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Treatment of Peptic Ulcer; Current Status And Potential Strategies

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***Abstract**: Peptic ulcer is disease of the gastric mucosa in which there is erosion and inflammation. The disease is caused by the imbalance between the bicarbonate and acid that is generated in the gastric and duodenal area of the gastrointestinal tract. Ulcers can develop in the esophagus, stomach or duodenum, or at the margin of a gastroenterostomy, in the jejunum, in Zollinger-Ellison syndrome, and in association with a Meckel's diverticulum containing ectopic gastric mucosa. Peptic ulcer disease is one of several disorders of the upper gastrointestinal tract that is caused, at least partially, by gastric acid. Gastric acid secretion is regulated by anextensive collection of neural stimuli and endocrine and paracrine agents, which act either directly at membrane receptors of the parietal cell or indirectly through other regulatory cells of the gastric mucosa, as well as mechanical and chemical stimuli. In this review, we have tried to condense the current body of knowledge about the modulating action of inflammatory mediators on the pathophysiology of gastric acid secretion and update its significance based on recent findings in gastric mucosa and parietal cells in humans and animal models as well the current and potential strategies for its therapy.*

***Keywords:**Ulcer, PUFA, mucosa, inflammation, carbonic anhydrase, stem cells*

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I. Introduction

Peptic ulcer disease is characterized by inflamed lesions or excavations (ulcers) of the gastric mucosa and underlying tissue of the upper gastrointestinal tract. The ulcers are caused by the damage to the mucous membrane that normally protects the esophagus, stomach and the duodenum from the gastric acid and pepsin. The damage can be caused by several factors, including excessive acid and pepsin production, bile acid reflux, advancing age, ischemia and in many cases infection with Helicobacter pylori bacteria and inhibition of the prostaglandins (1). Oxidative stress has been found to be the major pathogenic factor in the progression of ulcer that directly impairs the cellular functions and promotes cellular organelles damage in the cells, including mitochondria and nucleus. The nitric oxide (NO) is accepted as a vital mediator of GIT mucosal defense as decreased NO generation or synthesis contribute to the pathogenesis of ulcer disease (2). Recent findings show significance of polyunsaturated fatty acids (PUFAs) in numerous clinical ailments, so observing the consequence of PUFAs in several of the clinical situations.On the other hand it was suggested that insufficiency of PUFAs in particular the gamma-linoleic acid, di-homo-gamma-linolenic acid and eicosapentanoic acid might be accountable for the development of peptic ulcers (3,4). PUFAs hold the capacity to obstruct the development of H.pylori, decrease the acid formation and release in experimental animals, in individuals and also in the improvement in the condition by amplifying the action of PGE1 prostaglandin.There has been substantial progress in the understanding of the peptic ulcer patho-physiology and its treatment. This review tries to encompass some of the recent developments relating to this chronic disorder.

