FFAR2/FFAR3, FFAR4, GPR119, TGR5 and the calcium-sensing receptor, appeared from 2000 onwards and expanded mainly after 2010 (Edfalk et al. 2008; Lauffer et al. 2009; Thomas et al. 2009; Mace et al. 2012; Nohr et al. 2013).

The targets showed distinct temporal profiles (Table 6). Serotonergic drugs (16.1% of their articles published in 2018–2025), 5-HT3/5-HT4 receptors (18.0%), ATP-sensitive potassium channels (17.9%), non-nutritive sweeteners (24.4%) and somatostatin analogues (26.5%) were mature or declining topics. In contrast, Piezo2 (81.8%), the farnesoid X receptor (FXR; 64.5%), Toll-like receptors (59.0%), TRPM5/TRPV1 (54.2%), the GIP receptor (52.2%) and FFAR2/FFAR3 (50.6%) were the most recently emerging targets (Bogunovic et al. 2007; Trabelsi et al. 2015; Wang et al. 2017; Alcaino et al. 2018). Disease-context mapping revealed clear therapeutic orientations (Fig. 6b). DPP-4 inhibitors (85%), metformin (84%), GPR119 (83%), GLP-1 receptor agonists (81%), FXR (77%) and the GLP-1 receptor (76%) were mainly studied in the context of type 2 diabetes and glycaemic control. FFAR2/FFAR3 (75%), Toll-like receptors (72%) and olfactory receptors (59%) were predominantly linked to the microbiota and microbial metabolites, the serotonin transporter (66%), 5-HT3/5-HT4 receptors (53%) and tryptophan hydroxylase (51%) to irritable bowel syndrome and motility, and somatostatin analogues (62%) to neuroendocrine tumours. Piezo2 was most often studied in relation to motility and visceral sensation (45%).

Intellectual base

The co-citation network of the 60 most cited references contained 425 links and five clusters (Fig. 7). The largest cluster (28 references) represented incretin physiology and L-cell nutrient

sensing and was anchored by studies on glucose sensing in L cells, GLP-1 biology and incretin-based therapy (Drucker and Nauck 2006; Baggio and Drucker 2007; Holst 2007; Reimann et al. 2008). The second cluster (23 references) captured EEC lineage and identity, including intestinal stem cell and organoid studies, single-cell analyses and EC cell signalling (Barker et al. 2007; Sato et al. 2009; Egerod et al. 2012; Habib et al. 2012; Bellono et al. 2017; Haber et al. 2017; Gehart et al. 2019). Three smaller clusters represented gut taste-signalling machinery (Jang et al. 2007), mucosal serotonin signalling in irritable bowel syndrome (Spiller et al. 2000; Coates et al. 2004) and Drosophila intestinal stem cells (Ohlstein and Spradling 2006).

Discussion

To our knowledge, this study provides the first comprehensive bibliometric map of EEC research and the first systematic quantification of its pharmacological targets. Four main findings emerged. First, the field has grown exponentially for more than four decades and has accelerated since 2010. Second, knowledge production has been led by highly connected research centres in North America and Europe, while China has become a major contributor in recent years. Third, the conceptual structure of the field is organised around three domains, namely incretin and metabolic signalling, serotonin and gut–brain/disease signalling, and EEC development, with current research fronts in the microbiota, organoids, single-cell technologies and the gut–brain axis. Fourth, the pharmacological focus of the field is shifting from established incretin and serotonergic targets towards mechanosensory, microbial metabolite, bile acid and innate immune pathways.

The temporal profile of the literature mirrors the conceptual history of the EEC. Early research was dominated by immunocytochemical descriptions of endocrine cell populations and their hormone content (Sjolund et al. 1983; Eissele et al. 1992). The establishment of EEC cell lines and transgenic reporter models in the 1990s allowed the first mechanistic studies of hormone gene regulation and secretion (Drucker et al. 1994), which is consistent with the early bursts of transgenic mice and pancreas-related terms observed here. The acceleration after 2010 coincided with the identification of primary L-cell sensing mechanisms (Reimann et al. 2008), the availability of incretin-based drugs (Drucker and Nauck 2006) and the emergence of organoid and single-cell technologies (Sato et al. 2009; Grün et al. 2015; Haber et al. 2017). The local citation ranking confirms that the field's core knowledge rests on studies that defined how EECs sense nutrients and how their hormone

repertoire is organised (Jang et al. 2007; Reimann et al. 2008; Egerod et al. 2012; Habib et al. 2012; Tolhurst et al. 2012), while the global citation ranking highlights the wider impact of EEC research on microbiome science and central appetite regulation (Yano et al. 2015; Brierley et al. 2021).

The co-word and co-citation analyses consistently identified incretin physiology as the largest domain. This dominance is readily explained by the therapeutic success of GLP-1 receptor agonists and DPP-4 inhibitors (Drucker and Nauck 2006; Drucker 2018) and by the intense effort to identify L-cell secretagogue receptors as alternative or complementary targets (Edfalk et al. 2008; Lauffer et al. 2009; Thomas et al. 2009; Tolhurst et al. 2012). Our target map extends these observations by showing that most nutrient-sensing GPCRs were studied mainly in metabolic contexts (type 2 diabetes or obesity) and that, with the exception of FFAR2/FFAR3, their share of the literature plateaued or declined after 2017. Selective ligands for FFAR1 and FFAR4, including those reported in this journal (Hara et al. 2009), illustrate the pharmacological maturity of this target class. The more recent rise of the GIP receptor and the sustained interest in the GLP-1 receptor indicate that multi-receptor incretin pharmacology remains an active direction, in which EEC biology continues to provide the physiological rationale (Gribble and Reimann 2019).

The second domain centred on EC cells and serotonin. Altered mucosal serotonin signalling in irritable bowel syndrome (Spiller et al. 2000; Coates et al. 2004) and the development of 5-HT3 and 5-HT4 receptor ligands (Gershon and Tack 2007) defined this area in the 2000s, which explains the strong irritable bowel syndrome burst between 2006 and 2010. Our data show that classic serotonergic drugs and 5-HT3/5-HT4 receptors have since declined in relative terms, whereas tryptophan hydroxylase continued to grow. This shift reflects a reorientation from receptor-level modulation towards the regulation of serotonin synthesis by microbial metabolites (Reigstad et al. 2015; Yano et al. 2015), chemosensory and mechanosensory EC cell mechanisms (Nozawa et al. 2009; Bellono et al. 2017; Alcaino et al. 2018) and serotonin as a systemic signal (Mawe and Hoffman 2013). The emergence of Piezo2 as the most recent target in our dataset is consistent with the identification of mechanosensitive EC cells (Wang et al. 2017; Alcaino et al. 2018) and suggests that mechanotransduction may become a new pharmacological entry point for motility disorders and visceral pain.

The most dynamic research front was the interface between EECs, the gut microbiota and the nervous system. Gut microbiota showed the strongest burst of the entire study period, and

microbiota-related contexts dominated the literature on FFAR2/FFAR3, Toll-like receptors and olfactory receptors. Experimental studies have shown that short-chain fatty acids, bacterial tryptophan catabolites and specific bacterial proteins act directly on EECs (Tolhurst et al. 2012; Ye et al. 2021; Yoon et al. 2021), and that EECs express functional Toll-like receptors (Bogunovic et al. 2007) and odorant receptors that respond to microbial metabolites (Fleischer et al. 2015). Similarly, the rise of FXR together with TGR5 reflects the recognition that bile acids, which are modified by the microbiota, regulate EEC hormone output through both membrane and nuclear receptors (Thomas et al. 2009; Trabelsi et al. 2015; Pathak et al. 2018). The concurrent bursts for the gut–brain axis and the description of neuropod cells, which transmit nutrient signals to vagal neurons within milliseconds (Bohorquez et al. 2015; Kaelberer et al. 2018; Buchanan et al. 2022), indicate that EECs are increasingly viewed as sensory transducers of the gut–brain axis. From a pharmacological perspective, these findings identify microbiota-derived ligands, bile acid receptors and EEC–neuron communication as promising but still underexplored targets.

The third domain, EEC development, has evolved from a predominantly descriptive area into an enabling platform for pharmacology. Intestinal organoids derived from Lgr5-positive stem cells (Barker et al. 2007; Sato et al. 2009) now allow the generation of human L cells and other EEC subtypes (Petersen et al. 2014), and single-cell and real-time differentiation maps have identified regulators of EEC fate (Haber et al. 2017; Gehart et al. 2019; Hickey et al. 2023). The active bursts for organoids, stem cells and single-cell RNA sequencing show that these approaches are still expanding. They are likely to support human-relevant drug screening, the identification of subtype-specific receptors and strategies that increase the number or alter the hormone profile of EECs.

The geographic analysis revealed a field led by the United States with strong European centres in Denmark, the United Kingdom, Germany and Sweden. The leading institutions, including the University of Copenhagen, the University of Toronto and the University of Cambridge, host groups that made foundational contributions to incretin and L-cell research. China has rapidly increased its output, but its mean citations per article remain the lowest among the leading countries and its international collaboration rate is below that of the European centres. Strengthening international collaboration may therefore increase the visibility and impact of emerging contributors, in line with the increasing globalisation of pharmacological research networks (Kumar 2026).

