Perspective

Insights into gastric neuroendocrine tumors burden

Taíssa Maíra Thomaz Araújo, Williams Fernandes Barra, André Salim Khayat, Paulo Pimentel de Assumpção

Oncology Research Center, Federal University of Pará, Pará 66073-005, Brazil

Correspondence to: Paulo Pimentel de Assumpção, PhD. Mundurucus street, 4487-Guama-Belem-Pará, PA 66073-005. Email: assumpcaopp@gmail.com.

Abstract

Type 1 gastric neuroendocrine tumors (gNETs) are usually small lesions, restricted to mucosal and sub-mucosal layers of corpus and fundus, with low aggressive behavior, for the majority of cases. Nevertheless, some cases present aggressive behavior. The increasing incidence of gNETs brings together a new relevant problem: how to identify potentially aggressive type 1 gNETs. The challenging problem seems to be finding out signs or features able to predict potentially aggressive cases, allowing a tailored approach, since the involved societies dedicated to provide guidelines for management of these neoplasms apparently failed in producing staging systems able to accurately predict prognosis of these tumors. Additionally, it is also important to try to find out explanations for increasing incidence, as well as to identify potential targets aiming to reach better control of this neoplasia. Here, we discuss potential pathways implicated in aggressive behavior, as well as new strategies to improve clinical management of these tumors.

Keywords: gNETs; gastrin receptor; epidemiology

Submitted Dec 22, 2016. Accepted for publication Mar 17, 2017.
doi: 10.21147/j.issn.1000-9604.2017.02.06
View this article at: https://doi.org/10.21147/j.issn.1000-9604.2017.02.06

Introduction

Gastric neuroendocrine tumors (gNETs) are rare, occurring in 1 to 2 cases/1,000,000 persons per year, and accounting for 8.7% of all gastrointestinal neuroendocrine tumors (1), less than 2% of all neuroendocrine tumors and less than 1% of all gastric cancers (1-3). However, incidence of gNETs has increased in most countries over the past decades, in part because of better awareness of the disease among physicians, improved diagnostic techniques and more widespread use of upper gastrointestinal endoscopy (4). In many countries, including Brazil, epidemiological data on gNETs are scarce (5).

The increasing incidence of gNETs (6,7) brings together a new relevant problem: how to identify potentially aggressive type 1 gNETs.

Sporadic type 1 gNETs occur secondary to autoimmune gastritis, since antibodies against parietal cell from the gastric corpus cause atrophy of these cells and therefore reduce acid secretion (8). The resultant absence of acid implies in hyperplasia of G cells from the normal antrum, producing hypergastrinemia in an effort to stimulate the corpus parietal cells to start producing acid and re-establishing normal stomach pH. Since the atrophic parietal cells will not respond to gastrin stimulus, the hypergastrinemia is maintained and finally provokes enterochromaffin-like cell (ECLC) hyperplasia. As the stimulations persist, the ECLC suffers dysplasia and finally gives origin to type 1 gNETs (9).

Some hypotheses try to explain the increment in type 1 gNETs: 1) there is an ongoing global shift characterized by decrease of infection diseases and rise of immune diseases, and this includes reduction of gastric *Helicobacter pylori* (*H. pylori*) infection and intensification of autoimmune gastritis (10-13); 2) the excessive and liberal utilization of proton pump inhibitors (PPIs) provokes elevation of gastrin levels and this could contribute to higher indices of type 1 gNETs (14); 3) the incidence of type 1 gNETs remains the

same, but the higher number of endoscopy and improvement on quality of the exams and pathology analyses allowed the discovery of tumors that already existed (15); and 4) there are new yet unknown driven forces implicating in the actually increasing incidence.

None of the cited hypotheses seems to fulfill the gaps on the mechanism of this epidemiologic phenomenon. Moreover, management of type 1 gNETs remains a challenge for clinicians, surgeons and oncologists, as will be discussed below.

Clinical behavior and management

Type 1 gNETs are usually small lesions, restricted to mucosal and sub-mucosal layers of corpus and fundus, with low aggressive behavior, for the majority of cases, although being multiple and recurrent. Lymph nodes and distant metastasis are rare, but do occur (16,17).

