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**How does *Helicobacter pylori* cause gastric cancer through connexins: An** **opinion review**

Li H *et al*. *H. pylori* causes GC through connexins

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**Abstract**

*Helicobacter pylori* (*H. pylori*) is a Gram-negative bacterium with a number of virulence factors, such as cytotoxin-associated gene A, vacuolating cytotoxin A, its [pathogenicity island](https://www.sciencedirect.com/topics/medicine-and-dentistry/pathogenicity-island), and lipopolysaccharide, which cause gastrointestinal diseases. Connexins function in gap junctional homeostasis, and their downregulation is closely related to gastric carcinogenesis. Investigations into *H. pylori* infection and the fine-tuning of connexins in cells or tissues have been reported in previous studies. Therefore, in this review, the potential mechanisms of *H. pylori*-induced gastric cancer through connexins are summarized in detail.

**Key words:** *Helicobacter pylori*; Connexin; Gap junctional intercellular communications; Gap junction proteins; Gastric cancer; Transcription factors; DNA methylation; Proliferation; Apoptosis

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**Core tip:***Helicobacter pylori* (*H. pylori*) is an independent pathogenic factor for gastric cancer (GC), which is related to some virulence factors of *H. pylori*. It has long been proven that various connexins (Cxs) can regulate the development of GC. Thus, we discuss in detail how *H. pylori* regulates Cxs to cause gastric cancer.

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**INTRODUCTION**

*Helicobacter pylori* (*H. pylori*) is a Gram-negative and microaerophilic bacterium that colonizes the stomach in nearly 50% of the world’s population[[1](#_ENREF_1)]. *H. pylori* synthesizes many different virulence factors that dysregulate host intracellular signaling mechanisms and contribute to neoplastic transformation[[2](#_ENREF_2)]. *H. pylori* disrupts the balance between cell proliferation and apoptosis, which is an important driving force for the occurrence and development of gastric cancer (GC) by virulence factors[[3](#_ENREF_3)]. Of all virulence factors, cytotoxin-associated gene A ([CagA](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/caga)), vacuolating cytotoxin A (VacA), and lipopolysaccharide (LPS) are the most important[[2](#_ENREF_2),[4](#_ENREF_4)].

The CagA gene is located downstream of the 40 kb virulence gene cluster, called the Cag pathogenicity island (cagPAI). These genes encode a type IV secretory system, forming a syringe structure that injects CagA protein and peptidoglycan into gastric epithelial cells[[5](#_ENREF_5),[6](#_ENREF_6)]. CagA is an important oncoprotein that plays a critical role in gastric carcinogenesis[[7](#_ENREF_7)]; one of the mechanisms is that it can induce hypermethylation of tumor suppressor genes[[8](#_ENREF_8),[9](#_ENREF_9)]. CagA is delivered into host gastric epithelial cells, and it may trigger some signal transduction events, such as proliferation and inflammation, leading to a potential risk of GC[[10](#_ENREF_10),[11](#_ENREF_11)]. In addition, intact cagPAI strains may increase the [probability](javascript:;) of GC[[12](#_ENREF_12)].

VacA is one of the major virulence factors produced by *H. pylori*, and it is a 140 kDa precursor that produces an 88 kDa toxin after proteolysis[[13](#_ENREF_13),[14](#_ENREF_14)]. The vacA alleles in different *H. pylori* strains can be divided into several families according to their sequence heterogeneity in specific areas that are associated with the biological form of VacA. There are three most extensively studied regions of heterogeneity: the signal or “s” region, the intermediate or “i” region, and the middle or “m” region[[15-17](#_ENREF_15)]. Previous studies indicated that *H. pylori* strains with s1, i1, and m1 vacA alleles had a higher risk of GC or precancerous lesions than those with s2, i2, and m2 vacA alleles[[15](#_ENREF_15),[18-24](#_ENREF_18)]. VacA-induced gastric epithelial cell death is expected to lead to increased cell proliferation, which may be associated with an increased cancer risk. VacA may disrupt the epithelial cell monolayers[[25](#_ENREF_25)] and thereby promote the entry of carcinogens into gastric epithelial cells[[26](#_ENREF_26)].

LPS is an important [component](javascript:;) of the cell wall of Gram-negative bacteria, for example, *Escherichia coli*[[27](#_ENREF_27)], [*Shigella flexneri*](javascript:;)[[28](#_ENREF_28)], and *Yersinia enterocolitica*[[29](#_ENREF_29)], among others. Similar to other Gram-negative bacteria, *H. pylori* LPS is composed of three structural domains—lipid A, core oligosaccharide, and O polysaccharides[[30](#_ENREF_30),[31](#_ENREF_31)]. Recently, studies have reported that LPS has [close](javascript:;) relationships with the development of GC *via* TLR4-dependent pathways[[32-36](#_ENREF_32)].

Connexins (Cxs), also called [gap junction](http://libdb.csu.edu.cn/topics/immunology-and-microbiology/gap-junction) proteins, are the main component of gap junctional intercellular communications that may directly enhance cell cooperation both electrically and metabolically. This intercellular communication plays a crucial role in development and homeostasis[[37](#_ENREF_37),[38](#_ENREF_38)]. Cxs have complex functions in physiological and pathological processes[[39](#_ENREF_39),[40](#_ENREF_40)], and they may influence the proliferation, apoptosis, migration, and invasion of different cells[[41-48](#_ENREF_41)]. Their regulation is correlated with tumor development, and the evolution of Cxs may inhibit the progression of various cancers[[39](#_ENREF_39),[40](#_ENREF_40)]. Cxs are expressed in a tissue-specific manner. Gastric tissue mainly produces Cx26, Cx32, Cx37, Cx40, Cx43, and Cx45[[49-57](#_ENREF_49)]. Previous studies have shown that, compared to tissues or cells of the normal gastric mucosa, the expression of Cxs dramatically decreases in GC[[58-61](#_ENREF_58)]. Therefore, the [variation](javascript:;)s in Cxs can serve as important biomarkers that imply the development of different cancers. Apart from changes in the function and expression of Cxs in cancers, the aberrant cytoplasmic location of Cxs is also linked with various cancers[[62-67](#_ENREF_62)]. The expression of Cxs in the gastrointestinal tract and liver is presented in Table 1[68-91].

**LITERATURE SEARCH**

A scientific literature search was conducted using the PubMed, Web of Science, and Google Scholar databases with the keywords “*Helicobacter pylori*”, “Connexin”, “Gap junctional intercellular communications”, “[gap junction](https://en.wikipedia.org/wiki/Gap_junction) [proteins](https://en.wikipedia.org/wiki/Proteins)”, “gastric cancer”, “t[ranscription](javascript:;) [factor](javascript:;)s”, “DNA [methylation](javascript:;)”, “proliferation”, “apoptosis”, and combinations of the aforementioned.

**HOW TO REGULATE CONNEXINS**

Based on previous studies about the relation between *H. pylori* and Cxs, this relation may involve many mechanisms and signaling pathways that are complex and profound. *H. pylori* can regulate the expression of key molecules that have an effect on the expression and function of Cxs by its virulence factors. In other words, Cx expression can be regulated in many processes, such as transcription, RNA processing, RNA nucleocytoplasmic transport and localization, mRNA translation, mRNA degradation, and protein activity[[68](#_ENREF_68)]. Hence, in this review, we mainly discuss possible regulation between *H. pylori* and Cxs during the progression of GC.

**CX32**

Cx32, also named gap junction beta-1 protein, was primarily found in the peripheral nervous system[[69](#_ENREF_69),[70](#_ENREF_70)], liver[[71](#_ENREF_71),[72](#_ENREF_72)], gastric tissue[[55](#_ENREF_55),[73](#_ENREF_73)], intestinal system[[74](#_ENREF_74)], and other biological systems. It is clear that DNA hypermethylation may downregulate the level of the corresponding mRNA and protein[[8](#_ENREF_8),[75](#_ENREF_75)]. A previous study reported that the expression levels of Cx32 and Cx43 mRNA decreased gradually during *H. pylori*-associated gastric carcinogenesis, and this result is associated with the hypermethylation of the promoters of these genes[[76](#_ENREF_76)]. *H. pylori* infection may upregulate some transcription factors, such as GATA-3[[77](#_ENREF_77)] and PBX-1[[58](#_ENREF_58)]. These transcription factors can serve as the determinants in the Cx32 promoter targeting site and thereby inhibit Cx32 expression. However, the authors did not explain which of the virulence factors upregulate these transcription factors. Histone acetylation leads to the opening of chromatin structure, which increases the availability of gene promoters and is generally associated with enhanced transcription of DNA. Histone deacetylases (HDACs) lead to the termination of transcriptional processes *via* counteracting the function of histone acetylation[[78](#_ENREF_78)]. Several pathogens, including *H. pylori*, manipulate host cell antibacterial responses and evade the immune system by affecting histone acetylation and histone deacetylation status[[79](#_ENREF_79)]. It has been reported that *H. pylori* infection can decrease histone acetylation levels[[80](#_ENREF_80)]. Vinken *et al*[[81](#_ENREF_81),[82](#_ENREF_82)] have shown that HDAC inhibitors may elevate Cx32 protein levels in rat hepatocytes; however, the expression levels of Cx26 were downregulated and those of Cx43 were uncertain. Hence, histone acetylation can regulate the expression of Cxs. The p38 mitogen-activated protein kinase (MAPK) signaling pathway can be activated by a variety of extracellular signals. Extracellular signal-regulated kinase (ERK), p38 MAPK, Jun N-terminal kinase (JNK), and ERK5 are members of four subfamilies of MAPK[[83](#_ENREF_83),[84](#_ENREF_84)]. CagA can activate the p38 MAPK signaling pathway[[85](#_ENREF_85)]. [Yamamoto](https://www.ncbi.nlm.nih.gov/pubmed/?term=Yamamoto%20T%5BAuthor%5D&cauthor=true&cauthor_uid=15826721) *et al*[[86](#_ENREF_86)] reported that p38 MAPK was activated during partial hepatectomy, thereby inhibiting Cx32 expression. The first step for *H. pylori* to invade the gastric mucosa is to escape the host defense mechanism, and then the bacteria adhere to the epithelial surface through cell surface-specific receptors, releasing a large number of pathogenic factors and causing a mucosal inflammation response[[87-91](#_ENREF_87)]. *H. pylori* infection can regulate the expression level of interleukins. *H. pylori* CagPAI can promote IL-1β production, involving the NOD-like receptor (NLR) family, pyrin domain containing 3 (NLRP3), and its complex, known as the NLRP3 inflammasome[[92-94](#_ENREF_92)]. A previous study reported that in primary cultured rat hepatocytes, IL-1β causes the disappearance of Cx32, which is related to claudin-2 induction and cell membrane localization[[95](#_ENREF_95)]. According to previous studies, Cx32 can inhibit proliferation, metastasis, and invasion[[73](#_ENREF_73),[96-98](#_ENREF_96)] and has an antiapoptotic effect in different cancer cells[[42](#_ENREF_42),[43](#_ENREF_43),[99](#_ENREF_99)]. Cx32 may regulate the metastasis and proliferation of hepatocellular carcinoma cells through the p53 and Akt pathways[[97](#_ENREF_97)], also *via* cell cycle arrest and cell cycle regulatory proteins[[73](#_ENREF_73)]. In other words, downregulated Cx32 may promote cell proliferation, metastasis, and apoptosis. Breaking the balance of these pathological events can promote tumor development. In addition to the changes in Cx32 expression, alterations in Cx32 location are also related to GC development[[67](#_ENREF_67)]. However, studies about the changes in *H. pylori* and Cx32 localization are scarce.