This study has some methodological considerations. The analysis was based on the WoS Core Collection, which offers consistent metadata and complete cited-reference data required for co-citation and local citation analyses (Mongeon and Paul-Hus 2016); single-database designs are standard in bibliometric research, although inclusion of other databases could add regional journals (Abdelwahab et al. 2025). Only English-language original articles were included to ensure a homogeneous corpus of primary research. Citation counts depend on article age, so recent influential studies may be underrepresented in the citation rankings; this was addressed by reporting citations per citable year, local citation scores, trend topics and burst detection. Finally, target mapping relied on a curated dictionary applied to bibliographic fields, which captures the presence rather than the depth of pharmacological investigation; the dictionary and contextual categories were therefore defined from established EEC biology and applied uniformly across periods.

Conclusion

EEC research has grown exponentially over 46 years and has evolved from morphological description to a molecularly defined, interdisciplinary field with direct therapeutic relevance. Incretin and serotonin signalling form the established core of the field, whereas the gut microbiota, organoids, single-cell technologies and the gut–brain axis constitute its current research fronts. The pharmacological target map shows a transition from incretin and classic serotonergic targets towards Piezo2, FXR, Toll-like receptors, TRPM5/TRPV1, the GIP receptor and short-chain fatty acid receptors. These findings support the view of EECs as a druggable sensory platform and can guide future pharmacological studies, research funding and international collaboration in this field.

Author contributions Kemal Yüce: conceptualization, data curation, investigation, writing—original draft. Seçil Nazife Parlak: conceptualization, methodology, formal analysis, visualization, writing—original draft, writing—review and editing, supervision. Hakan Ocak: investigation, validation, writing—review and editing. All authors read and approved the manuscript. The authors declare that all data were generated in-house and that no paper mill was used.

Funding No funding was received for conducting this study.

Data availability The bibliographic records analysed in this study are available from the Web of Science Core Collection using the search strategy described in the Methods. The processed

datasets generated during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

References

Abdelwahab SI, Farasani A, Moshi JM, Alshahrani S, Hassan W (2025) Analysis of bibliometric research featured in Naunyn–Schmiedeberg's Archives of Pharmacology. Naunyn-Schmiedeberg's Arch Pharmacol 398:12781–12787. https://doi.org/10.1007/s00210-025-04190-z

Alcaino C, Knutson KR, Treichel AJ, Yildiz G, Strege PR, Linden DR, Li JH, Leiter AB, Szurszewski JH, Farrugia G, Beyder A (2018) A population of gut epithelial enterochromaffin cells is mechanosensitive and requires Piezo2 to convert force into serotonin release. Proc Natl Acad Sci USA 115(32):E7632–E7641. https://doi.org/10.1073/pnas.1804938115

Aria M, Cuccurullo C (2017) bibliometrix: an R-tool for comprehensive science mapping analysis. J Informetr 11(4):959–975. https://doi.org/10.1016/j.joi.2017.08.007

Baggio LL, Drucker DJ (2007) Biology of incretins: GLP-1 and GIP. Gastroenterology 132(6):2131–2157. https://doi.org/10.1053/j.gastro.2007.03.054

Barker N, van Es JH, Kuipers J, Kujala P, van den Born M, Cozijnsen M, Haegebarth A, Korving J, Begthel H, Peters PJ, Clevers H (2007) Identification of stem cells in small intestine and colon by marker gene Lgr5. Nature 449(7165):1003–1007. https://doi.org/10.1038/nature06196

Bellono NW, Bayrer JR, Leitch DB, Castro J, Zhang CC, O'Donnell TA, Brierley SM, Ingraham HA, Julius D (2017) Enterochromaffin Cells Are Gut Chemosensors that Couple to Sensory Neural Pathways. Cell 170(1):185–198.e16. https://doi.org/10.1016/j.cell.2017.05.034

Blondel VD, Guillaume JL, Lambiotte R, Lefebvre E (2008) Fast unfolding of communities in large networks. J Stat Mech 2008(10):P10008. https://doi.org/10.1088/1742-5468/2008/10/P10008

Bogunovic M, Davé SH, Tilstra JS, Chang DTW, Harpaz N, Xiong HB, Mayer LF, Plevy SE (2007) Enteroendocrine cells express functional Toll-like receptors. Am J Physiol Gastrointest Liver Physiol 292(6):G1770–G1783. https://doi.org/10.1152/ajpgi.00249.2006

Bohorquez DV, Shahid RA, Erdmann A, Kreger AM, Wang Y, Calakos N, Wang F, Liddle RA (2015) Neuroepithelial circuit formed by innervation of sensory enteroendocrine cells. J Clin Invest 125(2):782–786. https://doi.org/10.1172/JCI78361

Bradford SC (1934) Sources of information on specific subjects. Engineering 137:85–86

Brierley DI, Holt MK, Singh A, de Araujo A, McDougle M, Vergara M, Afaghani MH, Lee SJ, Scott K, Maske C, Langhans W, Krause E, de Kloet A, Gribble FM, Reimann F, Rinaman L, de Lartigue G, Trapp S (2021) Central and peripheral GLP-1 systems independently suppress eating. Nat Metab 3(2):258–273. https://doi.org/10.1038/s42255-021-00344-4

Buchanan KL, Rupprecht LE, Kaelberer MM, Sahasrabudhe A, Klein ME, Villalobos JA, Liu WW, Yang A, Gelman J, Park S, Anikeeva P, Bohórquez D (2022) The preference for sugar over sweetener depends on a gut sensor cell. Nat Neurosci 25(2):191–200. https://doi.org/10.1038/s41593-021-00982-7

Chen C (2006) CiteSpace II: detecting and visualizing emerging trends and transient patterns in scientific literature. J Am Soc Inf Sci Technol 57(3):359–377. https://doi.org/10.1002/asi.20317

Coates MD, Mahoney CR, Linden DR, Sampson JE, Chen J, Blaszyk H, Crowell MD, Sharkey KA, Gershon MD, Mawe GM, Moses PL (2004) Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and irritable bowel syndrome. Gastroenterology 126(7):1657–1664. https://doi.org/10.1053/j.gastro.2004.03.013

Cobo MJ, López-Herrera AG, Herrera-Viedma E, Herrera F (2011) An approach for detecting, quantifying, and visualizing the evolution of a research field: a practical application to the Fuzzy Sets Theory field. J Informetr 5(1):146–166. https://doi.org/10.1016/j.joi.2010.10.002

Date Y, Kojima M, Hosoda H, Sawaguchi A, Mondal MS, Suganuma T, Matsukura S, Kangawa K, Nakazato M (2000) Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. Endocrinology 141(11):4255–4261. https://doi.org/10.1210/en.141.11.4255

Donthu N, Kumar S, Mukherjee D, Pandey N, Lim WM (2021) How to conduct a bibliometric analysis: an overview and guidelines. J Bus Res 133:285–296. https://doi.org/10.1016/j.jbusres.2021.04.070

Drucker DJ (2018) Mechanisms of action and therapeutic application of glucagon-like peptide-1. Cell Metab 27(4):740–756. https://doi.org/10.1016/j.cmet.2018.03.001

Drucker DJ, Nauck MA (2006) The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 368(9548):1696–1705. https://doi.org/10.1016/S0140-6736(06)69705-5

Drucker DJ, Jin TR, Asa SL, Young TA, Brubaker PL (1994) Activation of proglucagon gene transcription by protein kinase-A in a novel mouse enteroendocrine cell line. Mol Endocrinol 8(12):1646–1655. https://doi.org/10.1210/me.8.12.1646

Edfalk S, Steneberg P, Edlund H (2008) Gpr40 is expressed in enteroendocrine cells and mediates free fatty acid stimulation of incretin secretion. Diabetes 57(9):2280–2287. https://doi.org/10.2337/db08-0307

Egerod KL, Engelstoft MS, Grunddal KV, Nohr MK, Secher A, Sakata I, Pedersen J, Windelov JA, Füchtbauer EM, Olsen J, Sundler F, Christensen JP, Wierup N, Olsen JV, Holst JJ, Zigman JM, Poulsen SS, Schwartz TW (2012) A Major Lineage of Enteroendocrine Cells Coexpress CCK, Secretin, GIP, GLP-1, PYY, and Neurotensin but Not Somatostatin. Endocrinology 153(12):5782–5795. https://doi.org/10.1210/en.2012-1595

Egghe L (2006) Theory and practise of the g-index. Scientometrics 69(1):131–152. https://doi.org/10.1007/s11192-006-0144-7

Eissele R, Goke R, Willemer S, Harthus HP, Vermeer H, Arnold R, Goke B (1992) Glucagon-like peptide-1 cells in the gastrointestinal tract and pancreas of rat, pig and man. Eur J Clin Invest 22(4):283–291. https://doi.org/10.1111/j.1365-2362.1992.tb01464.x

Fleischer J, Bumbalo R, Bautze V, Strotmann J, Breer H (2015) Expression of odorant receptor Olfr78 in enteroendocrine cells of the colon. Cell Tissue Res 361(3):697–710. https://doi.org/10.1007/s00441-015-2165-0

Gehart H, van Es JH, Hamer K, Beumer J, Kretzschmar K, Dekkers JF, Rios A, Clevers H (2019) Identification of Enteroendocrine Regulators by Real-Time Single-Cell Differentiation Mapping. Cell 176(5):1158–1173.e16. https://doi.org/10.1016/j.cell.2018.12.029

