Functional Regulation Between Matrix Metalloproteases and Cell Junction Proteins in Gastric Cancer

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Abstract

Gastric cancer (GC) is one of the most frequent malignancies of the digestive tract worldwide. The tumor microenvironment plays a key role in the complex process of GC development that involves invasion and metastasis. Several factors affecting the development of GC include life style, hereditary factors, as well as *Helicobacter pylori* infection. To maintain homeostasis of any tissue, proper contact between neighboring cells is prime need wherein cell-cell and cell-extracellular matrix (ECM) interactions are the key events which are guided by tightly controlled process attributed to specialized structures, for example, tight junction, adherens junction, and gap junction. The metastatic nature of the tumor during gastric cancer progression has relevance with the altered structural and functional regulation of matrix metalloproteinases (MMPs) along with their cross talk with cell junction proteins like claudin and occluding. Moreover, *H. pylori* infection and other extrinsic factors impair tight junction which lead to the

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activation of inflammatory cytokines. Further, mislocalization or altered function of gap junction and adherens junction proteins also responsible for gastric inflammation ultimately leads to carcinoma. In the treatment of GC, chemoresistance poses a major challenge with high chances of recurrence. Therefore, identification of the specific prognostic biomarkers in MMPs activation pathways and/or cell junction proteins may allow overcoming the problem by improving the early diagnostic procedures for GC. In this chapter, we focus on the roles of different MMPs, cell junction proteins, and cross talk between them in GC progression.

Keywords

Matrix metalloproteases · Gap junction · Tight junction · Adherence junction · *H. Pylori* · Gastric cancer

Introduction

GC is one of the most frequent malignancies of the digestive tract that develops from the lining of the stomach and characterized by late clinical development (Lochhead and El-Omar 2008). GC is the third most common cause of death among all reported cancer deaths throughout the world in 2018 (Rawla and Barsouk 2019). Between births and 74 years of age, the average risk of developing GC in males is 2.2 times more likely than in females. However, this ratio goes down to 1.83 in the developing countries (Rawla and Barsouk 2019). The Republic of Korea has the maximum rate of occurrence of GC with reportedly 60 cases per 100,000 males in contrast to the incidence rate for women which is only 25 per 100,000 (Rawla and Barsouk 2019). Several factors play a vital role in GC development including *H. pylori* infection, environmental factors, diet, smoking, genetic polymorphism, long-term stomach inflammation, and lifestyle. Based on the histological features GC is divided into intestinal and diffuse types (Lauren 1965).

H. pylori infection damages tight junction as well as activates cytokines of inflammatory pathways. Epithelial disruption is a significant phenomenon of *H. pylori*-mediated inflammation and neoplastic tissue transformation. Overexpression of CLDN2 is linked to *H. pylori*-induced carcinoma along with disruption of occludin and claudin-4 and claudin-5 and henceforth increases paracellular permeability (Fedwick et al. 2005). Epidermal growth factor (EGF) has a crucial role in regulating the biological behavior of GC (Reinmuth et al. 2003). It was reported that in tumor cells upregulation of EGF or EGFR may disrupt tight junction (Van Itallie et al. 1995).

Considerable numbers of reports have defined the process of the development of GC by the interplay of MMPs and their tissue inhibitors (TIMPs). Moreover, expression and activity of different MMPs correlate with advanced tumor, increased invasion and metastasis, and shortened survival (Isaacson et al. 2017). This chapter summarizes the current state of knowledge of functional

regulation between MMPs and cell junction proteins involved in gastric cancer development.