1.1Helicobacter Pylori and recent advances in its pathological role in ulcers

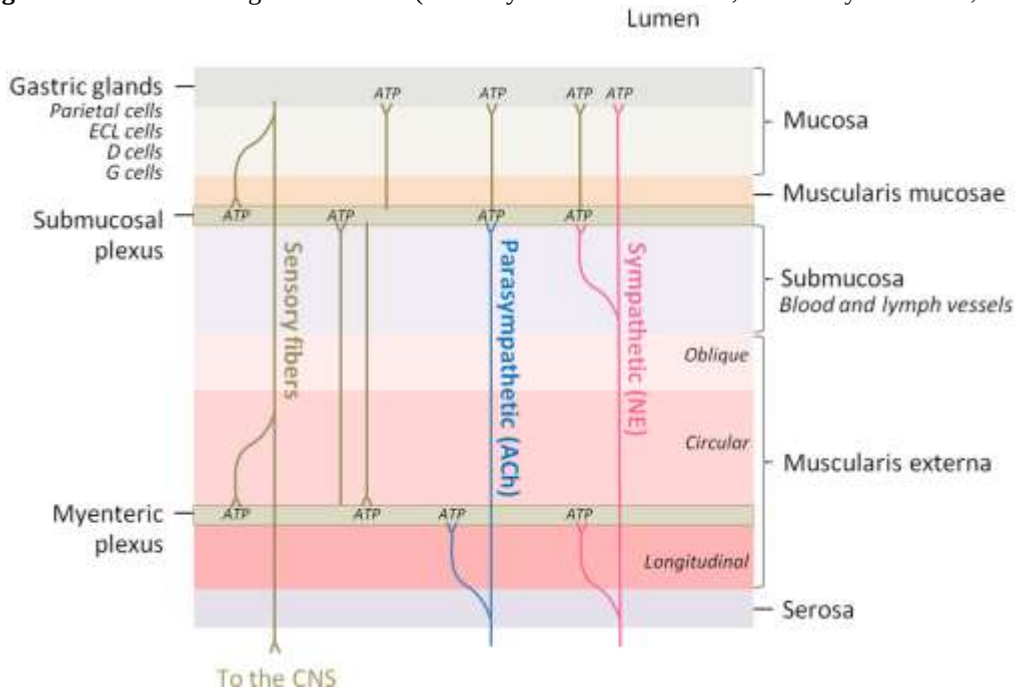
In the Western countries, the number of persons who harbour the H.pylori increases from under 5 % at birth to about 20 % and at the age of 45 years only a small proportion of persons harbouring this bacterial organisms will develop this disease. H.pylori induced gastritis precedes the development of peptic ulcers in most cases. H.pylori is found at gastrointestinal tract of duodenal ulcers and 70% patients of gastric ulcers (5). The organism is known to attach to the mucosa and mucosal epithelial cells and release enzymes that damage the mucous membrane and mucosal cells and cause inflammation and tissue destruction. Evidence also suggests that eradication of H.pylori heals peptic ulcers and reduces recurrence of duodenal and gastric ulcers. Approximately 10% of those infected with the H.pylori will develop peptic ulcer disease. The bacterial genetic locus most closely associated with the development of peptic ulcer and gastric cancer is the H.pylori Cag pathogenecity island (Cag PAI) a 40 kb DNA segment that

encodes a type IV secretion that encodes a type IV secretion system (6).

1.2 Influence of Adenosine in gastric acid secretion

The exact role adenosine has in the parietal cell function or the gastric gland physiology in humans is not well delineated. Although findings in the human gastric mucosa are the most attractive and important for obvious reasons, the inference is inconclusive yet. Studies addressed adenosine deaminase (ADA) activity in mucosal biopsies in patients with a diversity of pathologies. Adenosineis considered to have an anti-inflammatory action (7). However, in H. pylori-infected patients or in patients with chronic gastritis (8),no correlation between ADA activity and mucosal inflammationwas found. A positive correlation between ADA activity and basaland maximal gastric acid output was found in the fundic mucosa, suggesting a protective, negative influence of adenosine on acid secretion from fundic parietal cells. However, considering the low proportion of H+/K+-ATPasepositive cells in the fundic area of the human stomach and that 95% of parietal cells were found within the oxyntic mucosa of the stomach (9), the physiologic relevance ofthese findings may be under scrutiny. Given the differences between species, extrapolation of the findings in animalmodels to humans should be avoided (Fig.1).

Fig.1: Innervation of the gastric mucosa (Courtesy:Rosa M Amin *et al*, Front. Physiol. 8:737, 2017)



1.3 Role of Ghrelin and somatostatin

Ghrelin is a peptide that defines the anatomical body of the human stomach and seems to induce acid secretion and hunger by stimulating histamine production by ECL cells (10). Other compounds have been also reported to affect directly or indirectly gastric acid secretion. The effect of compounds like interleukin-1β, neurotensin, nitric oxide, oxyntomodulin, secretin, and serotonin is most likely inhibitory, although it remains a matter of debate (11).Somatostatin is themain negative regulator of acid secretion. It isa hormone and paracrine peptide produced in the stomach by D cells. These cells are present in the oxyntic mucosa, where they negatively regulate ECL and parietal cell function, and also inthe antral mucosa, where they negatively regulate G cell function (12). The physiology and morphology of both cell populations is also different. D cells secrete somatostatin in response to several stimuli. One of them is gastrin, which induces somatostatin secretion, which in turn inhibits gastrin secretion from G cells. Therefore, the gastrin-somatostatin axis constitutes a negative feedback mechanism that maintains gastrin levels and acid secretion under control. Another positive stimulus is cholecystokinin (CCK), a peptide hormone secreted by the small intestine I cells as a response to luminal lipids; by stimulating somatostatin secretion CCK inhibits acid secretion during intestinal digestion. Luminal pH is probably the most important inducer of somatostatin release. Antral D cells are often called open type, because they possess extensions that make contact with the luminal content (13).