Gershon MD, Tack J (2007) The serotonin signaling system: from basic understanding to drug development for functional GI disorders. Gastroenterology 132(1):397–414. https://doi.org/10.1053/j.gastro.2006.11.002

Gribble FM, Reimann F (2016) Enteroendocrine cells: chemosensors in the intestinal epithelium. Annu Rev Physiol 78:277–299. https://doi.org/10.1146/annurev-physiol-021115-105439

Gribble FM, Reimann F (2019) Function and mechanisms of enteroendocrine cells and gut hormones in metabolism. Nat Rev Endocrinol 15(4):226–237. https://doi.org/10.1038/s41574-019-0168-8

Grün D, Lyubimova A, Kester L, Wiebrands K, Basak O, Sasaki N, Clevers H, van Oudenaarden A (2015) Single-cell messenger RNA sequencing reveals rare intestinal cell types. Nature 525(7568):251–255. https://doi.org/10.1038/nature14966

Haber AL, Biton M, Rogel N, Herbst RH, Shekhar K, Smillie C, Burgin G, Delorey TM, Howitt MR, Katz Y, Tirosh I, Beyaz S, Dionne D, Zhang M, Raychowdhury R, Garrett WS, Rozenblatt-Rosen

526 O, Shi HN, Yilmaz O, Xavier RJ, Regev A (2017) A single-cell survey of the small intestinal
527 epithelium. Nature 551(7680):333–339. https://doi.org/10.1038/nature24489

528 Habib AM, Richards P, Cairns LS, Rogers GJ, Bannon CAM, Parker HE, Morley TCE, Yeo GSH,
529 Reimann F, Gribble FM (2012) Overlap of Endocrine Hormone Expression in the Mouse Intestine
530 Revealed by Transcriptional Profiling and Flow Cytometry. Endocrinology 153(7):3054–3065.
531 https://doi.org/10.1210/en.2011-2170

532 Hara T, Hirasawa A, Sun Q, Sadakane K, Itsubo C, Iga T, Adachi T, Koshimizu T, Hashimoto T,
533 Asakawa Y, Tsujimoto G (2009) Novel selective ligands for free fatty acid receptors GPR120 and
534 GPR40. Naunyn-Schmiedeberg's Arch Pharmacol 380(3):247–255.
535 https://doi.org/10.1007/s00210-009-0425-9

536 Hickey JW, Becker WR, Nevins SA, Horning A, Perez AE, Zhu CC, Zhu BK, Wei B, Chiu R, Chen
537 DC, Cotter DL, Esplin ED, Weimer AK, Caraccio C, Venkataraaman V, Schürch CM, Black S,
538 Brbic M, Cao KD, Chen SX, Zhang WR, Monte E, Zhang NR, Ma ZM, Leskovec J, Zhang ZY,
539 Lin S, Longacre T, Plevritis SK, Lin Y, Nolan GP, Greenleaf WJ, Snyder M (2023) Organization
540 of the human intestine at single-cell resolution. Nature 619(7970):572–584.
541 https://doi.org/10.1038/s41586-023-05915-x

542 Hirsch JE (2005) An index to quantify an individual's scientific research output. Proc Natl Acad Sci
543 USA 102(46):16569–16572. https://doi.org/10.1073/pnas.0507655102

544 Holst JJ (2007) The physiology of glucagon-like peptide 1. Physiol Rev 87(4):1409–1439.
545 https://doi.org/10.1152/physrev.00034.2006

546 Jang HJ, Kokrashvili Z, Theodorakis MJ, Carlson OD, Kim BJ, Zhou J, Kim HH, Xu X, Chan SL,
547 Juhaszova M, Bernier M, Mosinger B, Margolskee RF, Egan JM (2007) Gut-expressed gustducin
548 and taste receptors regulate secretion of glucagon-like peptide-1. Proc Natl Acad Sci USA
549 104(38):15069–15074. https://doi.org/10.1073/pnas.0706890104

550 Kaelberer MM, Buchanan KL, Klein ME, Barth BB, Montoya MM, Shen XL, Bohórquez DV (2018)
551 A gut-brain neural circuit for nutrient sensory transduction. Science 361(6408):eaat5236.
552 https://doi.org/10.1126/science.aat5236

553 Kleinberg J (2003) Bursty and hierarchical structure in streams. Data Min Knowl Discov 7(4):373–
554 397. https://doi.org/10.1023/A:1024940629314

555 Kumar N (2026) Pharmacology through the lens of bibliometrics: global trends, research hotspots, and
556 collaborations (2015–2026). Naunyn-Schmiedeberg's Arch Pharmacol 399:17451–17467.
557 https://doi.org/10.1007/s00210-026-05470-y

558 Lauffer LM, Lakoubov R, Brubaker PL (2009) GPR119 Is Essential for Oleoylethanolamide-Induced
559 Glucagon-Like Peptide-1 Secretion From the Intestinal Enteroendocrine L-Cell. Diabetes
560 58(5):1058–1066. https://doi.org/10.2337/db08-1237

561 Lotka AJ (1926) The frequency distribution of scientific productivity. J Wash Acad Sci 16(12):317–
562 323

563 Mace OJ, Schindler M, Patel S (2012) The regulation of K- and L-cell activity by GLUT2 and the
564 calcium-sensing receptor CasR in rat small intestine. J Physiol 590(12):2917–2936.
565 https://doi.org/10.1113/jphysiol.2011.223800

566 Mawe GM, Hoffman JM (2013) Serotonin signalling in the gut—functions, dysfunctions and
567 therapeutic targets. Nat Rev Gastroenterol Hepatol 10(8):473–486.
568 https://doi.org/10.1038/nrgastro.2013.105

569 Mongeon P, Paul-Hus A (2016) The journal coverage of Web of Science and Scopus: a comparative
570 analysis. Scientometrics 106(1):213–228. https://doi.org/10.1007/s11192-015-1765-5

571 Nohr MK, Pedersen MH, Gille A, Egerod KL, Engelstoft MS, Husted AS, Sichlau RM, Grunddal KV,
572 Poulsen SS, Han S, Jones RM, Offermanns S, Schwartz TW (2013) GPR41/FFAR3 and
573 GPR43/FFAR2 as Cosensors for Short-Chain Fatty Acids in Enteroendocrine Cells vs FFAR3 in
574 Enteric Neurons and FFAR2 in Enteric Leukocytes. Endocrinology 154(10):3552–3564.
575 https://doi.org/10.1210/en.2013-1142

576 Nozawa K, Kawabata-Shoda E, Doihara H, Kojima R, Okada H, Mochizuki S, Sano Y, Inamura K,
577 Matsushime H, Koizumi T, Yokoyama T, Ito H (2009) TRPA1 regulates gastrointestinal motility
578 through serotonin release from enterochromaffin cells. Proc Natl Acad Sci USA 106(9):3408–
579 3413. https://doi.org/10.1073/pnas.0805323106

580 Ohlstein B, Spradling A (2006) The adult Drosophila posterior midgut is maintained by pluripotent
581 stem cells. Nature 439(7075):470–474. https://doi.org/10.1038/nature04333

582 Pathak P, Xie C, Nichols RG, Ferrell JM, Boehme S, Krausz KW, Patterson AD, Gonzalez FJ, Chiang
583 JYL (2018) Intestine farnesoid X receptor agonist and the gut microbiota activate G-protein bile
584 acid receptor-1 signaling to improve metabolism. Hepatology 68(4):1574–1588.
585 https://doi.org/10.1002/hep.29857

586 Petersen N, Reimann F, Bartfeld S, Farin HF, Ringnalda FC, Vries RGJ, van den Brink S, Clevers H,
587 Gribble FM, de Koning EJP (2014) Generation of L Cells in Mouse and Human Small Intestine
588 Organoids. Diabetes 63(2):410–420. https://doi.org/10.2337/db13-0991

589 Reigstad CS, Salmonson CE, Rainey JF, Szurszewski JH, Linden DR, Sonnenburg JL, Farrugia G,
590 Kashyap PC (2015) Gut microbes promote colonic serotonin production through an effect of short-
591 chain fatty acids on enterochromaffin cells. FASEB J 29(4):1395–1403.
592 https://doi.org/10.1096/fj.14-259598

593 Reimann F, Habib AM, Tolhurst G, Parker HE, Rogers GJ, Gribble FM (2008) Glucose Sensing in L
594 Cells: A Primary Cell Study. Cell Metab 8(6):532–539. https://doi.org/10.1016/j.cmet.2008.11.002

595 Sato T, Vries RG, Snippert HJ, van de Wetering M, Barker N, Stange DE, van Es JH, Abo A, Kujala
596 P, Peters PJ, Clevers H (2009) Single Lgr5 stem cells build crypt-villus structures in vitro without
597 a mesenchymal niche. Nature 459(7244):262–265. https://doi.org/10.1038/nature07935

598 Sjolund K, Sanden G, Hakanson R, Sundler F (1983) Endocrine cells in human intestine: an
599 immunocytochemical study. Gastroenterology 85(5):1120–1130

600 Small H (1973) Co-citation in the scientific literature: a new measure of the relationship between two
601 documents. J Am Soc Inf Sci 24(4):265–269. https://doi.org/10.1002/asi.4630240406