Since this low metastatic potential and indolent behavior is the rule, recommendations from the majority of medical societies dedicated to NET management include surveillance, endoscopic resection of prominent lesions and, less frequently, surgical approach (18).

For multiple and more prominent lesions, the National Comprehensive Cancer Network (NCCN) guidelines consider antrectomy as a possible treatment strategy. Antrectomy should eliminate G cells and control hypergastrinemia, ending the stimulus to ECLCs (18). Although there are some followers of this approach, especially among United States surgeons (19), it remains an issue of intensive debate.

If antrectomy is reserved for patients at higher risk, and risk could be understood as local tumor aggressiveness including lymph nodes metastasis, as well as distance metastasis dissemination, antrectomy would not eliminate these possibilities, since the tumors are located at corpus and fundus, away from the resected antrum. Additionally, antrectomy does not include lymphadenectomy, neither as a staging process nor as a therapeutic measure (20-23).

In other words, if the supposed high-risk lesion is already an aggressive tumor, it might harbor local malignant features, as local invasion and lymph nodes metastasis, not reached by the antrectomy procedure. Additionally, antrectomy brings risk of complications and even mortality (24). Moreover, the recurrence rate is not completely abolished, since in some cases G cells are not completely removed (25).

By the other side, the conservative management is also unable to treat the aggressive cases, as extended disease and lymph nodes metastasis are not addressed by this approach.

Although the great majority of type 1 gNETs present indolent clinical course, with very low disease related mortality rates, so the lethality is currently considered low, the rising incidence causes a possible shift in mortality index.

The challenging problem seems to be finding out signs or features able to predict the potentially aggressive cases, allowing a tailored approach. The involved societies dedicated to provide guidelines for management of these neoplasms apparently failed in producing staging systems able to accurately predict prognosis of these tumors. Neither the World Health Organization (WHO) classification, nor European Neuroendocrine Tumor Society (ENETS) staging or even the American Joint Committee on Cancer (AJCC) staging for low-grade gNETs had high accuracy in prognosis prediction (26-28).

Tumor behavior is supposed to be a consequence of the molecular profile, as it was demonstrated for many tumor types. Therefore, a joint effort to provide data on molecular signatures of type 1 gNETs is urgent to fight against this growing medical problem.

Growing incidence hypotheses

As mentioned before, the increase in incidence of type 1 gNETs is not well explained. The main characteristics of these tumors are: hypergastrinemia and elevated stomach pH. Even though autoimmune gastritis is currently recognized as the unique origin of the disease, by causing corpus atrophy (9), several hypotheses have been considered to explain the occurrence of so many new cases, and some of that will be briefly discussed.

Autoimmune gastritis augmentation

The augmentation of immune diseases and diminishing of infections are a reality affecting diverse organs and systems, and might partially explain the growing incidence of autoimmune gastritis, taking in mind only the epidemiologic evidences (11,12). However, the mechanism of this shift in gastric mucosa requires further investigation.

The hypothesis of *H. pylori* antigens mimicking parietal cell antigens causing immune reaction to self gastric cells could explain an extra etiology and by so, contribute to new cases of type 1 gTNEs (29). Nevertheless, this new contributing factor — *H. pylori* infection, is decreasing in

recent years, bringing doubt to real impact of this mechanism on rising incidence of these tumors. Additionally, the ongoing shift on infection versus immune disease incidence implies in decreasing of the first impacting on increasing the last, instead of a collaborative pattern.

PPIs role

PPIs are largely used, even without medical prescription, to treat gastroesophageal reflux disease, peptic ulcers, gastritis, and to alleviate dyspeptic symptoms (14,30,31). The main mechanism of action is through impairment of H-K pump, leading to a diminishing of acid secretion and consequence elevated gastric pH (32). In the absence of physiologic acid pH, gastrin is secreted, as discussed above, to recover acid secretion, normalizing stomach pH. If blockage of proton pump is maintained by continuous PPIs administration, hypergastrinemia could cause a stimulus to ECLC and eventually favor type 1 gNETs occurrence (14,33).