**CX43**

Cx43, also called gap junction alpha-1 protein (GJA1), is expressed in many tissues and organs; it is ubiquitous in gastric tissues[[39](#_ENREF_39),[50](#_ENREF_50),[61](#_ENREF_61)]. Cx43-dependent intercellular communication could spread cell death signals between neighboring cells through gap junctions[[44](#_ENREF_44),[100](#_ENREF_100),[101](#_ENREF_101)], using some candidate messengers such as Ca2+, cAMP, cGMP, and ATP[[100](#_ENREF_100),[102](#_ENREF_102)]. *H. pylori* promoted the expression of GATA3, which can also directly bind to the promoter region of the Cx43 gene, inducing its expression inhibition, and the expression of Cx43 decreased with the progression of gastric mucosal lesions to precancerous lesions[[60](#_ENREF_60)]. CagPAI-induced IL-1β secretion may inhibit Cx43 expression *via* ERK1/2 and p38 MAPK[[93](#_ENREF_93),[94](#_ENREF_94),[103](#_ENREF_103)]. *H. pylori* infection triggers an inflammatory response and promotes the activity of some interleukins, such as IL-1β[[92-94](#_ENREF_92)], IL-17[[104](#_ENREF_104)], and IL-22[[105](#_ENREF_105),[106](#_ENREF_106)]. [Yu](https://www.ncbi.nlm.nih.gov/pubmed/?term=Yu%20J%5BAuthor%5D&cauthor=true&cauthor_uid=28938400) *et al*[[103](#_ENREF_103)] pointed out that IL-1β can inhibit the level of Cx43 *via* ERK1/2 and p38 MAP kinase in human endometrial stromal cells[[103](#_ENREF_103)]. Qin *et al*[[107](#_ENREF_107)] announced that IL-17 can inhibit the expression of CX43 through the AKT signaling pathway, inhibiting the occurrence and development of fungal keratitis. In psoriasis, IL-22 activates the JNK pathway, which will repress the transcriptional activity of the Cx43 gene promoter[[108](#_ENREF_108),[109](#_ENREF_109)]. The inflammation-cancer chain is an important theory in carcinogenesis. Interleukins are important signaling markers of the inflammatory response. The epidermal growth factor family (EGF, EGFR, and HB-EGF) plays a key role in the progression, invasion, and metastasis of GC. The EGF family proteins can be regarded as important biomarkers for GC[[110](#_ENREF_110),[111](#_ENREF_111)], and *H. pylori* infection can promote molecular expression[[112](#_ENREF_112),[113](#_ENREF_113)]. Among the members of the EGF family, [Yoshioka](https://www.ncbi.nlm.nih.gov/pubmed/?term=Yoshioka%20J%5BAuthor%5D&cauthor=true&cauthor_uid=16020536) *et al*[[114](#_ENREF_114)] reported that HB-EGF secretion from cardiomyocytes can decrease Cx43 in overexpressing cells and in immediately adjacent cells. We predict that HB-EGF may be seen as a negative regulator of Cx43 in gastric tissue. Moreover, a clinical [study](javascript:;) showed that HB-EGF enhances resistance to certain cancer drugs during the period of GC treatment[[115](#_ENREF_115)]. In contrast, Cx43 could enhance chemotherapy sensitivity in human GC[[116](#_ENREF_116)]. However, the effect of EGF and EGFR on Cx43 expression may be opposite to that of HB-EGF[[117-119](#_ENREF_117)]. *H. pylori* infection leads to increased reactive oxygen species as well as NADPH oxidase and Jak2/Stat3 activation[[120](#_ENREF_120)]. The activity of the JAK2/STAT3 signaling pathway has a positive effect on the proliferation and metastasis of carcinoma cells[[121](#_ENREF_121),[122](#_ENREF_122)]. Cell proliferation is a mechanism that contributes to tumorigenesis. Previous studies indicated that Cx43 downregulation promotes carcinogenesis development[[60](#_ENREF_60),[76](#_ENREF_76),[123](#_ENREF_123)]. [Tang](https://www.ncbi.nlm.nih.gov/pubmed/?term=Tang%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=29061394) *et al*[[124](#_ENREF_124)] indicated that JAK2/STAT3 signaling may inhibit Cx43 expression by blocking EGFR activation. Generally, protein phosphorylation may enhance the activity of proteins. Retinoic acid (RA) is an important intermediate metabolite of vitamin A. Among the different RA structures are all-trans RA, 9-cis RA, and 13-cis RA. The absence of RA in normal human development leads to defects in the immune system, embryonic development, vision, brain function, and other systems. In *H. pylori*-infected gastric mucosa, the expression of the gastric RA biosynthetic gene is seriously damaged, which may lead to decreased RA signaling pathways, thus leading to disease progression[[125](#_ENREF_125)]. However, RA can enhance gap junction intercellular communication by increasing the expression of Cx43[[126-128](#_ENREF_126)]. A previous study indicated that all-trans RA (ATRA) may inhibit gastric carcinoma tumor growth by targeting GC stem cells[[129](#_ENREF_129)]; therefore, we predict that it may be mainly due to the effect of ATRA. The LPS-TLR4 [signal](javascript:;)ing [path](javascript:;)way has an important role in LPS-mediated disease. LPS can induce an inflammatory response and upregulate inflammatory mediators, such as inducible nitric oxide synthase, IL-6, and TNF-α, among others, *via* activation of the TLR4/NF-κB signaling pathway[[130](#_ENREF_130),[131](#_ENREF_131)]. Subsequently, the activation of Cx43 may regress by inhibiting caveolin-3[[132](#_ENREF_132)]. VacA does not affect the mRNA expression of Cx43 and may enhance resistance to the degradation of autophagy, leading to cytoplasmic accumulation of Cx43. VacA can enhance ubiquitinated Cx43 movement to the lysosome for degradation *via* endosomal or autophagic mechanisms, eventually inducing apoptotic cell death *via* glutathione (GSH) and the Rac1/ERK signaling pathway[[133](#_ENREF_133)]. As a result, the cell membrane is destroyed, which may promote cell proliferation in response to damage repair[[134](#_ENREF_134)]. However, *H. pylori* disturbs the balance of the proliferation and apoptosis of cells, driving GC development[[3](#_ENREF_3)].

**CX26**

Cx26, also known as gap junction beta-2 protein, plays a role in tumor suppression through the regulation of the cell cycle[[135](#_ENREF_135)]. It is true that *H. pylori* promotes the DNA promoter methylation of some biomolecules[[136-138](#_ENREF_136)]. Some studies showed that *H. pylori* may be one of the driving forces to induce the promoter methylation of E-cadherin, mainly induced by CagA[[138](#_ENREF_138),[139](#_ENREF_139)]. Such methylation can downregulate E-cadherin expression, which promotes the localization of Cx26 from the cell membrane to the cytoplasm, thereby inhibiting gap junction communication between endometrial cancer cells[[140](#_ENREF_140)]. A loss of intercellular Cx26 expression or an increase in Cx26 expression in the cytoplasm has an important role in carcinogenesis and tumor progression[[62](#_ENREF_62),[64-66](#_ENREF_64)]. This finding can be interpreted as the downregulation of Cx26 that inhibits the proliferation and migration of cells and promotes apoptosis[[45](#_ENREF_45)]. All of these regulations may be drivers of GC development.

**CX37**

Cx37, also known as GJA4, like other Cxs proteins, forms connections between cells known as [gap junctions](https://en.wikipedia.org/wiki/Gap_junction). Cx37 can inhibit cell growth both *in vitro* and *in vivo* and inhibits angiogenesis[[141](#_ENREF_141),[142](#_ENREF_142)]. Cx37 may induce cell death and cell cycle arrest and slow down the cell cycle[[143](#_ENREF_143),[144](#_ENREF_144)]. All of those processes may produce a potential inhibitor of the proliferation of cancer cells[[144](#_ENREF_144),[145](#_ENREF_145)]. A clinical study reported that *H. pylori* infection may have a [close](javascript:;)ly [related](javascript:;) polymorphism of Cx37 (Cx37 C1019T) in GC by altering the frequency of the allele[[146](#_ENREF_146)]. Further, the Cx37 C1019T polymorphism may promote tumor cell proliferation[[145](#_ENREF_145)]. Moreover, many diseases are also associated with the Cx37 gene C1019T polymorphism, such as polycystic ovarian syndrome (PCOS)[[147](#_ENREF_147)] and cardiovascular diseases[[148-151](#_ENREF_148)], among others.

**CONCLUSION AND PERSPECTIVE**

*H. pylori* is a risk factor for GC. *H. pylori* eradication therapy may prevent GC occurrence[[152](#_ENREF_152)]. In the development of *H. pylori*-induced GC, there are a series of pathological and physiological changes, such as chronic gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, and gastric MALT lymphoma, among others[[153-155](#_ENREF_153)]. In this long process, there are many interactions of biological signaling pathways. Cxs are important biomarkers that reflect the status of GC. Currently, only a few members of Cxs have been reported to have an association with GC, such as Cx26, Cx32, Cx37, and Cx43. *H. pylori* may regulate those Cxs involved in different signaling pathways, such as DNA promoter methylation[[8](#_ENREF_8),[75](#_ENREF_75),[76](#_ENREF_76)], the p38 MAP signaling pathway[[85](#_ENREF_85),[86](#_ENREF_86)], histone acetylation[[79-82](#_ENREF_79),[156](#_ENREF_156)], and the JAK2/STAT3 signaling pathway[[120](#_ENREF_120),[157](#_ENREF_157)]. Further, changes in the expression of Cxs may regulate the proliferation, metastasis, invasion, and apoptosis of cells. For all this, further and deeper studies of the relationship between *H. pylori*-associated GC and Cxs are necessary. The dysregulation of Cxs could cause drug resistance in cancer[[116](#_ENREF_116),[158-160](#_ENREF_158)]. Moreover, improving the expression of intercellular Cxs may be a future therapeutic target for GC.