602 Spiller RC, Jenkins D, Thornley JP, Hebden JM, Wright T, Skinner M, Neal KR (2000) Increased
603 rectal mucosal enteroendocrine cells, T lymphocytes, and increased gut permeability following
604 acute Campylobacter enteritis and in post-dysenteric irritable bowel syndrome. Gut 47(6):804–
605 811. https://doi.org/10.1136/gut.47.6.804

606 Thomas C, Gioiello A, Noriega L, Strehle A, Oury J, Rizzo G, Macchiarulo A, Yamamoto H, Mataki
607 C, Pruzanski M, Pellicciari R, Auwerx J, Schoonjans K (2009) TGR5-Mediated Bile Acid Sensing
608 Controls Glucose Homeostasis. Cell Metab 10(3):167–177.
609 https://doi.org/10.1016/j.cmet.2009.08.001

610 Tolhurst G, Heffron H, Lam YS, Parker HE, Habib AM, Diakogiannaki E, Cameron J, Grosse J,
611 Reimann F, Gribble FM (2012) Short-Chain Fatty Acids Stimulate Glucagon-Like Peptide-1
612 Secretion via the G-Protein-Coupled Receptor FFAR2. Diabetes 61(2):364–371.
613 https://doi.org/10.2337/db11-1019

614 Trabelsi MS, Daoudi M, Prawitt J, Ducastel S, Touche V, Sayin SI, Perino A, Brighton CA, Sebti Y,
615 Kluza J, Briand O, Dehondt H, Vallez E, Dorchies E, Baud G, Spinelli V, Hennuyer N, Caron S,
616 Bantubungi K, Caiazzo R, Reimann F, Marchetti P, Lefebvre P, Bäckhed F, Gribble FM,
617 Schoonjans K, Pattou F, Tailleux A, Staels B, Lestavel S (2015) Farnesoid X receptor inhibits
618 glucagon-like peptide-1 production by enteroendocrine L cells. Nat Commun 6:7629.
619 https://doi.org/10.1038/ncomms8629

620 Wang F, Knutson K, Alcaino C, Linden DR, Gibbons SJ, Kashyap P, Grover M, Oeckler R, Gottlieb
621 PA, Li HJ, Leiter AB, Farrugia G, Beyder A (2017) Mechanosensitive ion channel Piezo2 is
622 important for enterochromaffin cell response to mechanical forces. J Physiol 595(1):79–91.
623 https://doi.org/10.1113/JP272718

624 Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, Nagler CR, Ismagilov RF, Mazmanian SK,
625 Hsiao EY (2015) Indigenous Bacteria from the Gut Microbiota Regulate Host Serotonin
626 Biosynthesis. Cell 161(2):264–276. https://doi.org/10.1016/j.cell.2015.02.047

627 Ye LH, Bae M, Cassilly CD, Jabba S, Thorpe DW, Martin AM, Lu HY, Wang JH, Thompson JD,
628 Lickwar CR, Poss KD, Keating DJ, Jordt SE, Clardy J, Liddle RA, Rawls JF (2021)

Enteroendocrine cells sense bacterial tryptophan catabolites to activate enteric and vagal neuronal pathways. Cell Host Microbe 29(2):179–196.e9. https://doi.org/10.1016/j.chom.2020.11.011

Yoon HS, Cho CH, Yun MS, Jang SJ, You HJ, Kim JH, Han D, Cha KH, Moon SH, Lee K, Kim YJ, Lee SJ, Nam TW, Ko G (2021) Akkermansia muciniphila secretes a glucagon-like peptide-1-inducing protein that improves glucose homeostasis and ameliorates metabolic disease in mice. Nat Microbiol 6(5):563–573. https://doi.org/10.1038/s41564-021-00880-5

Zupic I, Čater T (2015) Bibliometric methods in management and organization. Organ Res Methods 18(3):429–472. https://doi.org/10.1177/1094428114562629

Tables

Table 1 Main characteristics of the enteroendocrine cell research dataset (1980–2025)

Indicator	Value
Timespan	1980–2025
Sources (journals and books)	984
Articles	3,652
Annual growth rate (%)	6.90
Mean article age (years)	13.9
Total citations	206,196
Mean citations per article	56.46
h-index of the dataset	190
Distinct cited references	93,777
Keywords Plus	6,834
Author keywords	5,453
Authors	16,093
Authors of single-authored articles	120
Single-authored articles	142
Co-authors per article	6.70
International co-authorship (%)	25.79
Contributing countries	89

Mean article age was calculated relative to 2026. International co-authorship refers to articles with author affiliations in at least two countries.

Table 2 The ten most productive countries (a) and institutions (b)

(a) Country	Articles	Citations	Citations per article	SCP	MCP	MCP (%)
USA	1,129	94,673	83.9	654	200	23.4
Japan	428	21,534	50.3	302	40	11.7
United Kingdom	404	38,234	94.6	194	100	34.0
China	386	11,309	29.3	277	53	16.1
Canada	290	19,737	68.1	148	67	31.2
Germany	241	15,531	64.4	92	46	33.3
Denmark	221	17,929	81.1	81	60	42.6
France	174	13,003	74.7	71	40	36.0
Sweden	167	9,243	55.3	59	37	38.5
Australia	150	8,536	56.9	63	38	37.6

Articles and citations are based on all author affiliations; SCP and MCP are based on the corresponding-author country. SCP, single-country publications; MCP, multiple-country publications.

(b) Institution	Country	Articles	Citations	Citations per article
University of Copenhagen	Denmark	177	12,088	68.3
University of Toronto	Canada	116	9,214	79.4
University of Cambridge	United Kingdom	74	11,181	151.1
University of California, Los Angeles	USA	61	4,645	76.1
Hokkaido University	Japan	50	1,887	37.7
Addenbrooke's Hospital	United Kingdom	48	8,440	175.8
Baylor College of Medicine	USA	45	3,889	86.4
University of Melbourne	Australia	43	2,552	59.3
University of Michigan	USA	37	2,409	65.1
Columbia University	USA	37	4,008	108.3

647 Table 3 The ten most productive journals

Rank	Journal	Articles	Citations	h-index	First article
1	American Journal of Physiology-Gastrointestinal and Liver Physiology	124	7,475	51	1994
2	Endocrinology	97	9,760	49	1986
3	PLOS ONE	83	4,534	35	2008
4	Gastroenterology	71	9,408	54	1981
5	Neurogastroenterology and Motility	54	2,584	28	1996
6	Diabetes	52	8,592	38	1995
7	Cell and Tissue Research	50	1,830	25	1981
8	Biochemical and Biophysical Research Communications	47	2,428	20	1995
9	Scientific Reports	44	1,710	20	2015
10	Peptides	43	1,060	20	1985

648 All ten journals belong to Bradford zone 1. Citations and h-index refer to articles in the dataset.

649 Table 4 The ten most productive authors and their impact indicators

Rank	Author	Articles	Citations	h-index	g-index	m-index	First article
1	Holst JJ	112	8,275	49	90	1.63	1996
2	Reimann F	101	16,894	53	101	2.21	2002
3	Gribble FM	89	16,055	50	89	2.08	2002
4	Brubaker PL	49	3,998	35	49	1.25	1998
5	Drucker DJ	47	4,496	34	47	1.13	1996
6	Hartmann B	41	2,090	22	41	0.79	1998
7	Hira T	34	866	18	29	0.78	2003
8	Li J	31	1,137	17	31	1.13	2011
9	Schwartz TW	30	2,845	24	30	1.71	2012
10	El-Salhy M	28	711	16	26	0.64	2001

650 Indicators were calculated within the dataset; the m-index is the h-index divided by the number of years since the author's
651 first article in the dataset.

652 Table 5 The ten most locally cited articles

Rank	Article	Title	Journal	LCS	GCS
1	Reimann et al. (2008)	Glucose Sensing in L Cells: A Primary Cell Study	Cell Metab	250	626
2	Tolhurst et al. (2012)	Short-Chain Fatty Acids Stimulate Glucagon-Like Peptide-1 Secretion via the G-Protein-Coupled Receptor FFAR2	Diabetes	160	2,043
3	Jang et al. (2007)	Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1	Proc Natl Acad Sci USA	159	831
4	Habib et al. (2012)	Overlap of Endocrine Hormone Expression in the Mouse Intestine Revealed by Transcriptional Profiling and Flow Cytometry	Endocrinology	155	331
5	Eissele et al. (1992)	Glucagon-like peptide-1 cells in the gastrointestinal tract and pancreas of rat, pig and man	Eur J Clin Invest	140	550
6	Sjolund et al. (1983)	Endocrine cells in human intestine: an immunocytochemical study	Gastroenterology	136	461
7	Drucker et al. (1994)	Activation of proglucagon gene transcription by protein kinase-A in a novel mouse enteroendocrine cell line	Mol Endocrinol	132	248
8	Egerod et al. (2012)	A Major Lineage of Enteroendocrine Cells Coexpress CCK, Secretin, GIP, GLP-1, PYY, and Neurotensin but Not Somatostatin	Endocrinology	130	279
9	Coates et al. (2004)	Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and irritable bowel syndrome	Gastroenterology	116	622
10	Bellono et al. (2017)	Enterochromaffin Cells Are Gut Chemosensors that Couple to Sensory Neural Pathways	Cell	111	757

653 LCS, local citation score (citations from articles in the dataset); GCS, global citation score (WoS Core Collection citations at
654 retrieval).