This hypothesis is not proved, neither completely rejected, since there are few well-controlled trials addressing this evidence.

Aiming at shedding light on this issue, Calvete *et al*. (34) recently described a family with consanguineous parents and ten children, five of whom are affected by type 1 gNETs. They had atypical clinical behavior including: an earlier age of onset (around 30 years), high aggressiveness (3 with lymph node infiltration, and one with a synchronous focus of adenocarcinoma); iron-deficiency, rather than megaloblastic anemia (34). They identified a homozygous missense mutation in the 14th exon of *ATP4A* gene (c.2107C>T), which encodes the proton pump, and is responsible for acid secretion by gastric parietal cells. This mutation originates from a change in one of the transmembrane domains that avoid the liberation of protons from cells to stomach lumen, causing the achlorhydria observed in the affected individuals. Interestingly, no germline or somatic mutations in *ATP4A* gene were found in sporadic gastric NET patients (34). Then the group described a mouse model for the $ATP4A^{R703C}$ mutation. Homozygous mice developed premalignant condition with severe hyperplasia, dysplasia and glandular metaplasia in the stomach. Furthermore, when the homozygous mice were treated with 3% HCl acid in the drinking water, the development of glandular metaplasia and dysplasia were prevented (if treated from birth) or partially reverted (if treated during adulthood) (35).

Although this model did not reproduce typical human disease, it represents a new perspective in understanding molecular pathways leading to more aggressive behaviors, as well as, novel approaches to control the disease.

Cholecystokinin B receptor (CCK2R)

Gastrin is a peptide secreted by neuroendocrine G cells that triggers the release of hydrochloric acid by parietal cells, and binds to cholecystokinin B receptors, known as CCK2R and CCKBR, to produce its effects (36,37).

Besides its role in gastric acid secretion, some studies have revealed relevant cellular functions of gastrin, including regulation of proliferation, migration, invasion, differentiation, angiogenesis and apoptosis (38-40). These effects are also achieved by its binding to CCK2R, which in turn triggers downstream signaling involving many important pathways, such as protein kinase C (PKC), phosphatidyl inositol 3'-kinase (PI3K) and mitogen activated protein kinase (MAPK) (38,40).

Gastrin is also known to play an important role in the development of gastric adenocarcinoma (41,42) in addition to its participation in gNETs development (38).

To investigate the molecular mechanisms by which gastrin promotes tumor development, many studies using CCK2R expressing gastric cancer cell lines were performed. Sun *et al*. (43) observed that the proliferation of MKN-45 cells decreased when treated with CCK2R antagonist. Accordingly, the AGS-B cell line transfected with human CCK2R was found to proliferate more rapidly in the presence of gastrin, and it was correlated with the upregulation of cyclin D1 (44).

Sun *et al*. (43) also demonstrated that MKN-45 has been shown to be more susceptible to apoptosis when treated with a CCK2R antagonist, and this was associated with upregulation of Bax (proapototic protein) and downregulation of Bcl-2 (antiapoptotic protein). Similarly, Pritchard *et al*. (45) observed that gastrin increases mcl-1 (antiapoptotic member of the bcl-2 family of proteins) expression in type 1 gNETs and in a gastric epithelial cell line that expresses the CCK2R.

Furthermore, gastrin has been shown to increase cyclooxygenase-2 (COX-2) secretion in AGS-E cells transfected with human CCK2R (AGS-GR) via an Akt-dependent mechanism (46-49). Importantly, Xu *et al*. (50) demonstrated that antagonizing or silencing CCK2R blocked activation of signal transducers and activators of

transcription 3 (STAT3) and Akt induced by gastrin in gastric cancer cell lines. Moreover, they stated that gastrin-induced COX-2 overexpression and cell proliferation were blocked by antagonizing CCK2R and inhibiting PI3K and Janus kinase 2 (JAK2). In addition, STAT3 silencing significantly attenuated COX-2 expression, and PI3K/Akt activation, as well as cell proliferation stimulated by gastrin. These data strongly suggest that CCK2R has a key role in the proliferative effect of gastrin on human gastric cancer cells, by inducing overexpression of COX-2 through JAK2/STAT3/PI3K/Akt pathway (50).