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**REFERENCES**

1 **Fontes LES**, Martimbianco ALC, Zanin C, Riera R. N-acetylcysteine as an adjuvant therapy for Helicobacter pylori eradication. *Cochrane Database Syst Rev* 2019; **2**: CD012357 [PMID: 30746681 DOI: 10.1002/14651858.CD012357.pub2]

2 **Wang F**, Meng W, Wang B, Qiao L. Helicobacter pylori-induced gastric inflammation and gastric cancer. *Cancer Lett* 2014; **345**: 196-202 [PMID: 23981572 DOI: 10.1016/j.canlet.2013.08.016]

3 **Crabtree JE**, Court M, Aboshkiwa MA, Jeremy AH, Dixon MF, Robinson PA. Gastric mucosal cytokine and epithelial cell responses to Helicobacter pylori infection in Mongolian gerbils. *J Pathol* 2004; **202**: 197-207 [PMID: 14743502 DOI: 10.1002/path.1498]

4 **Maleki Kakelar H**, Barzegari A, Dehghani J, Hanifian S, Saeedi N, Barar J, Omidi Y. Pathogenicity of Helicobacter pylori in cancer development and impacts of vaccination. *Gastric Cancer* 2019; **22**: 23-36 [PMID: 30145749 DOI: 10.1007/s10120-018-0867-1]

5 **Backert S**, Meyer TF. Type IV secretion systems and their effectors in bacterial pathogenesis. *Curr Opin Microbiol* 2006; **9**: 207-217 [PMID: 16529981 DOI: 10.1016/j.mib.2006.02.008]

6 **Fischer W**, Püls J, Buhrdorf R, Gebert B, Odenbreit S, Haas R. Systematic mutagenesis of the Helicobacter pylori cag pathogenicity island: Essential genes for CagA translocation in host cells and induction of interleukin-8. *Mol Microbiol* 2001; **42**: 1337-1348 [PMID: 11886563 DOI: 10.1046/j.1365-2958.2001.02714.x]

7 **Hatakeyama M**. [H. pylori oncoprotein CagA and gastric cancer]. *Nihon Rinsho* 2012; **70**: 1699-1704 [PMID: 23198548]

8 **Zhang B**, Zhang X, Jin M, Hu L, Zang M, Qiu W, Wang S, Liu B, Liu S, Guo D. CagA increases DNA methylation and decreases PTEN expression in human gastric cancer. *Mol Med Rep* 2019; **19**: 309-319 [PMID: 30431097 DOI: 10.3892/mmr.2018.9654]

9 **Zhang BG**, Hu L, Zang MD, Wang HX, Zhao W, Li JF, Su LP, Shao Z, Zhao X, Zhu ZG, Yan M, Liu B. Helicobacter pylori CagA induces tumor suppressor gene hypermethylation by upregulating DNMT1 via AKT-NFκB pathway in gastric cancer development. *Oncotarget* 2016; **7**: 9788-9800 [PMID: 26848521 DOI: 10.18632/oncotarget.7125]

10 **Yamaoka Y**. Mechanisms of disease: Helicobacter pylori virulence factors. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 629-641 [PMID: 20938460 DOI: 10.1038/nrgastro.2010.154]

11 **Lai YP**, Yang JC, Lin TZ, Lin JT, Wang JT. Helicobacter pylori infection and CagA protein translocation in human primary gastric epithelial cell culture. *Helicobacter* 2006; **11**: 451-459 [PMID: 16961808 DOI: 10.1111/j.1523-5378.2006.00438.x]

12 **Khatoon J**, Prasad KN, Prakash Rai R, Ghoshal UC, Krishnani N. Association of heterogenicity of Helicobacter pylori cag pathogenicity island with peptic ulcer diseases and gastric cancer. *Br J Biomed Sci* 2017; **74**: 121-126 [PMID: 28571523 DOI: 10.1080/09674845.2017.1278887]

13 **Phadnis SH**, Ilver D, Janzon L, Normark S, Westblom TU. Pathological significance and molecular characterization of the vacuolating toxin gene of Helicobacter pylori. *Infect Immun* 1994; **62**: 1557-1565 [PMID: 8168917 DOI: 10.1007/BF01716716]

14 **Cover TL**, Tummuru MK, Cao P, Thompson SA, Blaser MJ. Divergence of genetic sequences for the vacuolating cytotoxin among Helicobacter pylori strains. *J Biol Chem* 1994; **269**: 10566-10573 [PMID: 8144644]

15 **Rhead JL**, Letley DP, Mohammadi M, Hussein N, Mohagheghi MA, Eshagh Hosseini M, Atherton JC. A new Helicobacter pylori vacuolating cytotoxin determinant, the intermediate region, is associated with gastric cancer. *Gastroenterology* 2007; **133**: 926-936 [PMID: 17854597 DOI: 10.1053/j.gastro.2007.06.056]

16 **Atherton JC**, Cao P, Peek RM Jr, Tummuru MK, Blaser MJ, Cover TL. Mosaicism in vacuolating cytotoxin alleles of Helicobacter pylori. Association of specific vacA types with cytotoxin production and peptic ulceration. *J Biol Chem* 1995; **270**: 17771-17777 [PMID: 7629077 DOI: 10.1074/jbc.270.30.17771]

17 **Atherton JC**, Blaser MJ. Coadaptation of Helicobacter pylori and humans: Ancient history, modern implications. *J Clin Invest* 2009; **119**: 2475-2487 [PMID: 19729845 DOI: 10.1172/JCI38605]

18 **Figueiredo C**, Machado JC, Pharoah P, Seruca R, Sousa S, Carvalho R, Capelinha AF, Quint W, Caldas C, van Doorn LJ, Carneiro F, Sobrinho-Simões M. Helicobacter pylori and interleukin 1 genotyping: An opportunity to identify high-risk individuals for gastric carcinoma. *J Natl Cancer Inst* 2002; **94**: 1680-1687 [PMID: 12441323 DOI: 10.1093/jnci/94.22.1680]

19 **Basso D**, Zambon CF, Letley DP, Stranges A, Marchet A, Rhead JL, Schiavon S, Guariso G, Ceroti M, Nitti D, Rugge M, Plebani M, Atherton JC. Clinical relevance of Helicobacter pylori cagA and vacA gene polymorphisms. *Gastroenterology* 2008; **135**: 91-99 [PMID: 18474244 DOI: 10.1053/j.gastro.2008.03.041]

20 **Miehlke S**, Kirsch C, Agha-Amiri K, Günther T, Lehn N, Malfertheiner P, Stolte M, Ehninger G, Bayerdörffer E. The Helicobacter pylori vacA s1, m1 genotype and cagA is associated with gastric carcinoma in Germany. *Int J Cancer* 2000; **87**: 322-327 [PMID: 10897035 DOI: 10.1002/1097-0215(20000801)87:3<322::AID-IJC3>3.3.CO;2-D]

21 **Nogueira C**, Figueiredo C, Carneiro F, Gomes AT, Barreira R, Figueira P, Salgado C, Belo L, Peixoto A, Bravo JC, Bravo LE, Realpe JL, Plaisier AP, Quint WG, Ruiz B, Correa P, van Doorn LJ. Helicobacter pylori genotypes may determine gastric histopathology. *Am J Pathol* 2001; **158**: 647-654 [PMID: 11159201 DOI: 10.1016/s0002-9440(10)64006-0]

22 **Memon AA**, Hussein NR, Miendje Deyi VY, Burette A, Atherton JC. Vacuolating cytotoxin genotypes are strong markers of gastric cancer and duodenal ulcer-associated Helicobacter pylori strains: A matched case-control study. *J Clin Microbiol* 2014; **52**: 2984-2989 [PMID: 24920772 DOI: 10.1128/JCM.00551-14]

23 **Winter JA**, Letley DP, Cook KW, Rhead JL, Zaitoun AA, Ingram RJ, Amilon KR, Croxall NJ, Kaye PV, Robinson K, Atherton JC. A role for the vacuolating cytotoxin, VacA, in colonization and Helicobacter pylori-induced metaplasia in the stomach. *J Infect Dis* 2014; **210**: 954-963 [PMID: 24625807 DOI: 10.1093/infdis/jiu154]

24 **McClain MS**, Beckett AC, Cover TL. Helicobacter pylori Vacuolating Toxin and Gastric Cancer. *Toxins (Basel)* 2017; **9**: pii: E316 [PMID: 29023421 DOI: 10.3390/toxins9100316]

25 **Papini E**, Satin B, Norais N, de Bernard M, Telford JL, Rappuoli R, Montecucco C. Selective increase of the permeability of polarized epithelial cell monolayers by Helicobacter pylori vacuolating toxin. *J Clin Invest* 1998; **102**: 813-820 [PMID: 9710450 DOI: 10.1172/JCI2764]

26 **Abdullah M**, Greenfield LK, Bronte-Tinkew D, Capurro MI, Rizzuti D, Jones NL. VacA promotes CagA accumulation in gastric epithelial cells during Helicobacter pylori infection. *Sci Rep* 2019; **9**: 38 [PMID: 30631092 DOI: 10.1038/s41598-018-37095-4]

27 **Xing Y**, Zhang Y, Jia L, Xu X. Lipopolysaccharide from Escherichia coli stimulates osteogenic differentiation of human periodontal ligament stem cells through Wnt/β-catenin-induced TAZ elevation. *Mol Oral Microbiol* 2019; **34** [PMID: 30387555 DOI: 10.1111/omi.12249]

28 **Niu C**, Shang N, Liao X, Feng E, Liu X, Wang D, Wang J, Huang P, Hua Y, Zhu L, Wang H. Analysis of Soluble protein complexes in Shigella flexneri reveals the influence of temperature on the amount of lipopolysaccharide. *Mol Cell Proteomics* 2013; **12**: 1250-1258 [PMID: 23378524 DOI: 10.1074/mcp.M112.025270]

29 **Kasperkiewicz K**, Swierzko AS, Bartlomiejczyk MA, Cedzynski M, Noszczynska M, Duda KA, Michalski M, Skurnik M. Interaction of human mannose-binding lectin (MBL) with Yersinia enterocolitica lipopolysaccharide. *Int J Med Microbiol* 2015; **305**: 544-552 [PMID: 26188838 DOI: 10.1016/j.ijmm.2015.07.001]

30 **Lee SJ**, Kim SW, Cho YH, Yoon MS. Anti-inflammatory effect of an Escherichia coli extract in a mouse model of lipopolysaccharide-induced cystitis. *World J Urol* 2006; **24**: 33-38 [PMID: 16389538 DOI: 10.1007/s00345-005-0046-y]

31 **Li H**, Liao T, Debowski AW, Tang H, Nilsson HO, Stubbs KA, Marshall BJ, Benghezal M. Lipopolysaccharide Structure and Biosynthesis in Helicobacter pylori. *Helicobacter* 2016; **21**: 445-461 [PMID: 26934862 DOI: 10.1111/hel.12301]

32 **Li N**, Xu H, Ou Y, Feng Z, Zhang Q, Zhu Q, Cai Z. LPS-induced CXCR7 expression promotes gastric Cancer proliferation and migration via the TLR4/MD-2 pathway. *Diagn Pathol* 2019; **14**: 3 [PMID: 30636642 DOI: 10.1186/s13000-019-0780-x]

33 **Li H**, Xia JQ, Zhu FS, Xi ZH, Pan CY, Gu LM, Tian YZ. LPS promotes the expression of PD-L1 in gastric cancer cells through NF-κB activation. *J Cell Biochem* 2018; **119**: 9997-10004 [PMID: 30145830 DOI: 10.1002/jcb.27329]

34 **Wang F**, Mao Z, Liu D, Yu J, Wang Y, Ye W, Lin D, Zhou N, Xie Y. Overexpression of Tim-3 reduces Helicobacter pylori-associated inflammation through TLR4/NFκB signaling in vitro. *Mol Med Rep* 2017; **15**: 3252-3258 [PMID: 28339054 DOI: 10.3892/mmr.2017.6346]