1.4 Nanolipobead based drug delivery system for treating peptic ulcer

Artificial particulate systems such as the polymeric beads and liposomes are finding a variety of biomedical applications in drug delivery, drug targeting, protein separation, enzyme immobilization and in

blood cell substitution. Liposomes have a flexible, cell-like lipidbilayer surface which acts as a permeability barrier such that compounds can be entrapped in their aqueous interior. However, liposomes can be mechanically unstable and their loading capacitylimited by the water solubility of the material to be loaded. Polymeric beads, although mechanically more stable and having a larger loading capacity then liposomes, lack many of the useful surface properties of a lipid bilayer shell (14-15). Recently the preparation and characterization a new hybrid vesicle system with structural similarity to natural cells that combines complementary advantages of liposomes and polymeric beads this system which have been called 'Lipobeads' consists of a lipid bilayer shell that is anchored on the surface of a hydrogel polymer core. *H. pylori was* shown previously to bind to a specific alkylacyl glycerolipid derived from human erythrocytes, HEP2 cells and human antral epithelium. Furthermore cultured human cells with less PE show minimal attachment of *H. pylori in vitro*emphasizing the importance of PE–*H. Pylori* interaction. In bacterial adhesion PE is a predominant lipid in the antrum of the human stomach and functions as a receptor for *H. pylori* adhesion. Correlation of the ability of *H. pylori* to adhere to eukaryotic cells with the detected presence of the PE receptor, however underscores the importance of this lipid as a major receptor in promoting *H.pylori* adhesion to intact cells. PE bacterial adhesin exists as a cell surfaceassociated ligand (16,17). On the basis of the above facts, anti-adhesion drug delivery system based on PE has been developed as a receptor-mediated drug delivery system for use in blocking adhesion of *Helicobacter* and thereby preventing the sequelae of chronic gastric infections.

1.5 Gastroprotective role of PUFAs

Amongst the long chain PUFAs theOmega-3 (n-3) polyunsaturated fatty acids [n-3 PUFAs,eicosapentaenoic acid (EPA 20:5n-3), and docosahexaenoic acid (DHA 22:6n-3)] are the PUFAs, which are essential fatty acids as they can be synthesized by mammals from other dietary precursors which contain n-3 PUFAs. They are sufficiently found in fish. Fatty acids are key nutrients affecting early growth and development and preventing chronic disease in later life (18). PUFAs that contain more than one carbon double bond are divided into two major classes, namely, the n-6 and n-3 (Figure 1). Several lipid metabolites can be made from these PUFAs. Linoleic acid (LA 18:2n-6) is a representative n-6 PUFA, which is the precursor of arachidonic acid (AA 20:4n-6) that is involved in inflammation, inducing cardiovascular diseases, diabetes, cancer, and age-related diseases. n-3 PUFAs suppressed the activation of EGFR, PKC and interleukin levels. Sardine oilcontains comparatively high amount of PUFA and n-3 PUFA dominant among fatty acids (19). The gas chromatographic analysis of Sardine (*Sardinella longiceps*) fish oil highlighting nutritionally significant n-3 PUFA (like EPA and DHA) and they contribute to the major bioactivity of the oil. The protective effects were linked to their anti-oxidant properties.The the anti-inflammatory activity of these n3 and n6containing PUFA containing oils reduced the TNF alpha levels and increased the PGE2 levels(20). This treatmentoffers cytoprotection by increasing inhibition of TNF-α andneutrophil infiltration in mucus. Thus these PUFA containingoils ultimately inhibit tissue destruction by reactive oxygenshowed good gastro-protective anti-ulcerogenic activityspecies.The data obtained from studies carried out by this author suggests that thePUFA containing oils used in this study i.e. the fish oil andArasco oil the n-6 PUFA contained in Arasco oil were able toattenuate the ulcer formation as calculated based on the ulcerindex (21). Dietary supplementation with n-6 fatty acid rich inLA has been found to influence the physiological function of various blood components, producing an inhibitory effect onleucocyte adhesion, platelet count, platelet aggregation andcollagen formation. Dietary supplementation with n-3PUFAs improved colonic anastomoses healing. n-3 PUFAsenhance the colonic wound healing in a rat model. Actually,n-3 PUFAs may prompt faster resolution of inflammationwithin the wound microenvironment, which leads tofacilitated regeneration and re-epithelialization.A smallrandomized controlled trial evaluated a formula supplementedwith fish oil in patients with pressure ulcers and noteddecreased progression of pressure ulcers in those receivingfish oil supplementation. There is growing evidence that thediverse biological roles of n-3 PUFAs contribute to theirregenerative actions against chronic inflammatory disease.