AGS-GR cells have also been used to elucidate the mechanisms responsible for the effects of gastrin on cellular migration and invasion. In the presence of gastrin, AGS-GR morphology was modified acquiring a branched shape, remodeling the cytoskeleton. These effects were not observed when cells were treated with a CCK-2 receptor antagonist (51).

One of the mechanisms by which gastrin leads to an increase in cell migration was recently described by Lloyd *et al*. (52). They observed that overexpression of miR-222 induced by gastrin is followed by a decrease in the expression of p27 *in vitro* and *in vivo*, via activation of CCK2R and subsequent PKC and PI3K pathways. Reduced expression of p27, therefore, triggered actin remodeling and increased migration in AGS-GR cells. Interestingly, miR-222 expression is increased in the serum and gastric corpus of patients with hypergastrinemia and type 1 gNETs, and is significantly reduced when patients are treated with a CCK2R antagonist. Since intervention on miRNAs expressions represent an important perspective in many human's disease, exploring the role of miR-222 and its interactions on regulation of gNETs mechanism and pathways might be relevant to future molecular approaches aiming to block these tumors development.

CCK2R polymorphisms

One hypothesis to explain the occurrence of gNETs or even differences in disease behavior could be the presence of polymorphisms in *CCK2R* gene, modifying the quantity or structure of the encoded protein, resulting in the amplification of the downstream response, which is known to be associated with tumor development. Although there are many single nucleotide polymorphisms (SNPs) described in genomic databanks [353 in National Center of Biotechnology Information (NCBI), of which 253 are missense], none was associated with the development of type 1 gNETs. However, one in particular (C>A; rs1800843) has been correlated with risk for pancreatic cancer (53,54).

This SNP occurs in position 32 of the 4th intron of *CCK2R* gene and originates from a novel splice variant of this gene with retention of intron 4, resulting in 69 additional amino acids ate portion of the receptor involved in signal transduction and cell proliferation (54,55).

Interestingly, the presence of A allele significantly increases aggressiveness and shortens survival of patients with pancreatic cancer. Although few patients with the AA genotype presented advanced stage of the disease compared to patients with the wild genotype CC, the survival of these patients was shorter (53).

These evidences highlight the need to investigate polymorphisms in *CCK2R* gene, which can bring extremely important information to understand the occurrence of type 1 gNETs, and also shed light on mechanism implicated in disease aggressiveness. Access to new gene sequencing technologies might improve the discovery of new SNPs eventually associated with disease behavior, accelerating the translation of the knowledge to clinical practice.

Targeting CCK2R

In non-clinical studies, netazepide is a potent and highly selective antagonist for CCK2R that has good oral bioavailability and effectively suppresses gastric acid secretion (56).

In healthy subjects, netazepide and the PPI rabeprazole were similarly effective in suppressing pentagastrin-stimulated gastric acid secretion and increasing serum gastrin level. Rabeprazole increased plasma chromogranin A (CgA), a sign of ECLC hyperactivity, whereas netazepide reduced plasma CgA, a sign of ECLC hypoactivity. Netazepide also prevented the increase in CgA resulted from rabeprazole-induced hypergastrinemia, probably by blocking CCK2R on ECLC (57). A clinical trial in patients with type 1 gNETs and autoimmune chronic atrophic gastritis had showed that netazepide can eradicate type 1 gNETs and is an alternative to regular gastroscopy management or even surgery (58).

There is accumulating evidence that gastrin influences tumor development by binding to CCK2R, which highlights potential role of netazepide as a targeted therapy, in addition to, or as an alternative, to traditional treatments of patients with gNETs.

In this regard, it is important to mention that the current therapy seems to be unable to control more aggressive type 1 gNETs. According to the majority of epidemiological data, at least 5% of patients with type 1 gNETs will experience a high aggressive disease, with regional, and even distal metastasis, not addressed by conventional recommended approaches. Moreover, it is actually not possible to identify these aggressive tumors at early stages, before metastasis development. Since netazepide seems to block the pathways involved in the disease occurrence, it is supposed to be effective in stopping the disease, regardless of being indolent or aggressive (9,23).