35 **Chochi K**, Ichikura T, Kinoshita M, Majima T, Shinomiya N, Tsujimoto H, Kawabata T, Sugasawa H, Ono S, Seki S, Mochizuki H. Helicobacter pylori augments growth of gastric cancers via the lipopolysaccharide-toll-like receptor 4 pathway whereas its lipopolysaccharide attenuates antitumor activities of human mononuclear cells. *Clin Cancer Res* 2008; **14**: 2909-2917 [PMID: 18483357 DOI: 10.1158/1078-0432.CCR-07-4467]

36 **Yokota S**, Okabayashi T, Rehli M, Fujii N, Amano K. Helicobacter pylori lipopolysaccharides upregulate toll-like receptor 4 expression and proliferation of gastric epithelial cells via the MEK1/2-ERK1/2 mitogen-activated protein kinase pathway. *Infect Immun* 2010; **78**: 468-476 [PMID: 19858308 DOI: 10.1128/IAI.00903-09]

37 **Vinken M**, Vanhaecke T, Papeleu P, Snykers S, Henkens T, Rogiers V. Connexins and their channels in cell growth and cell death. *Cell Signal* 2006; **18**: 592-600 [PMID: 16183253 DOI: 10.1016/j.cellsig.2005.08.012]

38 **Goodenough DA**, Goliger JA, Paul DL. Connexins, connexons, and intercellular communication. *Annu Rev Biochem* 1996; **65**: 475-502 [PMID: 8811187 DOI: 10.1146/annurev.bi.65.070196.002355]

39 **Xu CX**, Jia Y, Yang WB, Wang F, Shen SR. [Relationship between Helicobacter pylori infection and expression of connexin (Cx) 32 and Cx43 genes in gastric cancer and gastric precancerous lesions]. *Zhonghua Yi Xue Za Zhi* 2008; **88**: 1523-1527 [PMID: 18956631]

40 **Li X**, Zhou Z, Dou K, Wang Y. Connexin evolution ameliorates the risk of various cancers. *Eur Rev Med Pharmacol Sci* 2015; **19**: 1662-1672 [PMID: 26004607]

41 **Xu L**, Chen SW, Qi XY, Li XX, Sun YB. Ginsenoside improves papillary thyroid cancer cell malignancies partially through upregulating connexin 31. *Kaohsiung J Med Sci* 2018; **34**: 313-320 [PMID: 29747774 DOI: 10.1016/j.kjms.2017.12.006]

42 **Lai Y**, Tao L, Zhao Y, Zhang X, Sun X, Wang Q, Xu C. Cx32 inhibits TNFα-induced extrinsic apoptosis with and without EGFR suppression. *Oncol Rep* 2017; **38**: 2885-2892 [PMID: 28901517 DOI: 10.3892/or.2017.5950]

43 **Lai Y**, Fan L, Zhao Y, Ge H, Feng X, Wang Q, Zhang X, Peng Y, Wang X, Tao L. Cx32 suppresses extrinsic apoptosis in human cervical cancer cells via the NF‑κB signalling pathway. *Int J Oncol* 2017; **51**: 1159-1168 [PMID: 28902345 DOI: 10.3892/ijo.2017.4106]

44 **Radin JN**, González-Rivera C, Frick-Cheng AE, Sheng J, Gaddy JA, Rubin DH, Algood HM, McClain MS, Cover TL. Role of connexin 43 in Helicobacter pylori VacA-induced cell death. *Infect Immun* 2014; **82**: 423-432 [PMID: 24191302 DOI: 10.1128/IAI.00827-13]

45 **Yang J**, Qin GH, Chen JZ. Inhibitory effect of lentivirus targeting interference Cx26 on proliferation and migration of human highly metastatic hepatocellular carcinoma HCCLM3 cells. *Zhongguo Yaolixue Tongbao* 2014; **30**: 937-941 [DOI: 10.3969/j.issn.1001-1978.2014.07.012]

46 **Fong JT**, Kells RM, Gumpert AM, Marzillier JY, Davidson MW, Falk MM. Internalized gap junctions are degraded by autophagy. *Autophagy* 2012; **8**: 794-811 [PMID: 22635056 DOI: 10.4161/auto.19390]

47 **Krutovskikh VA**, Piccoli C, Yamasaki H. Gap junction intercellular communication propagates cell death in cancerous cells. *Oncogene* 2002; **21**: 1989-1999 [PMID: 11960371 DOI: 10.1038/sj.onc.1205187]

48 **Mine T**, Endo C, Kushima R, Kushima W, Kobayashi I, Muraoka H, Taki R, Fujita T. The effects of water extracts of CagA positive or negative Helicobacter pylori on proliferation, apoptosis and connexin formation in acetic acid-induced gastric ulcer of rats. *Aliment Pharmacol Ther* 2000; **14 Suppl 1**: 199-204 [PMID: 10807425 DOI: 10.1046/j.1365-2036.2000.014s1199.x]

49 **Liu X**, Furuya T, Li D, Xu J, Cao X, Li Q, Xu J, Xu Z, Sasaki K, Liu X. Connexin 26 expression correlates with less aggressive phenotype of intestinal type-gastric carcinomas. *Int J Mol Med* 2010; **25**: 709-716 [PMID: 20372813 DOI: 10.3892/ijmm\_00000395]

50 **Nishitani A**, Hirota S, Nishida T, Isozaki K, Hashimoto K, Nakagomi N, Matsuda H. Differential expression of connexin 43 in gastrointestinal stromal tumours of gastric and small intestinal origin. *J Pathol* 2005; **206**: 377-382 [PMID: 15938003 DOI: 10.1002/path.1799]

51 **Wang YF**, Daniel EE. Gap junctions in gastrointestinal muscle contain multiple connexins. *Am J Physiol Gastrointest Liver Physiol* 2001; **281**: G533-G543 [PMID: 11447034 DOI: 10.1152/ajpgi.2001.281.2.G533]

52 **Iino S**, Asamoto K, Nojyo Y. Heterogeneous distribution of a gap junction protein, connexin43, in the gastroduodenal junction of the guinea pig. *Auton Neurosci* 2001; **93**: 8-13 [PMID: 11695711 DOI: 10.1016/S1566-0702(01)00320-4]

53 **Takahashi N**, Joh T, Yokoyama Y, Seno K, Nomura T, Ohara H, Ueda F, Itoh M. Importance of gap junction in gastric mucosal restitution from acid-induced injury. *J Lab Clin Med* 2000; **136**: 93-99 [PMID: 10945237 DOI: 10.1067/mlc.2000.108158]

54 **Iwata F**, Joh T, Ueda F, Yokoyama Y, Itoh M. Role of gap junctions in inhibiting ischemia-reperfusion injury of rat gastric mucosa. *Am J Physiol* 1998; **275**: G883-G888 [PMID: 9815015 DOI: 10.1152/ajpgi.1998.275.5.G883]

55 **Uchida Y**, Matsuda K, Sasahara K, Kawabata H, Nishioka M. Immunohistochemistry of gap junctions in normal and diseased gastric mucosa of humans. *Gastroenterology* 1995; **109**: 1492-1496 [PMID: 7557130 DOI: 10.1016/0016-5085(95)90635-5]

56 **Jing Y**, Guo S, Zhang X, Sun A, Tao F, Ju H, Qian H. Effects of small interfering RNA interference of connexin 37 on subcutaneous gastric tumours in mice. *Mol Med Rep* 2014; **10**: 2955-2960 [PMID: 25310476 DOI: 10.3892/mmr.2014.2609]

57 **Radebold K**, Horakova E, Gloeckner J, Ortega G, Spray DC, Vieweger H, Siebert K, Manuelidis L, Geibel JP. Gap junctional channels regulate acid secretion in the mammalian gastric gland. *J Membr Biol* 2001; **183**: 147-153 [PMID: 11696856 DOI: 10.1007/s00232-001-0062-9]

58 **Liu XM**, Xu CX, Zhang LF, Huang LH, Hu TZ, Li R, Xia XJ, Xu LY, Luo L, Jiang XX, Li M. PBX1 attributes as a determinant of connexin 32 downregulation in Helicobacter pylori-related gastric carcinogenesis. *World J Gastroenterol* 2017; **23**: 5345-5355 [PMID: 28839434 DOI: 10.3748/wjg.v23.i29.5345]

59 **Zhou L**, Xu C, Hu T, Liu X, Xiao J, Luo L, Jiang X. [Effect of H. pylori on the expression of CCAAT enhancer binding protein α and Cx43 and its role in gastric carcinogenesis]. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2016; **41**: 700-706 [PMID: 27592574 DOI: 10.11817/j.issn.1672-7347.2016.07.007]

60 **Liu X**, Cao K, Xu C, Hu T, Zhou L, Cao D, Xiao J, Luo L, Guo Y, Qi Y. GATA-3 augmentation down-regulates Connexin43 in Helicobacter pylori associated gastric carcinogenesis. *Cancer Biol Ther* 2015; **16**: 987-996 [PMID: 25901741 DOI: 10.1080/15384047.2015.1030552]

61 **Tang B**, Peng ZH, Yu PW, Yu G, Qian F. Expression and significance of Cx43 and E-cadherin in gastric cancer and metastatic lymph nodes. *Med Oncol* 2011; **28**: 502-508 [PMID: 20373058 DOI: 10.1007/s12032-010-9492-5]

62 **Jamieson S**, Going JJ, D'Arcy R, George WD. Expression of gap junction proteins connexin 26 and connexin 43 in normal human breast and in breast tumours. *J Pathol* 1998; **184**: 37-43 [PMID: 9582525 DOI: 10.1002/(SICI)1096-9896(199801)184:1<37::AID-PATH966>3.0.CO;2-D]

63 **Mehta PP**, Perez-Stable C, Nadji M, Mian M, Asotra K, Roos BA. Suppression of human prostate cancer cell growth by forced expression of connexin genes. *Dev Genet* 1999; **24**: 91-110 [PMID: 10079514 DOI: 10.1002/(SICI)1520-6408(1999)24:1/2<91::AID-DVG10>3.3.CO;2-R]

64 **Kanczuga-Koda L**, Sulkowski S, Koda M, Sulkowska M. Alterations in connexin26 expression during colorectal carcinogenesis. *Oncology* 2005; **68**: 217-222 [PMID: 16015037 DOI: 10.1159/000086777]

65 **Hong R**, Lim SC. Pathological significance of connexin 26 expression in colorectal adenocarcinoma. *Oncol Rep* 2008; **19**: 913-919 [PMID: 18357375 DOI: 10.3892/or.19.4.913]

66 **Inose T**, Kato H, Kimura H, Faried A, Tanaka N, Sakai M, Sano A, Sohda M, Nakajima M, Fukai Y, Miyazaki T, Masuda N, Fukuchi M, Kuwano H. Correlation between connexin 26 expression and poor prognosis of esophageal squamous cell carcinoma. *Ann Surg Oncol* 2009; **16**: 1704-1710 [PMID: 19326169 DOI: 10.1245/s10434-009-0443-3]