Matrix Metalloproteinases (MMPs) and Gastric Cancer

The MMPs are zinc-dependent endoproteinases, collectively capable of degrading most of the ECM components. MMPs are synthesized as zymogen and their activation requires proteolytic modification of prodomains. Regulation of MMP functions can take place at various stages, including transcription, zymogen activation, interplay with ECM, and endogenous inhibition by TIMPs (Raychaudhary et al. 2019). The imbalance between the MMPs and TIMPs expression can lead to the disruption and deregulation of ECM degradation and basement membrane as well. Recent studies show that MMPs and TIMPs are involved in every stages of cancer progression including metastasis (Chen et al. 2020). Zhang et al. (2011) showed that the expression of MMP-2, MMP-7, MMP-9, MMP-14, and TIMP-1 and TIMP-2 mRNA levels in GC tissue was considerably elevated than normal tissue. These results are consistent with other findings, where the researchers have established a significant relationship between expression of MMP-2, MMP-9, or TIMP-2 and differentiation of tumors (Shan et al. 2015). The expression of MMP-2, MMP-7, MMP-9, and MMP-14 increased progressively with tumor stages than initial GC (Alpízar-Alpízar et al. 2016). The advanced stages of GC were found to be linked with downregulated TIMP-2 expression and contrasting upregulation of MMP-7 and MMP-9 (Chu et al. 2010). Additionally, various studies have shown that MMP-2 and MMP-9 expressions are correlated with tumor clinicopathology including tumor depth, occurrence of lymph nodes, and metastases (Lian et al. 2016) (Fig. 1).

MMPs are produced in the vicinity of cancer cells, by inflammatory and fibroblast cells. During cancer progression, mitogen-activated protein kinases (MAPKs) are vital in controlling MMP activation since many MMP promoters include AP-1 and nuclear factor-kappaB (NFκB) binding sites (Verma et al. 2014). Recently, increasing numbers of studies reveal the presence of the ERK/MAPK system in regulating cell proliferation in gastric malignant tumors and gastric cell lines. ERK can mediate MMP behavior which in turn influences the migration and invasion of GC cells (Akter et al. 2015). Moreover, the c-Jun N-terminal kinase (JNK) and NF-κB pathway are also involved in GC metastasis and invasion (Jiang et al. 2019). The JNK pathway is involved in p21-activated kinase1 (Pak1) modulation of MMP-2, which contributed significantly in the MKN45 cell invasiveness (Li et al. 2017). Similarly, cadherin-17 (CDH17) expression is enhanced in GC tissues than the paracarcinoma tissues along with increased MMP-2 expression, mediated via NF-κB pathway and lymph node metastasis (Jiang et al. 2019) (Table 1).

Moreover, MMPs have also been reported in regulation of angiogenesis which is related to GC. Activation of MMPs can be induced by various angiogenic factors including vascular endothelial growth factor (VEGF), basic fibroblast growth factors (FGF), transforming growth factors (TGF-α and TGF-β), and angiogenin (Quintero-Fabian et al. 2019). MMP-2, MMP-9, and MMP-14 are the most studied MMPs

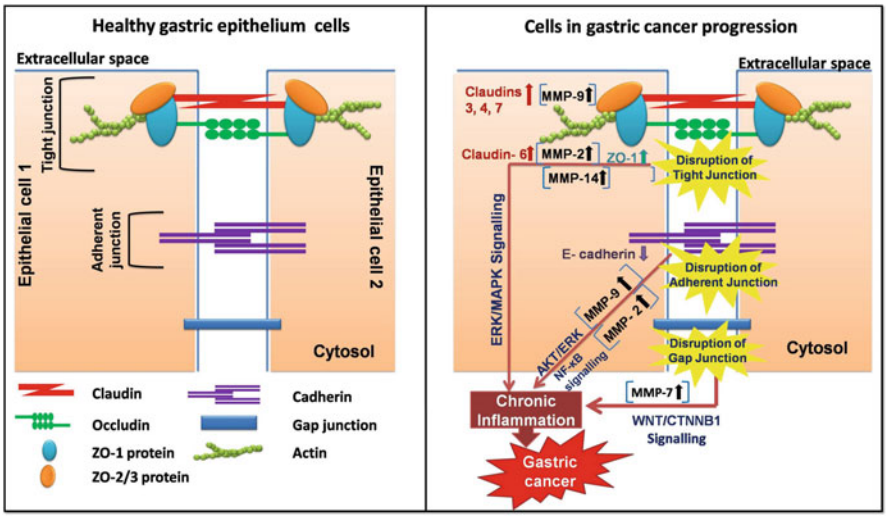

Fig. 1 Showing healthy gastric epithelia with major cell junction proteins vs. cells with gastric cancer progression where crosstalk between major cell junction proteins and matrix metalloproteinases (MMPs) has hampered

Table 1 Association of junctional proteins (Jps) with MMP and TIMPs expression in gastric cancer: [↑ = upregulation, ↓ = downregulation]