1.6 Carbonic Anhydrase (CA) Activity in the Intermediate Level of Acid Secretion

Carbonic anhydrase is an important enzyme regulating the acid-base balance in the body. The involvement of CA I and CA IV in gastric acid secretion, effect of CA inhibitors in reducing HCl secretion and their healing effect ongastric and duodenal ulcers is now well documented (22). *In vivo* results,performed in humans, show that omeprazole inhibits not only H+/K+ATPase, but also CA II and CA IV, isozymes present in large quantitiesin the cytosol, in the walls of the secretory canaliculi, and in theparietal cell membrane. Further, gastric acid secretion is inhibited inhumans after oral administration of acetazolamide in therapeuticdoses of 25 mg/kg of body weight (23). Acetazolamide exhibit anti-ulceraction in acute experiments because of inhibition of CA-II, but itseffect on Gastric ATPase is not clear.Sulfonamides with the general formula RSO2NH2 constitute a wideclass of inhibitors of the zinc enzyme carbonic anhydrase (CA). Acetazolamide, a classic sulfonamide drug has also been reported toreduce gastric acid secretion commensurate with gastric carbonic anhydrase

inhibition (23). Correlating *in vivo* results with the dataobtained in vitro suggests that gastric mucosa CA I, II, and IVinhibition is induced by sulfenamide, the active form of omeprazole, thus this class of compound can be interesting leads for furtherexploration of anti-ulcer action (Table 1).

1.7 Association of peptic ulcer disease with anthropometric, blood parameters and nutrition:

Recent findings areconsistent with the results of previous studies; specifically, as it was found that weight, hip circumference (HipC), and BMI in women and HipC in men were highly associated with peptic ulcer disease (PUD) in both thecrude and adjusted analyses. Therefore, it was suggested that PUD may be associated with anthropometric indices such as weight, BMI, and HipC in women, but not in men, although therewas not a strong association between PUD and anthropometric indices in the Koreanpopulation (24-26).Regarding nutritional components, some studies have argued that high dietary fiber intakeis associated with PUD, gastric cancer, and gastroesophageal reflux disease, when comparedwith low dietary fiber intake, and that intake of vitamin A and C is related to PUD. Anderson and colleagues suggested that a high intake of dietary fiber reducedthe risk of gastrointestinal and duodenal ulcer, coronary heart disease, diabetes, obesity, andstroke. Additionally, Ryan-Harshman and Aldoorireported that a high-fiber diet andsoluble fiber intake appeared to decrease the risk of duodenal ulcer (27).Aldoori and colleaguesreported that dietary fiber intake was inversely related to the risk of duodenal ulcer in USmen when comparing the highest and lowest quintiles of dietary fiber intake. In another study, Aldooriand colleagues found that vitamins A and E were associated with the risk of duodenalulcer and that vitamin A and fiber could possibly reduce the development of duodenal ulcer.They argued that vitamin B2 and potassium were inversely associated with the risk of duodenalulcer. Miyake and colleagues reported that a lack of water-soluble vitamins could accelerate the development of PUD in Japanese adults (28). Additionally, Aditi and Graham documented that Vitamin C (ascorbic acid) plays a very important role in the conservation andtreatment of the gastric mucosa and that deficiency in vitamin C has repeatedly been linked with PUD (29).