67 **Jee H**, Nam KT, Kwon HJ, Han SU, Kim DY. Altered expression and localization of connexin32 in human and murine gastric carcinogenesis. *Dig Dis Sci* 2011; **56**: 1323-1332 [PMID: 21082351 DOI: 10.1007/s10620-010-1467-z]

68 **Kojima T**, Kokai Y, Chiba H, Yamamoto M, Mochizuki Y, Sawada N. Cx32 but not Cx26 is associated with tight junctions in primary cultures of rat hepatocytes. *Exp Cell Res* 2001; **263**: 193-201 [PMID: 11161718 DOI: 10.1006/excr.2000.5103]

69 **Eugenín EA**, González HE, Sánchez HA, Brañes MC, Sáez JC. Inflammatory conditions induce gap junctional communication between rat Kupffer cells both in vivo and in vitro. *Cell Immunol* 2007; **247**: 103-110 [PMID: 17900549 DOI: 10.1016/j.cellimm.2007.08.001]

70 **Zhang JT**, Nicholson BJ. Sequence and tissue distribution of a second protein of hepatic gap junctions, Cx26, as deduced from its cDNA. *J Cell Biol* 1989; **109**: 3391-3401 [PMID: 2557354 DOI: 10.1083/jcb.109.6.3391]

71 **Fischer R**, Reinehr R, Lu TP, Schönicke A, Warskulat U, Dienes HP, Häussinger D. Intercellular communication via gap junctions in activated rat hepatic stellate cells. *Gastroenterology* 2005; **128**: 433-448 [PMID: 15685554 DOI: 10.1053/j.gastro.2004.11.065]

72 **Lim MC**, Maubach G, Zhuo L. TGF-beta1 down-regulates connexin 43 expression and gap junction intercellular communication in rat hepatic stellate cells. *Eur J Cell Biol* 2009; **88**: 719-730 [PMID: 19781809 DOI: 10.1016/j.ejcb.2009.08.003]

73 **Mitaka T**, Sato F, Mizuguchi T, Yokono T, Mochizuki Y. Reconstruction of hepatic organoid by rat small hepatocytes and hepatic nonparenchymal cells. *Hepatology* 1999; **29**: 111-125 [PMID: 9862857 DOI: 10.1002/hep.510290103]

74 **Maes M**, Crespo Yanguas S, Willebrords J, Cogliati B, Vinken M. Connexin and pannexin signaling in gastrointestinal and liver disease. *Transl Res* 2015; **166**: 332-343 [PMID: 26051630 DOI: 10.1016/j.trsl.2015.05.005]

75 **Hernández-Guerra M**, González-Méndez Y, de Ganzo ZA, Salido E, García-Pagán JC, Abrante B, Malagón AM, Bosch J, Quintero E. Role of gap junctions modulating hepatic vascular tone in cirrhosis. *Liver Int* 2014; **34**: 859-868 [PMID: 24350605 DOI: 10.1111/liv.12446]

76 **Shiojiri N**, Niwa T, Sugiyama Y, Koike T. Preferential expression of connexin37 and connexin40 in the endothelium of the portal veins during mouse liver development. *Cell Tissue Res* 2006; **324**: 547-552 [PMID: 16505993 DOI: 10.1007/s00441-006-0165-9]

77 **Chaytor AT**, Martin PE, Edwards DH, Griffith TM. Gap junctional communication underpins EDHF-type relaxations evoked by ACh in the rat hepatic artery. *Am J Physiol Heart Circ Physiol* 2001; **280**: H2441-H2450 [PMID: 11356596 DOI: 10.1152/ajpheart.2001.280.6.H2441]

78 **Kim EM**, Bae YM, Choi MH, Hong ST. Connexin 43 plays an important role in the transformation of cholangiocytes with Clonochis sinensis excretory-secretory protein and N-nitrosodimethylamine. *PLoS Negl Trop Dis* 2019; **13**: e0006843 [PMID: 30943209 DOI: 10.1371/journal.pntd.0006843]

79 **Bode HP**, Wang L, Cassio D, Leite MF, St-Pierre MV, Hirata K, Okazaki K, Sears ML, Meda P, Nathanson MH, Dufour JF. Expression and regulation of gap junctions in rat cholangiocytes. *Hepatology* 2002; **36**: 631-640 [PMID: 12198655 DOI: 10.1053/jhep.2002.35274]

80 **Jing YM**, Guo SX, Zhang XP, Sun AJ, Tao F, Qian HX. Association between C1019T polymorphism in the connexin 37 gene and Helicobacter pylori infection in patients with gastric cancer. *Asian Pac J Cancer Prev* 2012; **13**: 2363-2367 [PMID: 22901223 DOI: 10.7314/apjcp.2012.13.5.2363]

81 **Fink C**, Hembes T, Brehm R, Weigel R, Heeb C, Pfarrer C, Bergmann M, Kressin M. Specific localisation of gap junction protein connexin 32 in the gastric mucosa of horses. *Histochem Cell Biol* 2006; **125**: 307-313 [PMID: 16205941 DOI: 10.1007/s00418-005-0047-3]

82 **Nakamura K**, Nishii K, Shibata Y. [Networks of pacemaker cells for gastrointestinal motility]. *Nihon Yakurigaku Zasshi* 2004; **123**: 134-140 [PMID: 14993724 DOI: 10.1254/fpj.123.134]

83 **Frinchi M**, Di Liberto V, Turimella S, D'Antoni F, Theis M, Belluardo N, Mudò G. Connexin36 (Cx36) expression and protein detection in the mouse carotid body and myenteric plexus. *Acta Histochem* 2013; **115**: 252-256 [PMID: 22897942 DOI: 10.1016/j.acthis.2012.07.005]

84 **Bracken S**, Byrne G, Kelly J, Jackson J, Feighery C. Altered gene expression in highly purified enterocytes from patients with active coeliac disease. *BMC Genomics* 2008; **9**: 377 [PMID: 18691394 DOI: 10.1186/1471-2164-9-377]

85 **King TJ**, Lampe PD. Mice deficient for the gap junction protein Connexin32 exhibit increased radiation-induced tumorigenesis associated with elevated mitogen-activated protein kinase (p44/Erk1, p42/Erk2) activation. *Carcinogenesis* 2004; **25**: 669-680 [PMID: 14742325 DOI: 10.1093/carcin/bgh071]

86 **Nemeth L**, Maddur S, Puri P. Immunolocalization of the gap junction protein Connexin43 in the interstitial cells of Cajal in the normal and Hirschsprung's disease bowel. *J Pediatr Surg* 2000; **35**: 823-828 [PMID: 10873019 DOI: 10.1053/jpsu.2000.6851]

87 **Mattii L**, Ippolito C, Segnani C, Battolla B, Colucci R, Dolfi A, Bassotti G, Blandizzi C, Bernardini N. Altered expression pattern of molecular factors involved in colonic smooth muscle functions: An immunohistochemical study in patients with diverticular disease. *PLoS One* 2013; **8**: e57023 [PMID: 23437299 DOI: 10.1371/journal.pone.0057023]

88 **Kanczuga-Koda L**, Sulkowski S, Koda M, Skrzydlewska E, Sulkowska M. Connexin 26 correlates with Bcl-xL and Bax proteins expression in colorectal cancer. *World J Gastroenterol* 2005; **11**: 1544-1548 [PMID: 15770735 DOI: 10.3748/wjg.v11.i10.1544]

89 **Ismail R**, Rashid R, Andrabi K, Parray FQ, Besina S, Shah MA, Ul Hussain M. Pathological implications of Cx43 down-regulation in human colon cancer. *Asian Pac J Cancer Prev* 2014; **15**: 2987-2991 [PMID: 24815435 DOI: 10.7314/apjcp.2014.15.7.2987]

90 **Kanczuga-Koda L**, Sulkowski S, Koda M, Sobaniec-Lotowska M, Sulkowska M. Expression of connexins 26, 32 and 43 in the human colon--an immunohistochemical study. *Folia Histochem Cytobiol* 2004; **42**: 203-207 [PMID: 15704645]

91 **Kanady JD**, Munger SJ, Witte MH, Simon AM. Combining Foxc2 and Connexin37 deletions in mice leads to severe defects in lymphatic vascular growth and remodeling. *Dev Biol* 2015; **405**: 33-46 [PMID: 26079578 DOI: 10.1016/j.ydbio.2015.06.004]

92 **Oyamada M**, Oyamada Y, Takamatsu T. Regulation of connexin expression. *Biochim Biophys Acta* 2005; **1719**: 6-23 [PMID: 16359940 DOI: 10.1016/j.bbamem.2005.11.002]

93 **Senderek J**, Hermanns B, Bergmann C, Boroojerdi B, Bajbouj M, Hungs M, Ramaekers VT, Quasthoff S, Karch D, Schröder JM. X-linked dominant Charcot-Marie-Tooth neuropathy: Clinical, electrophysiological, and morphological phenotype in four families with different connexin32 mutations(1). *J Neurol Sci* 1999; **167**: 90-101 [PMID: 10521546 DOI: 10.1016/s0022-510x(99)00146-x]

94 **Nicholson SM**, Ressot C, Gomès D, D'Andrea P, Perea J, Duval N, Bruzzone R. Connexin32 in the Peripheral Nervous System: Functional Analysis of Mutations Associated with X-linked Charcot-Marie-Tooth Syndrome and Implications for the Pathophysiology of the Disease. *Ann N Y Acad Sci* 1999; **883**: 168-185 [PMID: 29086926 DOI: 10.1111/j.1749-6632.1999.tb08580.x]

95 **Nakashima Y**, Ono T, Yamanoi A, El-Assal ON, Kohno H, Nagasue N. Expression of gap junction protein connexin32 in chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. *J Gastroenterol* 2004; **39**: 763-768 [PMID: 15338370 DOI: 10.1007/s00535-003-1386-2]

96 **Yang J**, Ichikawa A, Tsuchiya T. A novel function of connexin 32: Marked enhancement of liver function in a hepatoma cell line. *Biochem Biophys Res Commun* 2003; **307**: 80-85 [PMID: 12849984 DOI: 10.1016/s0006-291x(03)01117-3]

97 **Jee H**, Lee SH, Park JW, Lee BR, Nam KT, Kim DY. Connexin32 inhibits gastric carcinogenesis through cell cycle arrest and altered expression of p21Cip1 and p27Kip1. *BMB Rep* 2013; **46**: 25-30 [PMID: 23351380 DOI: 10.5483/bmbrep.2013.46.1.078]

98 **Kanczuga-Koda L**, Koda M, Sulkowski S, Wincewicz A, Zalewski B, Sulkowska M. Gradual loss of functional gap junction within progression of colorectal cancer -- a shift from membranous CX32 and CX43 expression to cytoplasmic pattern during colorectal carcinogenesis. *In Vivo* 2010; **24**: 101-107 [PMID: 20133984 DOI: 10.1089/hum.2009.1214]

99 **Hirai A**, Yano T, Nishikawa K, Suzuki K, Asano R, Satoh H, Hagiwara K, Yamasaki H. Down-regulation of connexin 32 gene expression through DNA methylation in a human renal cell carcinoma cell. *Am J Nephrol* 2003; **23**: 172-177 [PMID: 12690227 DOI: 10.1159/000070653]