Risk prediction

Since most of discussed topics are still elusive, and clinicians need references for management of these tumors, it is important to take in mind the available information on risk factors for aggressive behavior. The occurrence of tumor size over 1 cm, deep of penetration beyond mucosa layer, and early recurrence after endoscopic treatment are signals of more aggressive disease and should require rigorous follow up, clinical intervention, or even surgical approach. If confirmed by large series and multi-institutional investigations, the identification of individuals with polymorphisms in *CCK2R* gene should also be consider as additional risk factor for medical decision.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Modlin IM, Lye KD, Kidd M. Carcinoid tumors of the stomach. Surg Oncol 2003;12:153-72.
2. Modlin IM, Kidd M, Lye KD. Biology and management of gastric carcinoid tumours: a review. Eur J Surg 2002;168:669-83.
3. Mulkeen A, Cha C. Gastric carcinoid. Curr Opin Oncol 2005;17:1-6.
4. Chen WF, Zhou PH, Li QL, et al. Clinical impact of endoscopic submucosal dissection for gastric neuroendocrine tumors: a retrospective study from mainland China. Scientific World Jounal 2012;2012:869769.
5. Estrozi B, Bacchi CE. Neuroendocrine tumors involving the gastroenteropancreatic tract: a clinico-pathological evaluation of 773 cases. Clinics (Sao Paulo) 2011;66:1671-5.
6. Jung M, Kim JW, Jang JY, et al. Recurrent gastric neuroendocrine tumors treated with total gastrectomy. World J Gastroenterol 2015;21:13195-200.
7. Tsikitis VL, Wertheim BC, Guerrero MA. Trends of incidence and survival of gastrointestinal neuroendocrine tumors in the United States: a seer analysis. J Cancer 2012;3:292-302.
8. Postlewait LM, Baptiste GG, Ethun CG, et al. A 15-year experience with gastric neuroendocrine tumors: Does type make a difference? J Surg Oncol 2016;114:576-80.
9. Zhang L, Ozao J, Warner R, et al. Review of the pathogenesis, diagnosis, and management of type I gastric carcinoid tumor. World J Surg 2011;35:1879-86.
10. Lee YC, Chiang TH, Chou CK, et al. Association between Helicobacter pylori eradication and gastric cancer incidence: a systematic review and Meta-analysis. Gastroenterology 2016;150:1113-24.e5.
11. Coati I, Fassan M, Farinati F, et al. Autoimmune gastritis: Pathologist's viewpoint. World J Gastroenterol 2015;21:12179-89.
12. Kobayashi M, Sato Y, Terai S. Endoscopic surveillance of gastric cancers after Helicobacter pylori eradication. World J Gastroenterol 2015;21:10553-62.
13. Testerman TL, Morris J. Beyond the stomach: an updated view of Helicobacter pylori pathogenesis, diagnosis, and treatment. World J Gastroenterol 2014;20:12781-808.
14. Heidelbaugh JJ, Kim AH, Chang R, et al. Overutilization of proton-pump inhibitors: what the clinician needs to know. Therap Adv Gastroenterol 2012;5:219-32.
15. Hirai M, Matsumoto K, Ueyama H, et al. A case of neuroendocrine tumor G1 with unique histo-pathological growth progress. World J Gastrointest Endosc 2013;5:605-9.