1.8Stem cell based therapy for peptic ulcer

Stem cell based transplantation has been found to be effective for the treatment of various disorders.Engevik and colleagues show that gastric stem cells isolated from young mice can be transplanted into sites of injury within the stomachs of older mice, and that this results in accelerated repair (30). The ability of the transplanted young mouse cells, but not stem cells from older mice, to differentiate into a specialized cell type, termed SPEM, which is central to the healing process, appears to be a key component of this intervention. While more work needs to be done, it is clear that this approach, or other means of inducing older cells to differentiate into SPEM, would be powerful in treatment of gastric injury.Gastric stem cells isolated from young mice have been experimentally transplanted into older mice with stomach ulcer (31-32). The transplanted cells which replaced cells at the site of injury were observed and found to speed-up the healing process. These stem cells from older mice were unable to differentiate into the specialized cell type which is responsible for the healing process.

II. Conclusions

The advent of peptic ulcer disease with time is both complex and interesting. Although its incidences were rare before the 18th century, withtime and change in life style its incidences have increased significantly. Various therapeutic strategies have evolved over time for itsclinical management. However, considering the involvement of multiple factorsin its etiology, it has not been possible to provide an ideal solution tocompletely cure its manifestations. Traditional use of antacids and use ofhistamine inhibitors are important for the management ofpeptic ulcer disease. Irreversible inhibition of proton pump although reducesulceration, but in the long run leads to adverse issues. It has not been possible to develop an ideal proton pump inhibitor. In this scenario,search for alternatives by capitalizing on the multifactorial etiology ofulceration holds promise. However, these searches are far from overand require further investigations to develop ideal antiulcer agents, although the disease can be substantially controlled by pharmacotherapeutic interventions.

Table 1: Current treatment regimen for H.pylori infected peptic ulcer

Therapy	Drugs	Dose	Duration
Triple therapy	1.Lansoprazole 2.Amoxicillin 3.Clarithromycin	60 mg/12 hourly 1g/ 12 hourly 500mg/12 hourly	10-15 days
Triple therapy (Penicillin allergy)	1.Omeprazole 2.Metronidazole 3.Clarithomycin	40mg/12 hourly 500mg/12 hourly 500mg/12 hourly	10-15 days
Quadrapule therapy	1.Lansoprazole 2 Amoxicillin	30 mg/12 hourly 500mg/12 hourly	10-15 days

	3.Clarithromycin 4.Metronidazole	500mg/12 hourly 500mg/12 hourly	
Therapy in resistant cases I	1.Lansoprazole 2 Amoxicillin 3.Levofloxacin	30 mg/12 hourly 1g/12 hourly 500mg/12 hourly	10-12 days
Therapy in resistant cases II	1.Lansoprazole 2Bismuth 3.Tetracycline 4.Metronidazole	30 mg/12 h 120 mg/6 h 500 mg/6 h 500 mg/8 h	10-15 days

References

[1]. Wroblewski L.E, Peek R.M Jr., Wilson KT.Helicobacter pylori and gastric cancer, factors that modulate disease risk. Clin.Microbiol. Rev. 2010; 23, 713-739

[2]. A Kaur, R Singh, R Sharma, S Kumar. Peptic ulcer: A review or etiology and pathogenesis. Int.Res.Jr.Pharm., 3(6), 34-38, 2012

[3]. Manjari V, Das UN. Oxidant stress, anti-oxidants, nitric oxide and essential fatty acids in peptic ulcer disease. Prostaglandins Leukot.Essent. Fatty Acids. 1998, 59 (6): 401-6

[4]. S. E. Lee, J. W. Lim, J. M. Kim, and H. Kim, "Anti-inflammatorymechanism of polyunsaturated fatty acids in Helicobacterpylori-infected gastric epithelial cells," Mediators of Inflammation, vol. 2014, Article ID 128919

[5]. Segal ED, Lange C. Covacci A et al. Induction of host signal transduction pathways by Helicobacter pylori. Proc.Natl.Acad.Sci.USA. 1997; 94: 7595-7599

[6]. Subudhi BB, Sahoo SP, Sahu PK (2016) Updates in Drug Development Strategies against Peptic ulcer. J Gastrointest Dig Syst 6: 398.