100 **Wang Y**, Huang LH, Xu CX, Xiao J, Zhou L, Cao D, Liu XM, Qi Y. Connexin 32 and 43 promoter methylation in Helicobacter pylori-associated gastric tumorigenesis. *World J Gastroenterol* 2014; **20**: 11770-11779 [PMID: 25206281 DOI: 10.3748/wjg.v20.i33.11770]

101 **Huang L**, Guo Y, Cao D, Liu X, Zhang L, Cao K, Hu T, Qi Y, Xu C. Effects of Helicobacter pylori on the expression levels of GATA-3 and connexin 32 and the GJIC function in gastric epithelial cells and their association by promoter analysis. *Oncol Lett* 2018; **16**: 1650-1658 [PMID: 30008849 DOI: 10.3892/ol.2018.8796]

102 **Verdin E**, Ott M. 50 years of protein acetylation: From gene regulation to epigenetics, metabolism and beyond. *Nat Rev Mol Cell Biol* 2015; **16**: 258-264 [PMID: 25549891 DOI: 10.1038/nrm3931]

103 **Grabiec AM**, Potempa J. Epigenetic regulation in bacterial infections: Targeting histone deacetylases. *Crit Rev Microbiol* 2018; **44**: 336-350 [PMID: 28971711 DOI: 10.1080/1040841X.2017.1373063]

104 **Ding SZ**, Fischer W, Kaparakis-Liaskos M, Liechti G, Merrell DS, Grant PA, Ferrero RL, Crowe SE, Haas R, Hatakeyama M, Goldberg JB. Helicobacter pylori-induced histone modification, associated gene expression in gastric epithelial cells, and its implication in pathogenesis. *PLoS One* 2010; **5**: e9875 [PMID: 20368982 DOI: 10.1371/journal.pone.0009875]

105 **Vinken M**, Henkens T, Snykers S, Lukaszuk A, Tourwé D, Rogiers V, Vanhaecke T. The novel histone deacetylase inhibitor 4-Me2N-BAVAH differentially affects cell junctions between primary hepatocytes. *Toxicology* 2007; **236**: 92-102 [PMID: 17482745 DOI: 10.1016/j.tox.2007.04.003]

106 **Vinken M**, Henkens T, Vanhaecke T, Papeleu P, Geerts A, Van Rossen E, Chipman JK, Meda P, Rogiers V. Trichostatin a enhances gap junctional intercellular communication in primary cultures of adult rat hepatocytes. *Toxicol Sci* 2006; **91**: 484-492 [PMID: 16531468 DOI: 10.1093/toxsci/kfj152]

107 **Cuadrado A**, Nebreda AR. Mechanisms and functions of p38 MAPK signalling. *Biochem J* 2010; **429**: 403-417 [PMID: 20626350 DOI: 10.1042/BJ20100323]

108 **Zarubin T**, Han J. Activation and signaling of the p38 MAP kinase pathway. *Cell Res* 2005; **15**: 11-18 [PMID: 15686620 DOI: 10.1038/sj.cr.7290257]

109 **Yang M**, Wang L, Gu LJ, Yuan WJ. Helicobacter pylori cytotoxin-associated gene A impairs the filtration barrier function of podocytes via p38 MAPK signaling pathway. *Acta Biochim Pol* 2017; **64**: 471-475 [PMID: 28803254 DOI: 10.18388/abp.2016\_1322]

110 **Yamamoto T**, Kojima T, Murata M, Takano K, Go M, Hatakeyama N, Chiba H, Sawada N. p38 MAP-kinase regulates function of gap and tight junctions during regeneration of rat hepatocytes. *J Hepatol* 2005; **42**: 707-718 [PMID: 15826721 DOI: 10.1016/j.jhep.2004.12.033]

111 **Slomiany BL**, Slomiany A. Role of LPS-elicited signaling in triggering gastric mucosal inflammatory responses to H. pylori: Modulatory effect of ghrelin. *Inflammopharmacology* 2017; **25**: 415-429 [PMID: 28516374 DOI: 10.1007/s10787-017-0360-1]

112 **Fallone CA**, Chiba N, van Zanten SV, Fischbach L, Gisbert JP, Hunt RH, Jones NL, Render C, Leontiadis GI, Moayyedi P, Marshall JK. The Toronto Consensus for the Treatment of Helicobacter pylori Infection in Adults. *Gastroenterology* 2016; **151**: 51-69.e14 [PMID: 27102658 DOI: 10.1053/j.gastro.2016.04.006]

113 **Slomiany BL**, Slomiany A. Cytosolic phospholipase A2 activation in Helicobacter pylori lipopolysaccharide-induced interference with gastric mucin synthesis. *IUBMB Life* 2006; **58**: 217-223 [PMID: 16754300 DOI: 10.1080/15216540600732021]

114 **Dhar SK**, Soni RK, Das BK, Mukhopadhyay G. Molecular mechanism of action of major Helicobacter pylori virulence factors. *Mol Cell Biochem* 2003; **253**: 207-215 [PMID: 14619971 DOI: 10.1023/A:1026051530512]

115 **Slomiany BL**, Piotrowski J, Slomiany A. Anti-Helicobacter pylori activities of ebrotidine. A review of biochemical and animal experimental studies and data. *Arzneimittelforschung* 1997; **47**: 475-482 [PMID: 9205747 DOI: 10.1007/BF02974011]

116 **Kameoka S**, Kameyama T, Hayashi T, Sato S, Ohnishi N, Hayashi T, Murata-Kamiya N, Higashi H, Hatakeyama M, Takaoka A. Helicobacter pylori induces IL-1β protein through the inflammasome activation in differentiated macrophagic cells. *Biomed Res* 2016; **37**: 21-27 [PMID: 26912137 DOI: 10.2220/biomedres.37.21]

117 **Semper RP**, Mejías-Luque R, Groß C, Anderl F, Müller A, Vieth M, Busch DH, Prazeres da Costa C, Ruland J, Groß O, Gerhard M. Helicobacter pylori-induced IL-1β secretion in innate immune cells is regulated by the NLRP3 inflammasome and requires the cag pathogenicity island. *J Immunol* 2014; **193**: 3566-3576 [PMID: 25172489 DOI: 10.4049/jimmunol.1400362]

118 **Kim DJ**, Park JH, Franchi L, Backert S, Núñez G. The Cag pathogenicity island and interaction between TLR2/NOD2 and NLRP3 regulate IL-1β production in Helicobacter pylori infected dendritic cells. *Eur J Immunol* 2013; **43**: 2650-2658 [PMID: 23818043 DOI: 10.1002/eji.201243281]

119 **Yamamoto T**, Kojima T, Murata M, Takano K, Go M, Chiba H, Sawada N. IL-1beta regulates expression of Cx32, occludin, and claudin-2 of rat hepatocytes via distinct signal transduction pathways. *Exp Cell Res* 2004; **299**: 427-441 [PMID: 15350541 DOI: 10.1016/j.yexcr.2004.06.011]

120 **Ji YT**, Yang Y, Zheng RS, Zhang WQ, Liu J. Construction of lentiviral vector-mediated Cx32 stably over-expressed Huh7 cell line and its effect on cell proliferation. *Zhongguo Yaolixue Tongbao* 2018; **34**: 284-289 [DOI: 10.3969/j.issn.1001-1978.2018.02.026]

121 **Luo C**, Yuan D, Yao W, Cai J, Zhou S, Zhang Y, Hei Z. Dexmedetomidine protects against apoptosis induced by hypoxia/reoxygenation through the inhibition of gap junctions in NRK-52E cells. *Life Sci* 2015; **122**: 72-77 [PMID: 25529146 DOI: 10.1016/j.lfs.2014.12.009]

122 **Sato H**, Hagiwara H, Ohde Y, Senba H, Virgona N, Yano T. Regulation of renal cell carcinoma cell proliferation, invasion and metastasis by connexin 32 gene. *J Membr Biol* 2007; **216**: 17-21 [PMID: 17565422 DOI: 10.1007/s00232-007-9020-5]

123 **Zhao Y**, Lai Y, Ge H, Guo Y, Feng X, Song J, Wang Q, Fan L, Peng Y, Cao M, Harris AL, Wang X, Tao L. Non-junctional Cx32 mediates anti-apoptotic and pro-tumor effects via epidermal growth factor receptor in human cervical cancer cells. *Cell Death Dis* 2017; **8**: e2773 [PMID: 28492539 DOI: 10.1038/cddis.2017.183]

124 **Decrock E**, De Vuyst E, Vinken M, Van Moorhem M, Vranckx K, Wang N, Van Laeken L, De Bock M, D'Herde K, Lai CP, Rogiers V, Evans WH, Naus CC, Leybaert L. Connexin 43 hemichannels contribute to the propagation of apoptotic cell death in a rat C6 glioma cell model. *Cell Death Differ* 2009; **16**: 151-163 [PMID: 18820645 DOI: 10.1038/cdd.2008.138]

125 **Cusato K**, Zakevicius J, Ripps H. An experimental approach to the study of gap-junction-mediated cell death. *Biol Bull* 2003; **205**: 197-199 [PMID: 14583527 DOI: 10.2307/1543250]

126 **Kalvelyte A**, Imbrasaite A, Bukauskiene A, Verselis VK, Bukauskas FF. Connexins and apoptotic transformation. *Biochem Pharmacol* 2003; **66**: 1661-1672 [PMID: 14555247 DOI: 10.1016/s0006-2952(03)00540-9]

127 **Yu J**, Berga SL, Zou W, Yook DG, Pan JC, Andrade AA, Zhao L, Sidell N, Bagchi IC, Bagchi MK, Taylor RN. IL-1β Inhibits Connexin 43 and Disrupts Decidualization of Human Endometrial Stromal Cells Through ERK1/2 and p38 MAP Kinase. *Endocrinology* 2017; **158**: 4270-4285 [PMID: 28938400 DOI: 10.1210/en.2017-00495]

128 **El-Fakhry AA**, El-Daker MA, Badr RI, El-Nady GM, Mesbah MR, Youssef T, Arafa M, Arafa M, El-Naggar MM. Association of the CagA gene positive Helicobacter pylori and tissue levels of interleukin-17 and interleukin-8 in gastric ulcer patients. *Egypt J Immunol* 2012; **19**: 51-62 [PMID: 23888551]

129 **Shamsdin SA**, Alborzi A, Rasouli M, Ghaderi A, Lankrani KB, Dehghani SM, Pouladfar GR. The importance of TH22 and TC22 cells in the pathogenesis of Helicobacter pylori-associated gastric diseases. *Helicobacter* 2017; **22** [PMID: 27990709 DOI: 10.1111/hel.12367]

130 **Zhuang Y**, Cheng P, Liu XF, Peng LS, Li BS, Wang TT, Chen N, Li WH, Shi Y, Chen W, Pang KC, Zeng M, Mao XH, Yang SM, Guo H, Guo G, Liu T, Zuo QF, Yang HJ, Yang LY, Mao FY, Lv YP, Zou QM. A pro-inflammatory role for Th22 cells in Helicobacter pylori-associated gastritis. *Gut* 2015; **64**: 1368-1378 [PMID: 25134787 DOI: 10.1136/gutjnl-2014-307020]