16. Rindi G, Azzoni C, La Rosa S, et al. ECL cell tumor and poorly differentiated endocrine carcinoma of the stomach: prognostic evaluation by pathological analysis. Gastroenterology 1999;116:532-42.
17. Rindi G, Luinetti O, Cornaggia M, et al. Three subtypes of gastric argyrophil carcinoid and the gastric neuroendocrine carcinoma: a clinicopathologic study. Gastroenterology 1993;104:994-1006.
18. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine Tumors, Version 1. 2015. NCCN. Available online: http://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf
19. Jenny HE, Ogando PA, Fujitani K, et al. Laparoscopic antrectomy: a safe and definitive treatment in managing type 1 gastric carcinoids. Am J Surg 2016;211:778-82.
20. Thomas D, Tsolakis AV, Grozinsky-Glasberg S, et al. Long-term follow-up of a large series of patients with type 1 gastric carcinoid tumors: data from a multicenter study. Eur J Endocrinol 2013;168:185-93.
21. Nikou GC, Angelopoulos TP. Current concepts on gastric carcinoid tumors. Gastroenterol Res Pract 2012;2012:287825.
22. Dakin GF, Warner RR, Pomp A, et al. Presentation, treatment, and outcome of type 1 gastric carcinoid tumors. J Surg Oncol 2006;93:368-72.
23. Borch K, Ahrén B, Ahlman H, et al. Gastric carcinoids: biologic behavior and prognosis after differentiated treatment in relation to type. Ann Surg 2005;242:64-73.
24. Woodfield CA, Levine MS. The postoperative stomach. Eur J Radiol 2005;53:341-52.
25. Sato Y. Endoscopic diagnosis and management of type I neuroendocrine tumors. World J Gastrointest Endosc 2015;7:346-53.
26. Bosman FT, Carneiro F, Hruban RH, et al. World Health Organization Classification of Tumours of the Digestive System. 4th Edition. Lyon: IARC, 2010.
27. Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual. 7th Edition. New York: Springer, 2010.
28. Rindi G, Klöppel G, Alhman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch 2006;449:395-401.
29. Guruge JL, Falk PG, Lorenz RG, et al. Epithelial attachment alters the outcome of Helicobacter pylori infection. Proc Natl Acad Sci U S A 1998;95:3925-30.
30. Harmon RC, Peura DA. Evaluation and management of dyspepsia. Therap Adv Gastroenterol 2010;3:87-98.
31. Schwartz MD. Dyspepsia, peptic ulcer disease, and esophageal reflux disease. West J Med 2002;176:98-103.
32. Shin JM, Sachs G. Pharmacology of proton pump inhibitors. Curr Gastroenterol Rep 2008;10:528-34.
33. Dacha S, Razvi M, Massaad J, et al. Hypergastrinemia. Gastroenterol Rep (Oxf) 2015;3:201-8.
34. Calvete O, Reyes J, Zuñiga S, et al. Exome sequencing identifies ATP4A gene as responsible of an atypical familial type I gastric neuroendocrine tumour. Hum Mol Genet 2015;24:2914-22.
35. Calvete O, Varro A, Pritchard DM, et al. A knockin mouse model for human ATP4aR703C mutation identified in familial gastric neuroendocrine tumors recapitulates the premalignant condition of the human disease and suggests new therapeutic strategies. Dis Model Mech 2016;9:975-84.
36. Han YM, Park JM, Kangwan N, et al. Role of proton pump inhibitors in preventing hypergastrinemia-associated carcinogenesis and in antagonizing the trophic effect of gastrin. J Physiol Pharmacol 2015;66:159-67.
37. Chao C, Hellmich MR. Gastrin, inflammation, and carcinogenesis. Curr Opin Endocrinol Diabetes Obes 2010;17:33-9.
38. Burkitt MD, Varro A, Pritchard DM. Importance of gastrin in the pathogenesis and treatment of gastric tumors. World J Gastroenterol 2009;15:1-16.
39. Dockray G, Dimaline R, Varro A. Gastrin: old hormone, new functions. Pflugers Arch 2005;449:344-55.
40. Dockray GJ, Varro A, Dimaline R, et al. The gastrins: their production and biological activities. Annu Rev Physiol 2001;63:119-39.
41. Zhuang K, Yan Y, Zhang X, et al. Gastrin promotes the metastasis of gastric carcinoma through the β-catenin/TCF-4 pathway. Oncol Rep 2016;36:1369-76.
42. Hur K, Kwak MK, Lee HJ, et al. Expression of gastrin and its receptor in human gastric cancer