655 Table 6 Pharmacological targets and drug classes in enteroendocrine cell research

Class	Target / drug class	Articles	First year	Median year	2018–2025 (%)	Leading context (%)
Nutrient-sensing GPCRs	FFAR1 (GPR40)	76	2005	2017	48.7	Type 2 diabetes/glycaemia (62)
	FFAR2/FFAR3 (GPR43/GPR41)	87	2006	2018	50.6	Microbiota/metabolites (75)
	FFAR4 (GPR120)	64	2005	2015.5	34.4	Type 2 diabetes/glycaemia (53)
	GPR119	70	2008	2016	42.9	Type 2 diabetes/glycaemia (83)
	TGR5 (GPBAR1)	83	2005	2017	47.0	Type 2 diabetes/glycaemia (67)
	CaSR / GPRC6A	61	2000	2017	47.5	Obesity/energy balance (51)
	Taste receptors (T1R/T2R)	151	2002	2015	37.7	Obesity/energy balance (38)
	Olfactory receptors	29	2007	2017	48.3	Microbiota/metabolites (59)
Ion channels & mechanosensors	TRPA1	47	2009	2016	40.4	IBS/motility/visceral pain (36)
	Piezo2	11	2017	2023	81.8	IBS/motility/visceral pain (45)
	KATP channel	28	1998	2014	17.9	Type 2 diabetes/glycaemia (68)
	TRPM5 / TRPV1	24	2006	2018	54.2	Type 2 diabetes/glycaemia; IBS/motility/visceral pain (25)
Nutrient transporters	SGLT1 (SLC5A1)	57	2005	2016	33.3	Type 2 diabetes/glycaemia (47)
	PEPT1 (SLC15A1)	13	2005	2015	38.5	Obesity/energy balance; Type 2 diabetes/glycaemia (23)
Serotonergic machinery	TPH (TPH1)	121	1983	2017	47.9	IBS/motility/visceral pain (51)
	SERT (SLC6A4)	95	1996	2013	28.4	IBS/motility/visceral pain (66)
	5-HT3 / 5-HT4 receptors	139	1988	2009	18.0	IBS/motility/visceral pain (53)
Hormone receptors & degradation	GLP-1R	201	1992	2016	40.3	Type 2 diabetes/glycaemia (76)
	GIPR	23	2007	2019	52.2	Type 2 diabetes/glycaemia (70)
	CCK1R / Y2R / GHSR	32	1998	2014.5	37.5	Obesity/energy balance (62)
	DPP-4	113	1999	2015	37.2	Type 2 diabetes/glycaemia (76)
Nuclear & other receptors	FXR (NR1H4)	31	2008	2020	64.5	Type 2 diabetes/glycaemia (77)
	TLRs	39	2006	2019	59.0	Microbiota/metabolites (72)
Drugs & drug classes	GLP-1R agonists	126	2002	2017	49.2	Type 2 diabetes/glycaemia (81)
	DPP-4 inhibitors	68	2004	2015.5	33.8	Type 2 diabetes/glycaemia (85)
	Metformin	32	2000	2016	37.5	Type 2 diabetes/glycaemia (84)
	SGLT inhibitors	15	1997	2015	26.7	Type 2 diabetes/glycaemia (53)
	Somatostatin analogues	34	1992	2009	26.5	Neuroendocrine tumours (62)
	Serotonergic drugs	87	1980	2008	16.1	IBS/motility/visceral pain (47)
	Bile acid-based agents	33	1995	2016	42.4	Type 2 diabetes/glycaemia (70)
	Non-nutritive sweeteners	45	2007	2013	24.4	Obesity/energy balance; Type 2 diabetes/glycaemia

(40)

Articles were identified by target-specific terms in titles, abstracts, author keywords and Keywords Plus. 2018–2025 (%), proportion of the target's articles published in 2018–2025; leading context, the disease or biological context most frequently co-mentioned with the target (ties are listed together) and the percentage of target articles mentioning it. 5-HT, 5-hydroxytryptamine; CaSR, calcium-sensing receptor; DPP-4, dipeptidyl peptidase-4; FFAR, free fatty acid receptor; FXR, farnesoid X receptor; GHSR, growth hormone secretagogue receptor; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP-1R, glucagon-like peptide-1 receptor; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; KATP, ATP-sensitive potassium; SERT, serotonin transporter; SGLT, sodium–glucose cotransporter; TGR5, Takeda G protein-coupled receptor 5; TLRs, Toll-like receptors; TPH, tryptophan hydroxylase; TRP, transient receptor potential.

Figure legends

Fig. 1 Flow diagram of data retrieval, screening and analysis.

Fig. 2 Publication and citation trends of enteroendocrine cell research, 1980–2025. **a** Annual number of articles; the dashed line shows the exponential fit, and shaded and unshaded bands mark the four study periods. **b** Mean citations per article per citable year by publication year.

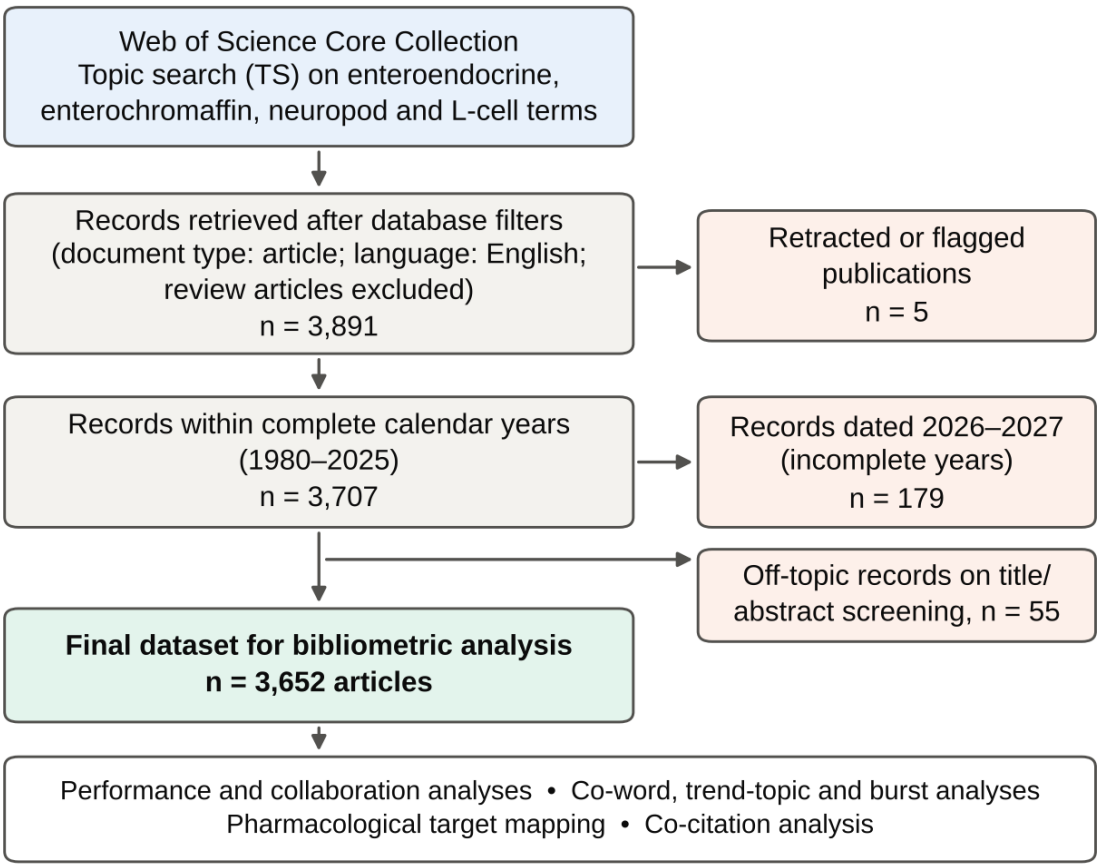
Fig. 3 Country contributions and international collaboration. **a** The 15 most productive countries ranked by all-author article counts; bars show corresponding-author articles split into single-country (SCP) and multiple-country publications (MCP). **b** Collaboration network of the 20 most productive countries; node size is proportional to the number of articles and edge width to the number of co-authored articles (links with at least five articles are shown).

Fig. 4 Co-occurrence network of author keywords. The network includes 67 normalised author keywords connected by at least three co-occurrences. Node size is proportional to keyword frequency, edge width to co-occurrence strength, and colours indicate clusters identified with the Louvain algorithm.

Fig. 5 Thematic evolution and research bursts. **a** Trend topics: dots indicate the median publication year of each keyword (author keywords and Keywords Plus, at least 12 occurrences), bars the interquartile range, and dot size keyword frequency. **b** The 25 keywords with the strongest bursts (Kleinberg algorithm, 1991–2025); red segments show the burst period, grey segments the remaining period, and numbers the burst strength.

Fig. 6 Pharmacological target landscape of enteroendocrine cell research. **a** Share of articles in each period that mention each target or drug class (%); for 1980–1999, values are based predominantly on titles and keywords. **b** Percentage of articles on each target that also mention each disease or biological context. Rows are grouped by target class. T2D, type 2 diabetes; IBS, irritable bowel syndrome; IBD, inflammatory bowel disease.

Fig. 7 Co-citation network of the 60 most frequently cited references. Links indicate at least ten co-citations; node size is proportional to citation frequency in the dataset, and colours indicate clusters identified with the Louvain algorithm. Labels show the first author and publication year of the cited reference.