131 **Qin XH**, Ma X, Fang SF, Zhang ZZ, Lu JM. IL-17 produced by Th17 cells alleviates the severity of fungal keratitis by suppressing CX43 expression in corneal peripheral vascular endothelial cells. *Cell Cycle* 2019; **18**: 274-287 [PMID: 30661459 DOI: 10.1080/15384101.2018.1556059]

132 **Liang J**, Chen P, Li C, Li D, Wang J, Xue R, Zhang S, Ruan J, Zhang X. IL-22 Down-Regulates Cx43 Expression and Decreases Gap Junctional Intercellular Communication by Activating the JNK Pathway in Psoriasis. *J Invest Dermatol* 2019; **139**: 400-411 [PMID: 30171832 DOI: 10.1016/j.jid.2018.07.032]

133 **Yan J**, Thomson JK, Zhao W, Wu X, Gao X, DeMarco D, Kong W, Tong M, Sun J, Bakhos M, Fast VG, Liang Q, Prabhu SD, Ai X. The stress kinase JNK regulates gap junction Cx43 gene expression and promotes atrial fibrillation in the aged heart. *J Mol Cell Cardiol* 2018; **114**: 105-115 [PMID: 29146153 DOI: 10.1016/j.yjmcc.2017.11.006]

134 **Takemura S**, Yashiro M, Sunami T, Tendo M, Hirakawa K. Novel models for human scirrhous gastric carcinoma in vivo. *Cancer Sci* 2004; **95**: 893-900 [PMID: 15546507 DOI: 10.1111/j.1349-7006.2004.tb02199.x]

135 **Chung HW**, Kong HY, Lim JB. Clinical significance and usefulness of soluble heparin binding-epidermal growth factor in gastric cancer. *World J Gastroenterol* 2015; **21**: 2080-2088 [PMID: 25717241 DOI: 10.3748/wjg.v21.i7.2080]

136 **Gunawardhana N**, Jang S, Choi YH, Hong YA, Jeon YE, Kim A, Su H, Kim JH, Yoo YJ, Merrell DS, Kim J, Cha JH. Helicobacter pylori-Induced HB-EGF Upregulates Gastrin Expression via the EGF Receptor, C-Raf, Mek1, and Erk2 in the MAPK Pathway. *Front Cell Infect Microbiol* 2018; **7**: 541 [PMID: 29379775 DOI: 10.3389/fcimb.2017.00541]

137 **Jurkowska G**, Piotrowska-Staworko G, Guzińska-Ustymowicz K, Kemona A, Świdnicka-Siergiejko A, Łaszewicz W, Dąbrowski A. The impact of Helicobacter pylori on EGF, EGF receptor, and the c-erb-B2 expression. *Adv Med Sci* 2014; **59**: 221-226 [PMID: 25051417 DOI: 10.1016/j.advms.2014.01.006]

138 **Yoshioka J**, Prince RN, Huang H, Perkins SB, Cruz FU, MacGillivray C, Lauffenburger DA, Lee RT. Cardiomyocyte hypertrophy and degradation of connexin43 through spatially restricted autocrine/paracrine heparin-binding EGF. *Proc Natl Acad Sci U S A* 2005; **102**: 10622-10627 [PMID: 16020536 DOI: 10.1073/pnas.0501198102]

139 **Kneissl J**, Hartmann A, Pfarr N, Erlmeier F, Lorber T, Keller S, Zwingenberger G, Weichert W, Luber B. Influence of the HER receptor ligand system on sensitivity to cetuximab and trastuzumab in gastric cancer cell lines. *J Cancer Res Clin Oncol* 2017; **143**: 573-600 [PMID: 27933395 DOI: 10.1007/s00432-016-2308-z]

140 **Liu D**, Zhou H, Wu J, Liu W, Li Y, Shi G, Yue X, Sun X, Zhao Y, Hu X, Wang T, Zhang X. Infection by Cx43 adenovirus increased chemotherapy sensitivity in human gastric cancer BGC-823 cells: Not involving in induction of cell apoptosis. *Gene* 2015; **574**: 217-224 [PMID: 26318481 DOI: 10.1016/j.gene.2015.08.052]

141 **Bolamba D**, Floyd AA, McGlone JJ, Lee VH. Epidermal growth factor enhances expression of connexin 43 protein in cultured porcine preantral follicles. *Biol Reprod* 2002; **67**: 154-160 [PMID: 12080012 DOI: 10.1095/biolreprod67.1.154]

142 **Park JH**, Lee MY, Heo JS, Han HJ. A potential role of connexin 43 in epidermal growth factor-induced proliferation of mouse embryonic stem cells: Involvement of Ca2+/PKC, p44/42 and p38 MAPKs pathways. *Cell Prolif* 2008; **41**: 786-802 [PMID: 18823499 DOI: 10.1111/j.1365-2184.2008.00552.x]

143 **Dubé E**, Dufresne J, Chan PT, Cyr DG. Epidermal growth factor regulates connexin 43 in the human epididymis: Role of gap junctions in azoospermia. *Hum Reprod* 2012; **27**: 2285-2296 [PMID: 22611165 DOI: 10.1093/humrep/des164]

144 **Cho SO**, Lim JW, Kim H. Red ginseng extract inhibits the expression of MCP-1 and iNOS in Helicobacter pylori-infected gastric epithelial cells by suppressing the activation of NADPH oxidase and Jak2/Stat3. *J Ethnopharmacol* 2013; **150**: 761-764 [PMID: 24055641 DOI: 10.1016/j.jep.2013.09.013]

145 **Liu K**, Tian T, Zheng Y, Zhou L, Dai C, Wang M, Lin S, Deng Y, Hao Q, Zhai Z, Dai Z. Scutellarin inhibits proliferation and invasion of hepatocellular carcinoma cells via down-regulation of JAK2/STAT3 pathway. *J Cell Mol Med* 2019; **23**: 3040-3044 [PMID: 30697962 DOI: 10.1111/jcmm.14169]

146 **Hou J**, Lv A, Deng Q, Zhang G, Hu X, Cui H. TROP2 promotes the proliferation and metastasis of glioblastoma cells by activating the JAK2/STAT3 signaling pathway. *Oncol Rep* 2019; **41**: 753-764 [PMID: 30431125 DOI: 10.3892/or.2018.6859]

147 **Ai XL**, Chi Q, Qiu Y, Li HY, Li DJ, Wang JX, Wang ZY. Gap junction protein connexin43 deregulation contributes to bladder carcinogenesis via targeting MAPK pathway. *Mol Cell Biochem* 2017; **428**: 109-118 [PMID: 28074341 DOI: 10.1007/s11010-016-2921-9]

148 **Tang Y**, Tong X, Li Y, Jiang G, Yu M, Chen Y, Dong S. JAK2/STAT3 pathway is involved in the protective effects of epidermal growth factor receptor activation against cerebral ischemia/reperfusion injury in rats. *Neurosci Lett* 2018; **662**: 219-226 [PMID: 29061394 DOI: 10.1016/j.neulet.2017.10.037]

149 **Bimczok D**, Kao JY, Zhang M, Cochrun S, Mannon P, Peter S, Wilcox CM, Mönkemüller KE, Harris PR, Grams JM, Stahl RD, Smith PD, Smythies LE. Human gastric epithelial cells contribute to gastric immune regulation by providing retinoic acid to dendritic cells. *Mucosal Immunol* 2015; **8**: 533-544 [PMID: 25249167 DOI: 10.1038/mi.2014.86]

150 **Han X**, Tong XH, Dong SY, Zheng C, Yu BB. [Effects of retinoic acid on the expression of Cx43 and its gap juncion intercellular communication function in testicular cancer cell]. *Sichuan Da Xue Xue Bao Yi Xue Ban* 2013; **44**: 924-927 [PMID: 24490503]

151 **Dong S**, Tong X, Jiang G, Gu Y, Jiao H, Li J. [Expression of connexin 43 and functional modulation of gap junction in neonatal rat astrocytes in vitro]. *Nan Fang Yi Ke Da Xue Xue Bao* 2012; **32**: 1423-1426 [PMID: 23076176]

152 **Tanmahasamut P**, Sidell N. Up-regulation of gap junctional intercellular communication and connexin43 expression by retinoic acid in human endometrial stromal cells. *J Clin Endocrinol Metab* 2005; **90**: 4151-4156 [PMID: 15811935 DOI: 10.1210/jc.2004-0663]

153 **Nguyen PH**, Giraud J, Staedel C, Chambonnier L, Dubus P, Chevret E, Bœuf H, Gauthereau X, Rousseau B, Fevre M, Soubeyran I, Belleannée G, Evrard S, Collet D, Mégraud F, Varon C. All-trans retinoic acid targets gastric cancer stem cells and inhibits patient-derived gastric carcinoma tumor growth. *Oncogene* 2016; **35**: 5619-5628 [PMID: 27157616 DOI: 10.1038/onc.2016.87]

154 **Wu X**, Gao H, Hou Y, Yu J, Sun W, Wang Y, Chen X, Feng Y, Xu QM, Chen X. Dihydronortanshinone, a natural product, alleviates LPS-induced inflammatory response through NF-κB, mitochondrial ROS, and MAPK pathways. *Toxicol Appl Pharmacol* 2018; **355**: 1-8 [PMID: 29906494 DOI: 10.1016/j.taap.2018.06.007]

155 **Liao W**, He X, Yi Z, Xiang W, Ding Y. Chelidonine suppresses LPS-Induced production of inflammatory mediators through the inhibitory of the TLR4/NF-κB signaling pathway in RAW264.7 macrophages. *Biomed Pharmacother* 2018; **107**: 1151-1159 [PMID: 30257328 DOI: 10.1016/j.biopha.2018.08.094]

156 **Liao CK**, Wang SM, Chen YL, Wang HS, Wu JC. Lipopolysaccharide-induced inhibition of connexin43 gap junction communication in astrocytes is mediated by downregulation of caveolin-3. *Int J Biochem Cell Biol* 2010; **42**: 762-770 [PMID: 20093193 DOI: 10.1016/j.biocel.2010.01.016]

157 **Yahiro K**, Akazawa Y, Nakano M, Suzuki H, Hisatune J, Isomoto H, Sap J, Noda M, Moss J, Hirayama T. Helicobacter pylori VacA induces apoptosis by accumulation of connexin 43 in autophagic vesicles via a Rac1/ERK-dependent pathway. *Cell Death Discov* 2015; **1**: 15035 [PMID: 27551466 DOI: 10.1038/cddiscovery.2015.35]

158 **Lin LL**, Huang HC, Ogihara S, Wang JT, Wu MC, McNeil PL, Chen CN, Juan HF. Helicobacter pylori disrupts host cell membranes, initiating a repair response and cell proliferation. *Int J Mol Sci* 2012; **13**: 10176-10192 [PMID: 22949854 DOI: 10.3390/ijms130810176]