[7]. Bulbuloglu, E., Inanc, F., Bakaris, S., Kantarceken, B., Cetinkaya, A., Caglar,R., et al. (2005). Association of adenosine deaminase, superoxide dismutase,and catalase activities with Helicobacter pylori. Dig. Dis. Sci. 50, 2296–2299.

[8]. Namiot, Z., Rutkiewicz, J., Stasiewicz, J., and Gorski, J. (1990). Adenosinedeaminase activity in the human gastric mucosa in relation to acid secretion.Digestion 45, 172–175

[9]. Fredholm, B. B. (2007). Adenosine, an endogenous distress signalmodulates tissue damage and repair. Cell Death Differ. 14, 1315–1323

[10]. Kamoshida, S., Saito, E., Fukuda, S., Kato, K., Iwasaki, A., and Arakawa, Y. (1999).Anatomical location of enterochromaffin-like (ECL) cells, parietal cells, andchief cells in the stomach demonstrated by immunocytochemistry and electronmicroscopy. J. Gastroenterol. 34, 315–320

[11]. Zavros, Y., Rathinavelu, S., Kao, J. Y., Todisco, A., Del Valle, J., Weinstock,J. V., et al. (2003). Treatment of Helicobacter gastritis with IL-4requires somatostatin. Proc. Natl. Acad. Sci. U.S.A. 100, 12944–12949.

[12]. Lamberts, R., Stumps, D., Plumpe, L., and Creutzfeldt, W. (1991). Somatostatincells in rat antral mucosa: qualitative and quantitative ultrastructural analysesin different states of gastric acid secretion. Histochemistry 95, 373–382

[13]. Kopic, S., and Geibel, J. P. (2013). Gastric acid, calcium absorption, and their impact on bone health. Physiol. Rev. 93, 189–268.

[14]. Lingwood CA., Huessca M.,. Kuksis A. The glycerolipid receptorfor H. pylori (and Exoenzyme S) is phosphatidyl ethanolamine.Infect. Immun., 1992; 60: 2470– 2476

[15]. Rothe U., Aurich H., Engelhard H., Oesterhelt D. Lipid-coatedparticles--a new approach to fix membrane-bound enzymesonto carrier surfaces. FEBS Lett., 1990; 263: 308-312.

[16]. Spinke J., Yang J., Wolf H., Liley M., Ringsdorf H., Knoll W.Polymer-supported bilayer on a solid substrate. Biophys. J.,1992; 63:1667-1671

[17]. Ashish K. Jain, Abhinav Agarwal and Govind P. Agrawal.Nanolipobeads based drug delivery system for effective management of peptic ulcer. Int J Curr Pharm Res, Vol 3, Issue 2, 141149

[18]. Jihye Kim, Keun Ho Kim, Bum Ju Lee. Association of peptic ulcer disease with obesity, nutritional components, and blood parameters in the Korean population.PLoS ONE 12(8): 1-14, e0183777

[19]. KV Vishnu, KK Ajeeshkumar, KR Remyakumari, B Ganesan, SC.Niladri, RGK Lekshmi, K Shyni and S Mathew. Gastroprotective effect of Sardine oil (Sardinella longiceps) against HCl/ethanol induced ulceration in Wistar rats. International Journal of Fisheries and Aquatic Studies 2017; 5(2): 118-124

[20]. K. Arumugasamy, S. Kannan, P. A. Vora, Manoj G. Tyagi.Anti-ulcer activity of arachidonic acid (PUFA) oilsin different induced ulcer animal models. International Journal of Research in Medical Sciences. Int J Res Med Sci. 2015 May;3(5):1142-1148