694

695 **Fig. 1**

696

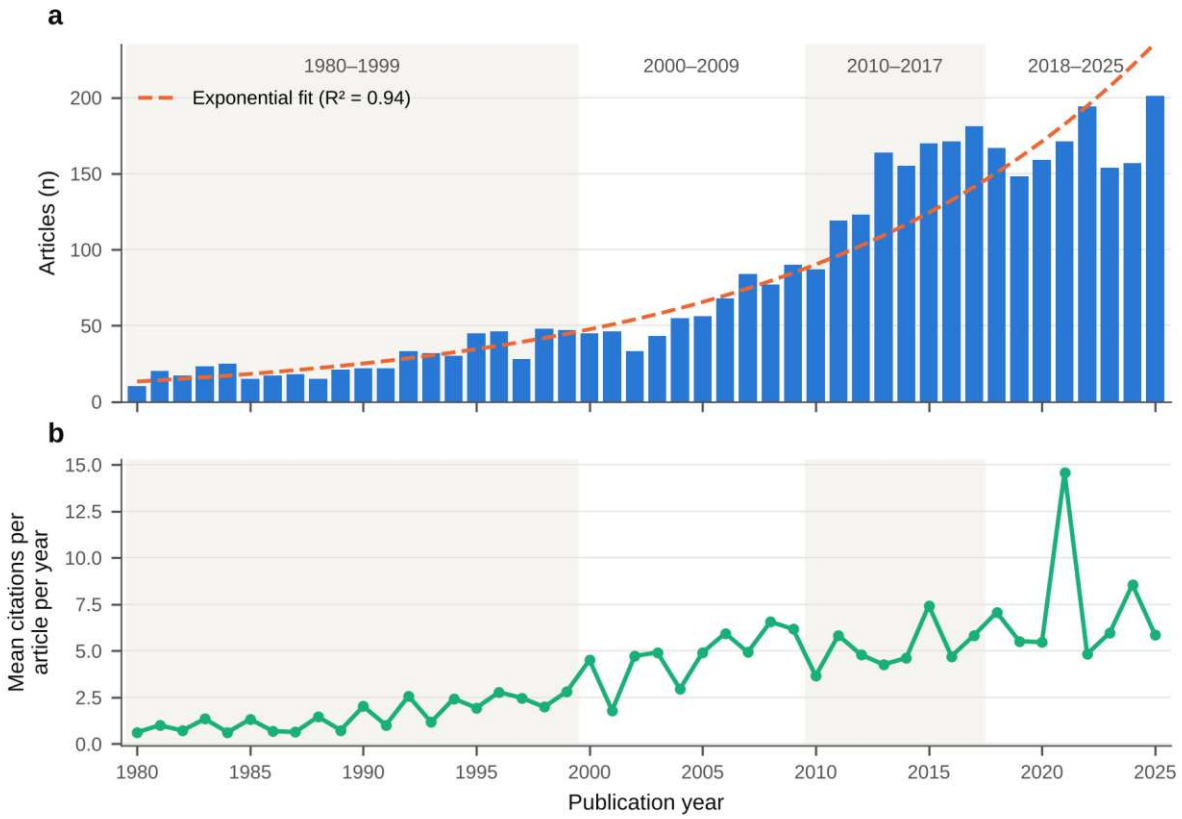

a
1980–1999
2000–2009
2010–2017
2018–2025
Exponential fit (R² = 0.94)
Articles (n)
200
150
100
50
0
b
Mean citations per article per year
15.0
12.5
10.0
7.5
5.0
2.5
0.0
1980
1985
1990
1995
2000
2005
2010
2015
2020
2025
Publication year

Fig. 2

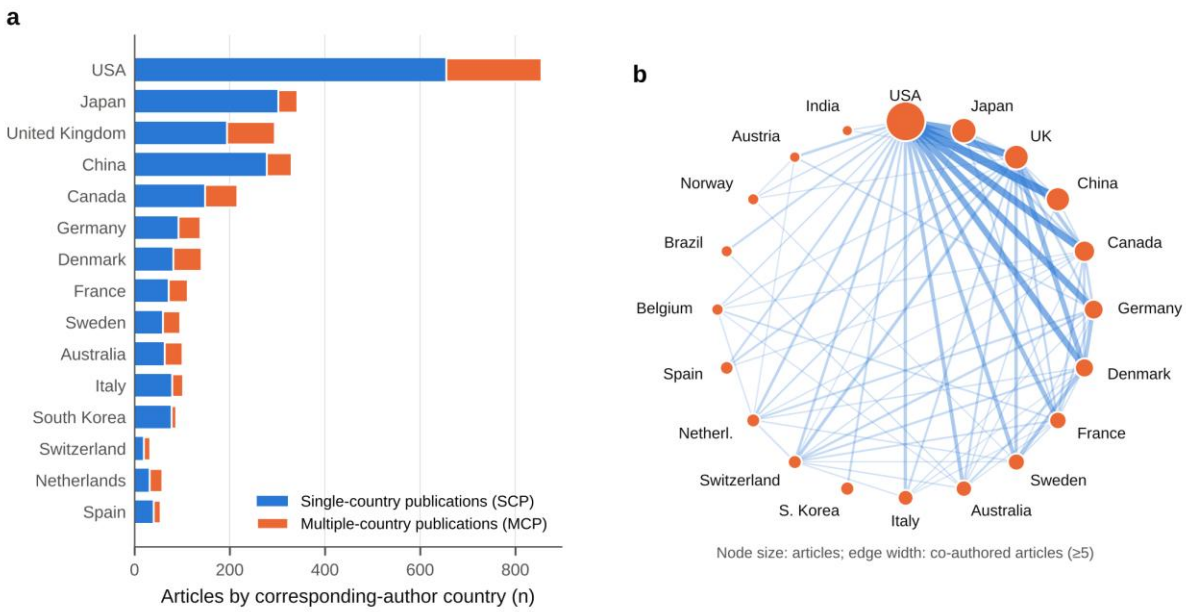

a
USA
Japan
United Kingdom
China
Canada
Germany
Denmark
France
Sweden
Australia
Italy
South Korea
Switzerland
Netherlands
Spain
Single-country publications (SCP)
Multiple-country publications (MCP)
0
200
400
600
800
Articles by corresponding-author country (n)
b
India
USA
Japan
Austria
UK
Norway
China
Brazil
Canada
Belgium
Germany
Spain
Denmark
Netherl.
France
Switzerland
Sweden
S. Korea
Italy
Australia
Node size: articles; edge width: co-authored articles (≥5)