159 **Tanaka M**, Grossman HB. Connexin 26 induces growth suppression, apoptosis and increased efficacy of doxorubicin in prostate cancer cells. *Oncol Rep* 2004; **11**: 537-541 [PMID: 14719096 DOI: 10.3892/or.11.2.537]

160 **Yang HJ**, Kim SG, Lim JH, Choi JM, Kim WH, Jung HC. Helicobacter pylori-induced modulation of the promoter methylation of Wnt antagonist genes in gastric carcinogenesis. *Gastric Cancer* 2018; **21**: 237-248 [PMID: 28643146 DOI: 10.1007/s10120-017-0741-6]

161 **Lim JH**, Kim SG, Choi JM, Yang HJ, Kim JS, Jung HC. Helicobacter pylori Is Associated with miR-133a Expression through Promoter Methylation in Gastric Carcinogenesis. *Gut Liver* 2018; **12**: 58-66 [PMID: 28950691 DOI: 10.5009/gnl17263]

162 **Ferrasi AC**, Pinheiro NA, Rabenhorst SH, Caballero OL, Rodrigues MA, de Carvalho F, Leite CV, Ferreira MV, Barros MA, Pardini MI. Helicobacter pylori and EBV in gastric carcinomas: Methylation status and microsatellite instability. *World J Gastroenterol* 2010; **16**: 312-319 [PMID: 20082476 DOI: 10.3748/wjg.v16.i3.312]

163 **Bahnassy AA**, Helal TE, El-Ghazawy IM, Samaan GF, Galal El-Din MM, Abdellateif MS, Desouky E, Zekri AN. The role of E-cadherin and Runx3 in Helicobacter Pylori - Associated gastric carcinoma is achieved through regulating P21waf and P27 expression. *Cancer Genet* 2018; **228-229**: 64-72 [PMID: 30553475 DOI: 10.1016/j.cancergen.2018.08.006]

164 **Nishimura M**, Saito T, Yamasaki H, Kudo R. Suppression of gap junctional intercellular communication via 5' CpG island methylation in promoter region of E-cadherin gene in endometrial cancer cells. *Carcinogenesis* 2003; **24**: 1615-1623 [PMID: 12896902 DOI: 10.1093/carcin/bgg121]

165 **Allagnat F**, Dubuis C, Lambelet M, Le Gal L, Alonso F, Corpataux JM, Déglise S, Haefliger JA. Connexin37 reduces smooth muscle cell proliferation and intimal hyperplasia in a mouse model of carotid artery ligation. *Cardiovasc Res* 2017; **113**: 805-816 [PMID: 28449099 DOI: 10.1093/cvr/cvx079]

166 **Fang JS**, Angelov SN, Simon AM, Burt JM. Cx37 deletion enhances vascular growth and facilitates ischemic limb recovery. *Am J Physiol Heart Circ Physiol* 2011; **301**: H1872-H1881 [PMID: 21856908 DOI: 10.1152/ajpheart.00683.2011]

167 **Jacobsen NL**, Pontifex TK, Li H, Solan JL, Lampe PD, Sorgen PL, Burt JM. Regulation of Cx37 channel and growth-suppressive properties by phosphorylation. *J Cell Sci* 2017; **130**: 3308-3321 [PMID: 28818996 DOI: 10.1242/jcs.202572]

168 **Burt JM**, Nelson TK, Simon AM, Fang JS. Connexin 37 profoundly slows cell cycle progression in rat insulinoma cells. *Am J Physiol Cell Physiol* 2008; **295**: C1103-C1112 [PMID: 18753315 DOI: 10.1152/ajpcell.299.2008]

169 **Morel S**, Burnier L, Roatti A, Chassot A, Roth I, Sutter E, Galan K, Pfenniger A, Chanson M, Kwak BR. Unexpected role for the human Cx37 C1019T polymorphism in tumour cell proliferation. *Carcinogenesis* 2010; **31**: 1922-1931 [PMID: 20705954 DOI: 10.1093/carcin/bgq170]

170 **Guruvaiah P**, Govatati S, Reddy TV, Beeram H, Deenadayal M, Shivaji S, Bhanoori M. Analysis of Connexin37 gene C1019T polymorphism and PCOS susceptibility in South Indian population: Case-control study. *Eur J Obstet Gynecol Reprod Biol* 2016; **196**: 17-20 [PMID: 26656196 DOI: 10.1016/j.ejogrb.2015.11.002]

171 **Tang J**, Li L, Hu LQ, Cai QY, Chen L. Association between 1019C/T polymorphism in the connexin 37 gene and dilated cardiomyopathy. *Minerva Cardioangiol* 2016; **64**: 114-120 [PMID: 25501978]

172 **Zhao L**, Li Y, Wu D, Ma T, Xia SY, Liu Z. Cx37 C1019T polymorphism may contribute to the pathogenesis of coronary heart disease. *Genet Test Mol Biomarkers* 2014; **18**: 497-504 [PMID: 24773516 DOI: 10.1089/gtmb.2014.0034]

173 **Wen D**, Du X, Nie SP, Dong JZ, Ma CS. Association of Connexin37 C1019T with myocardial infarction and coronary artery disease: A meta-analysis. *Exp Gerontol* 2014; **58**: 203-207 [PMID: 24937033 DOI: 10.1016/j.exger.2014.06.011]

174 **Guo S**, Chen W, Yang Y, Yang Z, Cao M. Association between 1019C/T polymorphism in the connexin 37 gene and essential hypertension. *Heart Lung Circ* 2014; **23**: 924-929 [PMID: 24685073 DOI: 10.1016/j.hlc.2014.02.016]

175 **Wu JY**, Lee YC, Graham DY. The eradication of Helicobacter pylori to prevent gastric cancer: A critical appraisal. *Expert Rev Gastroenterol Hepatol* 2019; **13**: 17-24 [PMID: 30791844 DOI: 10.1080/17474124.2019.1542299]

176 **Salar A**. Gastric MALT lymphoma and Helicobacter pylori. *Med Clin (Barc)* 2019; **152**: 65-71 [PMID: 30424932 DOI: 10.1016/j.medcli.2018.09.006]

177 **Akeel M**, Shehata A, Elhafey A, Elmakki E, Aboshouk T, Ageely H, Mahfouz M. Helicobacter pylori vacA, cagA and iceA genotypes in dyspeptic patients from southwestern region, Saudi Arabia: Distribution and association with clinical outcomes and histopathological changes. *BMC Gastroenterol* 2019; **19**: 16 [PMID: 30683054 DOI: 10.1186/s12876-019-0934-z]

178 **Suerbaum S**, Michetti P. Helicobacter pylori infection. *N Engl J Med* 2002; **347**: 1175-1186 [PMID: 12374879 DOI: 10.1056/NEJMra020542]

179 **Byun SW**, Chang YJ, Chung IS, Moss SF, Kim SS. Helicobacter pylori decreases p27 expression through the delta opioid receptor-mediated inhibition of histone acetylation within the p27 promoter. *Cancer Lett* 2012; **326**: 96-104 [PMID: 22867947 DOI: 10.1016/j.canlet.2012.07.032]

180 **Chen B**, Yang L, Chen J, Chen Y, Zhang L, Wang L, Li X, Li Y, Yu H. Inhibition of Connexin43 hemichannels with Gap19 protects cerebral ischemia/reperfusion injury via the JAK2/STAT3 pathway in mice. *Brain Res Bull* 2019; **146**: 124-135 [PMID: 30593877 DOI: 10.1016/j.brainresbull.2018.12.009]

181 **Yeh ES**, Williams CJ, Williams CB, Bonilla IV, Klauber-DeMore N, Phillips SL. Dysregulated connexin 43 in HER2-positive drug resistant breast cancer cells enhances proliferation and migration. *Oncotarget* 2017; **8**: 109358-109369 [PMID: 29312613 DOI: 10.18632/oncotarget.22678]

182 **Arora S**, Heyza JR, Chalfin EC, Ruch RJ, Patrick SM. Gap Junction Intercellular Communication Positively Regulates Cisplatin Toxicity by Inducing DNA Damage through Bystander Signaling. *Cancers (Basel)* 2018; **10**: pii: E368 [PMID: 30279363 DOI: 10.3390/cancers10100368]

183 **Yang Y**, Yao JH, Du QY, Zhou YC, Yao TJ, Wu Q, Liu J, Ou YR. Connexin 32 downregulation is critical for chemoresistance in oxaliplatin-resistant HCC cells associated with EMT. *Cancer Manag Res* 2019; **11**: 5133-5146 [PMID: 31213923 DOI: 10.2147/CMAR.S203656]

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**Table 1 Connexin expression in the gastrointestinal tract and liver**

|  |  |  |  |
| --- | --- | --- | --- |
| **Tissue** | **Cell type** | **Cx members** | **Ref.** |
| Liver |  |  |  |
|  | Hepatocytes | Cx32/Cx26 | [[161](#_ENREF_161)] |
|  | Kupffer cells | Cx43/Cx26 | [[162-164](#_ENREF_162)] |
|  | Stellate cells | Cx43/Cx26 | [[163-165](#_ENREF_163)] |
|  | Sinusoidal endothelial cells | Cx43/Cx32/Cx26 | [[163](#_ENREF_163),[164](#_ENREF_164),[166](#_ENREF_166),[167](#_ENREF_167)] |
|  | Portal vein endothelial cells | Cx43/Cx40/Cx37 | [[168-170](#_ENREF_168)] |
|  | Hepatic artery endothelial cells | Cx43/Cx40/37 | [[168-170](#_ENREF_168)] |
|  | Cholangiocytes | Cx43/Cx32 | [[171](#_ENREF_171),[172](#_ENREF_172)] |
| Stomach |  | Cx45/Cx43/Cx40/Cx37/Cx32/Cx26 | [[49-57](#_ENREF_49),[146](#_ENREF_146)] |
|  | Foveolar cells | Cx32 | [[173](#_ENREF_173)] |
| Small intestine | | | |
|  | Musculus externa cells | Cx43/Cx40 | [[51](#_ENREF_51)] |
|  | Myenteric plexus cells | Cx45/Cx43/Cx40/Cx36 | [[51](#_ENREF_51),[174](#_ENREF_174),[175](#_ENREF_175)] |
|  | Epithelial cells | Cx43/Cx37/Cx32 | [[51](#_ENREF_51),[176](#_ENREF_176),[177](#_ENREF_177)] |
|  | Interstitial cells  of Cajal | Cx43 | [[51](#_ENREF_51),[178](#_ENREF_178)] |
| Colon | | | |
|  | Musculus externa cells | Cx43/Cx40/Cx26 | [[51](#_ENREF_51),[179](#_ENREF_179)] |
|  | Myenteric plexus cells | Cx45/Cx43/Cx40/Cx36 | [[51](#_ENREF_51),[175](#_ENREF_175)] |
|  | Epithelial cells | Cx43/Cx37/Cx32/Cx26 | [[177](#_ENREF_177),[180-183](#_ENREF_180)] |
|  | Muscularis mucosal cells | Cx43 | [[51](#_ENREF_51)] |
|  | Interstitial cells of Cajal | Cx43 | [[178](#_ENREF_178)] |
|  |  |  |  |