[21]. S. Prakash, K Arumugasamy, S. Saravanan1, S Purushotaman and M G Tyagi.Peptic Ulcer aetiology; role of H, K-ATPase enzyme and biochemical mediators in a reserpine induced ulcer mode International Journal of Biomedical Research 2015; 6(12): 947-952

[22]. Puscas I, Coltau M, Baican M, Domuta G (1999) Omeprazole has a dualmechanism of action: it inhibits both H+K+ATPase and gastric mucosacarbonic anhydrase enzyme in humans (in vitro and in vivoexperiments). The Journal of Pharmacology and Experimentaltherapeutics 290: 530-534.

[23]. Puscas I, Coltau M, Baican M, Domuta G (1999) A new conceptregarding the mechanism of action of omeprazole. Int J Clin Pharmacol.ther 37: 286-293.DH Malinowska, AM Sherry, K P Tewari, J Cuppoletti.Characterization, regulation and localization of the gastric Cl- channel associated with gastric acid secretion. 237-245

[24]. Choi, E., Roland, J. T., Barlow, B. J., O'Neal, R., Rich, A. E., Nam, K. T., et al. (2014). Cell lineage distribution atlas of the human stomach reveals heterogeneous gland populations in the gastric antrum. Gut 63, 1711–1720.

[25]. Kalichman L, Livshits G, Kobyliansky E. Indices of body composition and chronic morbidity: a cross-sectional study of a rural population in central Russia. Am J Hum Biol. 2006; 18(3): 350–358

[26]. Aldoori WH, Giovannucci EL, Stampfer MJ, Rimm EB, Wing AL, Willett WC. Prospective study of diet and the risk of duodenal ulcer in men. Am J Epidemiol. 1997; 145(1): 42–50.

[27]. Schubert, M. L. (2015). Functional anatomy and physiology of gastric secretion. Curr. Opin. Gastroenterol. 31, 479–485.

[28]. Miyake K, Akimoto T, Kusakabe M, Sato W, Yamada A, Yamawaki H, et al. Water-soluble vitamin deficiencies in complicated peptic ulcer patients soon after ulcer onset in Japan. J Nutr Sci Vitaminol.(Tokyo). 2013; 59(6): 503–508.Peptic ulcer disease, obesity, and nutrition in the Korean population. PLOS ONE August 24, 2017 12 / 14

[29]. Aditi A, Graham DY. Vitamin C, gastritis, and gastric disease: a historical review and update. Dig Dis. Sci. 2012; 57(10): 2504–2515
[30]. Amy C. Engevik, Rui Feng, Eunyoung Choi, Shana White, Nina Bertaux-Skeirik, Jing Li, Maxime M. Mahe, Eitaro Aihara, Li Yang, Betsy DiPasquale, Sunghee Oh, Kristen A. Engevik, Andrew S. Giraud, Marshall H. Montrose, Mario Medvedovic, Michael A. Helmrath, James R. Goldenring, Yana Zavros. The Development of Spasmolytic Polypeptide/TFF2-Expressing Metaplasia (SPEM) During Gastric Repair Is Absent in the Aged Stomach. CMGH Cellular and Molecular Gastroenterology and Hepatology, 2016; DOI: 10.1016/j.jcmgh.2016.05.004
[31]. Weis V.G., Petersen C.P., Mills J.C. Establishment of novel in vitro mouse chief cell and SPEM cultures identifies MAL2 as a marker of metaplasia in the stomach. Am J Physiol Gastrointest.liver Physiol. 2014;307:G777–G792.
[32]. Eitaro Aihara, Andrea L. Matthis, Rebekah A. Karns, Kristen A. Engevik,Peihua Jiang,Jiang Wang,Bruce R. Yacyshyn, and Marshall H. Montrose. Epithelial Regeneration After Gastric Ulceration Causes Prolonged Cell-Type Alterations.Cell Mol.Gastroenterol Hepatol. 2016 Sep; 2(5): 625–647.

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