Fig. 3

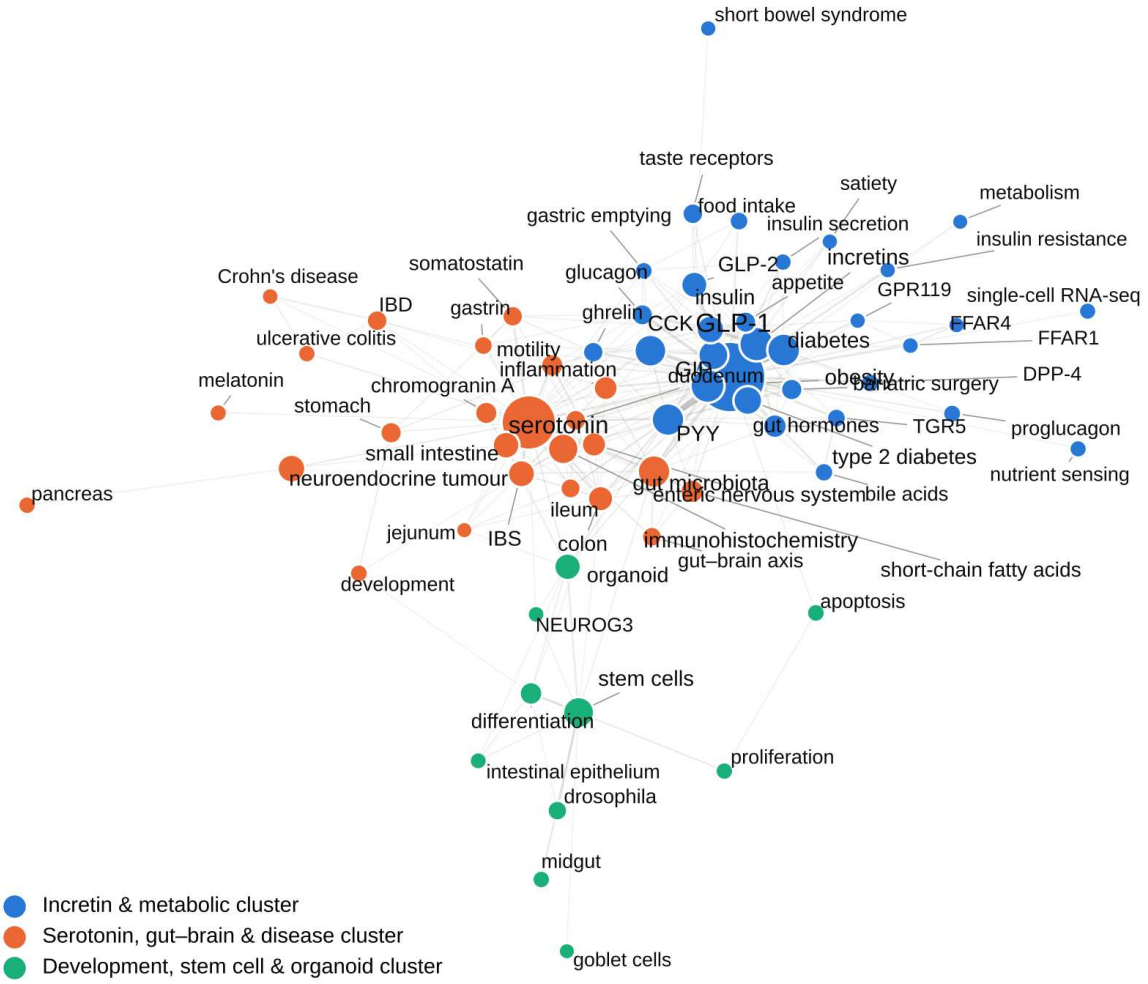
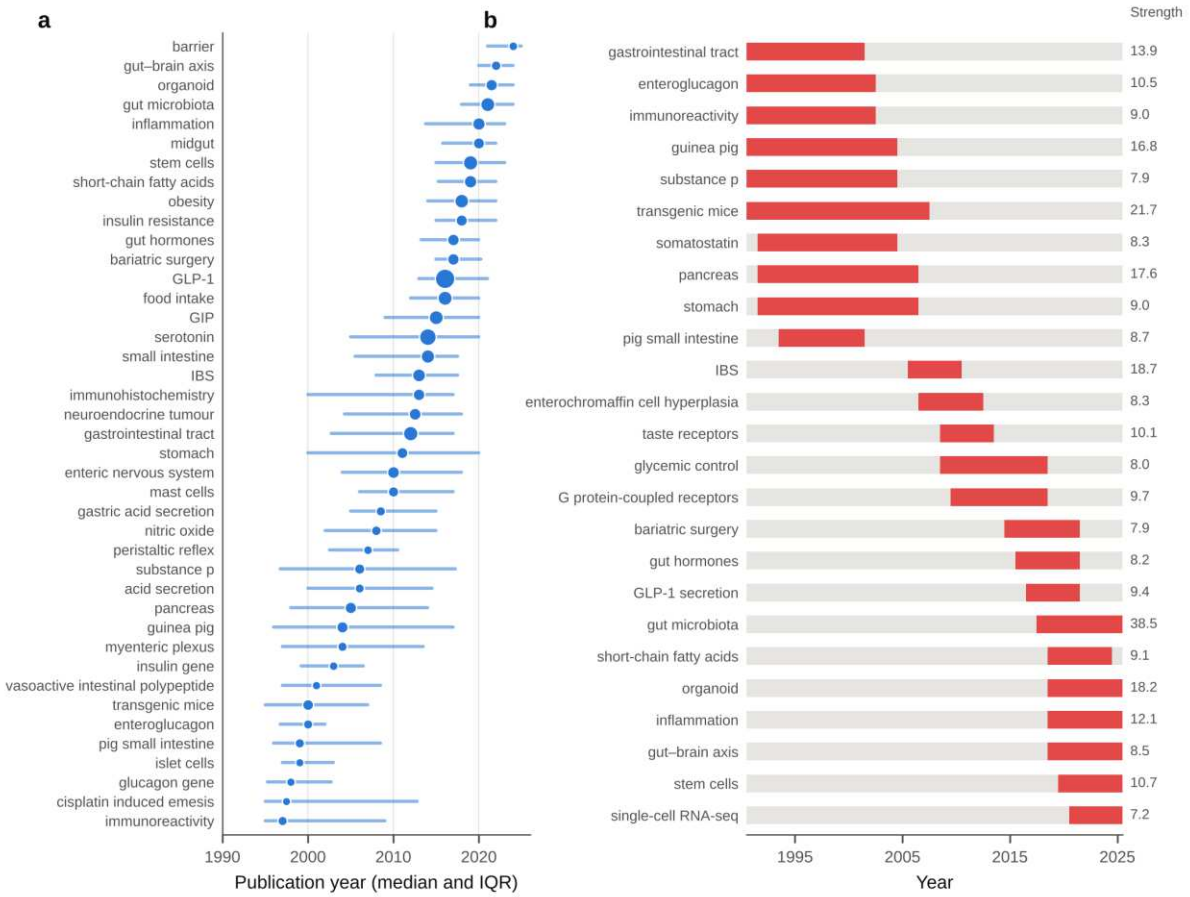

short bowel syndrome
taste receptors
satiety
metabolism
food intake
gastric emptying
insulin secretion
insulin resistance
somatostatin
glucagon
GLP-2
incretins
Crohn's disease
appetite
GPR119
single-cell RNA-seq
IBD
gastrin
ghrelin
insulin
CCK
GLP-1
FFAR4
ulcerative colitis
motility
diabetes
FFAR1
inflammation
GIP
duodenum
obesity
DPP-4
melatonin
chromogranin A
bariatric surgery
stomach
serotonin
PYY
gut hormones
TGR5
proglucagon
small intestine
type 2 diabetes
nutrient sensing
neuroendocrine tumour
gut microbiota
pancreas
enteric nervous systemile acids
ileum
jejunum
IBS
colon
immunohistochemistry
gut–brain axis
short-chain fatty acids
development
organoid
apoptosis
NEUROG3
stem cells
differentiation
proliferation
intestinal epithelium
drosophila
midgut
Incretin & metabolic cluster
Serotonin, gut–brain & disease cluster
Development, stem cell & organoid cluster
goblet cells