tissues. J Cancer Res Clin Oncol 2006;132:85-91.
43. Sun WH, Zhu F, Chen GS, et al. Blockade of cholecystokinin-2 receptor and cyclooxygenase-2 synergistically induces cell apoptosis, and inhibits the proliferation of human gastric cancer cells in vitro. Cancer Lett 2008;263:302-11.
44. Song DH, Rana B, Wolfe JR, et al. Gastrin-induced gastric adenocarcinoma growth is mediated through cyclin D1. Am J Physiol Gastrointest Liver Physiol 2003;285:G217-22.
45. Pritchard DM, Berry D, Przemeck SM, et al. Gastrin increases mcl-1 expression in type I gastric carcinoid tumors and a gastric epithelial cell line that expresses the CCK-2 receptor. Am J Physiol Gastrointest Liver Physiol 2008;295:G798-805.
46. Hafez NH, Tahoun NS. Expression of cyclo-oxygenase 2 and vascular endothelial growth factor in gastric carcinoma: Relationship with clinico-pathological parameters. J Egypt Natl Canc Inst 2016;28:149-56.
47. Subramaniam D, Ramalingam S, May R, et al. Gastrin-mediated interleukin-8 and cyclooxygenase-2 gene expression: differential transcriptional and posttranscriptional mechanisms. Gastroenterology 2008;134:1070-82.
48. Mrena J, Wiksten JP, Kokkola A, et al. COX-2 is associated with proliferation and apoptosis markers and serves as an independent prognostic factor in gastric cancer. Tumour Biol 2010;31:1-7.
49. Williams CS, Mann M, DuBois RN. The role of cyclooxygenases in inflammation, cancer, and development. Oncogene 1999;18:7908-16.
50. Xu W, Chen GS, Shao Y, et al. Gastrin acting on the cholecystokinin2 receptor induces cyclooxygenase-2 expression through JAK2/STAT3/PI3K/Akt pathway in human gastric cancer cells. Cancer Lett 2013;332:11-8.
51. Noble PJ, Wilde G, White MR, et al. Stimulation of gastrin-CCKB receptor promotes migration of gastric AGS cells via multiple paracrine pathways. Am J Physiol Gastrointest Liver Physiol 2003;284:G75-84.
52. Lloyd KA, Moore AR, Parsons BN, et al. Gastrin-induced miR-222 promotes gastric tumor development by suppressing p27kip1. Oncotarget 2016;7:45462-78.
53. Smith JP, Whitcomb DC, Matters GL, et al. Distribution of cholecystokinin-B receptor genotype between patients with pancreatic cancer and controls and its impact on survival. Pancreas 2015;44:236-42.
54. Smith JP, Harms JF, Matters GL, et al. A single nucleotide polymorphism of the cholecystokinin-B receptor predicts risk for pancreatic cancer. Cancer Biol Ther 2012;13:164-74.
55. Smith JP, Verderame MF, McLaughlin P, et al. Characterization of the CCK-C (cancer) receptor in human pancreatic cancer. Int J Mol Med 2002; 10:689-94.
56. Takinami Y, Yuki H, Nishida A, et al. YF476 is a new potent and selective gastrin/cholecystokinin-B receptor antagonist in vitro and in vivo. Aliment Pharmacol Ther 1997;11:113-20.
57. Boyce M, Dowen S, Turnbull G, et al. Effect of netazepide, a gastrin/CCK2 receptor antagonist, on gastric acid secretion and rabeprazole-induced hypergastrinaemia in healthy subjects. Br J Clin Pharmacol 2015;79:744-55.
58. Boyce M, Moore AR, Sagatun L, et al. Netazepide, a gastrin/cholecystokinin-2 receptor antagonist, can eradicate gastric neuroendocrine tumours in patients with autoimmune chronic atrophic gastritis. Br J Clin Pharmacol 2017;83:466-75.

Cite this article as: Thomaz Araújo TM, Barra WF, Khayat AS, de Assumpção PP. Insights into gastric neuroendocrine tumors burden. Chin J Cancer Res 2017;29(2):137-143. doi: 10.21147/j.issn.1000-9604.2017.02.06