Fig. 4



706

707 **Fig. 5**

708

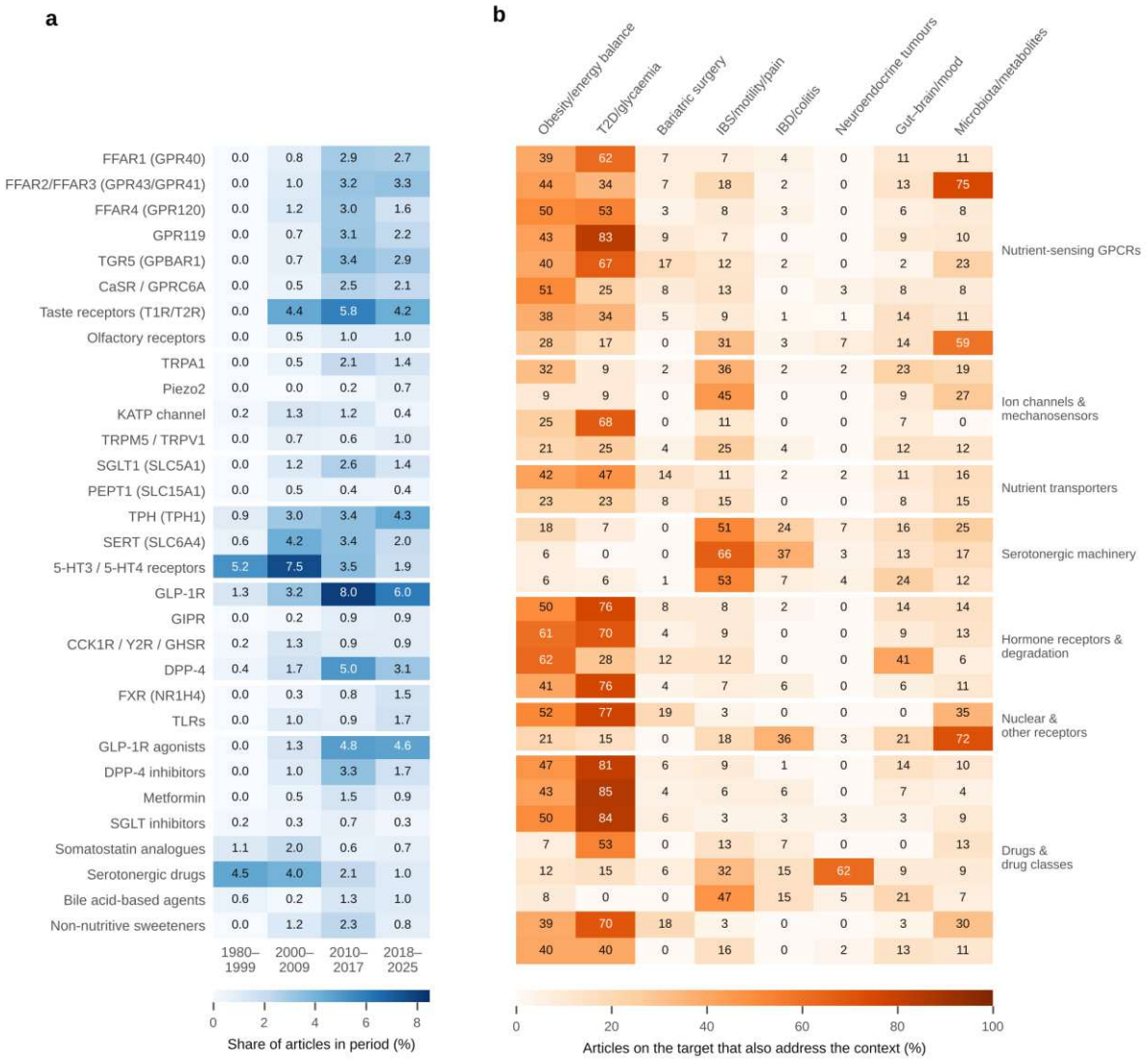
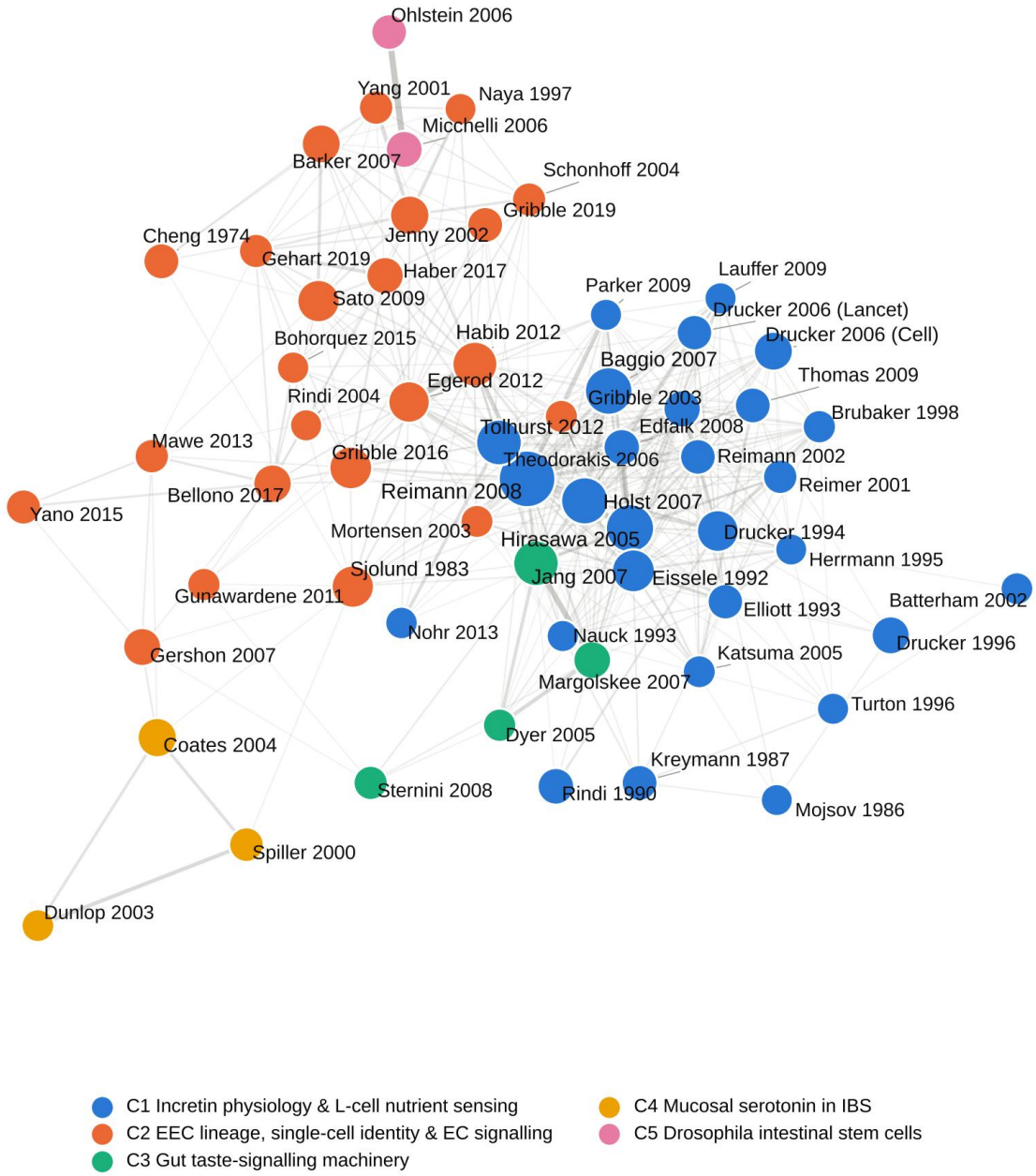

a
FFAR1 (GPR40) 0.0 0.8 2.9 2.7
FFAR2/FFAR3 (GPR43/GPR41) 0.0 1.0 3.2 3.3
FFAR4 (GPR120) 0.0 1.2 3.0 1.6
GPR119 0.0 0.7 3.1 2.2
TGR5 (GPBAR1) 0.0 0.7 3.4 2.9
CaSR / GPRC6A 0.0 0.5 2.5 2.1
Taste receptors (T1R/T2R) 0.0 4.4 5.8 4.2
Olfactory receptors 0.0 0.5 1.0 1.0
TRPA1 0.0 0.5 2.1 1.4
Piezo2 0.0 0.0 0.2 0.7
KATP channel 0.2 1.3 1.2 0.4
TRPM5 / TRPV1 0.0 0.7 0.6 1.0
SGLT1 (SLC5A1) 0.0 1.2 2.6 1.4
PEPT1 (SLC15A1) 0.0 0.5 0.4 0.4
TPH (TPH1) 0.9 3.0 3.4 4.3
SERT (SLC6A4) 0.6 4.2 3.4 2.0
5-HT3 / 5-HT4 receptors 5.2 7.5 3.5 1.9
GLP-1R 1.3 3.2 8.0 6.0
GIPR 0.0 0.2 0.9 0.9
CCK1R / Y2R / GHSR 0.2 1.3 0.9 0.9
DPP-4 0.4 1.7 5.0 3.1
FXR (NR1H4) 0.0 0.3 0.8 1.5
TLRs 0.0 1.0 0.9 1.7
GLP-1R agonists 0.0 1.3 4.8 4.6
DPP-4 inhibitors 0.0 1.0 3.3 1.7
Metformin 0.0 0.5 1.5 0.9
SGLT inhibitors 0.2 0.3 0.7 0.3
Somatostatin analogues 1.1 2.0 0.6 0.7
Serotonergic drugs 4.5 4.0 2.1 1.0
Bile acid-based agents 0.6 0.2 1.3 1.0
Non-nutritive sweeteners 0.0 1.2 2.3 0.8
1980–1999
2000–2009
2010–2017
2018–2025
0 2 4 6 8
Share of articles in period (%)
b
Obesity/energy balance
T2D/glycaemia
Bariatric surgery
IBS/motility/pain
IBD/colitis
Neuroendocrine tumours
Gut-brain/mood
Microbiota/metabolites
39 62 7 7 4 0 11 11
44 34 7 18 2 0 13 75
50 53 3 8 3 0 6 8
43 83 9 7 0 0 9 10
40 67 17 12 2 0 2 23
Nutrient-sensing GPCRs
51 25 8 13 0 3 8 8
38 34 5 9 1 1 14 11
28 17 0 31 3 7 14 59
32 9 2 36 2 2 23 19
9 9 0 45 0 0 9 27
Ion channels & mechanosensors
25 68 0 11 0 0 7 0
21 25 4 25 4 0 12 12
42 47 14 11 2 2 11 16
Nutrient transporters
23 23 8 15 0 0 8 15
18 7 0 51 24 7 16 25
6 0 0 66 37 3 13 17
Serotonergic machinery
6 6 1 53 7 4 24 12
50 76 8 8 2 0 14 14
61 70 4 9 0 0 9 13
Hormone receptors & degradation
62 28 12 12 0 0 41 6
41 76 4 7 6 0 6 11
52 77 19 3 0 0 0 35
Nuclear & other receptors
21 15 0 18 36 3 21 72
47 81 6 9 1 0 14 10
43 85 4 6 6 0 7 4
50 84 6 3 3 3 3 9
7 53 0 13 7 0 0 13
Drugs & drug classes
12 15 6 32 15 62 9 9
8 0 0 47 15 5 21 7
39 70 18 3 0 0 3 30
40 40 0 16 0 2 13 11
0 20 40 60 80 100
Articles on the target that also address the context (%)

Fig. 6


Ohlstein 2006
Yang 2001
Naya 1997
Micchelli 2006
Barker 2007
Schonhoff 2004
Gribble 2019
Jenny 2002
Cheng 1974
Gehart 2019
Haber 2017
Sato 2009
Parker 2009
Lauffer 2009
Drucker 2006 (Lancet)
Drucker 2006 (Cell)
Bohorquez 2015
Habib 2012
Baggio 2007
Thomas 2009
Rindi 2004
Egerod 2012
Gribble 2003
Brubaker 1998
Tolhurst 2012
Edfalk 2008
Mawe 2013
Gribble 2016
Theodorakis 2006
Reimann 2002
Reimer 2001
Bellono 2017
Reimann 2008
Holst 2007
Yano 2015
Mortensen 2003
Hirasawa 2005
Drucker 1994
Herrmann 1995
Sjolund 1983
Jang 2007
Eissele 1992
Batterham 2002
Gunawardene 2011
Elliott 1993
Nohr 2013
Nauck 1993
Drucker 1996
Gershon 2007
Katsuma 2005
Margolskee 2007
Turton 1996
Dyer 2005
Coates 2004
Kreymann 1987
Sternini 2008
Rindi 1990
Mojsov 1986
Spiller 2000
Dunlop 2003
C1 Incretin physiology & L-cell nutrient sensing
C2 EEC lineage, single-cell identity & EC signalling
C3 Gut taste-signalling machinery
C4 Mucosal serotonin in IBS
C5 Drosophila intestinal stem cells

712

713 **Fig. 7**

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- OnlineResource1.docx