Type of JPs proteins	Expression of JPs in Gastric cancer	Expression of MMPs and TIMPs	References
Adherence junction proteins	↓**E-Cadherin**	↑MMP7, MMP2 and MMP9	Lee et al. (2006), Gao et al. (2017)
	↑**α-catenine and other minor catenines**	↑MMP2, MMP7 and MMP9	Wu et al. (2015)
Tight junction proteins	↓**Claudin-7**	↑MMP9	Wroblewski et al. (2015)
	↑**Claudin-4**, **Claudin-6, Claudin-1**, **Claudin-3** at late stage GC	↑MMP9 and MMP2	Hwang et al. (2014), Torres-Martinez et al. (2017), Hewitt et al. (2006)
	↑**Occludin(ZO-1)**	↑MMP14	Resnick (2005)
	↓**Occludin (ZO-1)**	↑MMP2, MMP9 and MMP10	Lv et al. (2019), Turksen and Troy (2011)
Gap junction proteins	↓**Connexins(CX-43)**	↓TIMP-3	Zhu et al. (2018)

participating in angiogenesis by acting as a key mediator in VEGF production. Upregulation in the MMP-2 and MMP-9 expression during GC development is correlated with VEGF expression suggesting an important role played by MMP-2

and MMP-9 in GC progression via degradation of ECM and neovascularization (Zheng et al. 2006). In another study, a plant hormone methyl jasmonate attenuates the expression of MMP-14 by downregulating the specificity protein 1 expression, thereby inhibiting the angiogenesis along with GC progression (Zheng et al. 2013).

Cell Junction Proteins in Gastric Cancer

Homeostasis of surrounding epithelial cells is maintained through adhesion between adjacent cells which is a tightly controlled process and essential factor. Specialized structures like tight junction, adherens junctions, and gap junctions are responsible for the adhesion between neighboring cells of epithelium (Hollande et al. 2003). The development and maintenance of tight junctions and adherens junctions are controlled by several growth factors, hormones, and cytokines. These can have a major influence on tumor progression and metastasis (Hollande et al. 2003).

Tight Junctions

Tight junctions are restricted to the apical end of the intracellular junctions playing a vital role in the epithelial polarity (Farquhar and Palade 1963). They also act as adhesion mediating structures between cells which maintain paracellular permeability and provide protection against intruding pathogens (Naz et al. 2017). However, cell polarity is maintained by the fence function. Permeability of tight junction is amplified and transepithelial electrical resistance (TER) is declined well with the tumor formation (Soler et al. 1999).

Cells undergoing tumorigenesis generally reveal deficiencies of structure and function in their tight junctions (Weinstein et al. 1976), with subsequent release or transport of pro-tumorigenic factors, inducing tumor growth (Mullin 1997). Additionally, the loss of polarity, differentiation, and adhesive characteristics related with damaged tight junctions may be significant in obtaining a metastatic phenotype (Martin and Jiang 2001). Anomalies in tight junction-linked proteins may correspond to epithelial-mesenchymal transition (EMT) and thereby altering cancer cells motility and their invasiveness (Agarwal et al. 2009). The tight junction complex comprises of transmembrane proteins like claudin, occludin, and membrane linked proteins like zona occludens (ZO-1, ZO-2, and ZO-3) (Tsukita et al. 2001). Other than zona occludens there are connexions and junction-adhesion molecules that play a vital role in the functioning of the epithelial tight junctions.

Claudins are necessary for epithelial barrier integrity and for maintaining tight junction structure and function (Elkouby-Naor and Ben-Yosef 2010). Claudins are also involved in intracellular signaling, because of the presence of PDZ binding domains at their COOH termini (Morita et al. 1999). Alterations in claudin expression are common with tumorigenesis and cancer progression (Kwon 2013). Claudin proteins are poorly expressed in tumor cells and are compliant with the conception of

tight junction damage triggering epithelial cell cohesion disruption and inducing cell invasiveness (Yang et al. 2018).

The expression of claudin-2 promotes pore formation and thereby modulates paracellular transport by epithelial cells (Rosenthal et al. 2010). It is downregulated along with claudin-6, claudin-7, claudin-8, claudin-10, and claudin-17, while upregulation of claudin-5, claudin-11, and claudin-14 is found in GC tissues compared with tissues adjacent to the tumor (Gao et al. 2013). Additionally, claudin-7 and claudin-8 were simultaneously expressed in the mucosa and GC tissues, suggesting their participation in tight junction structure. Patients with tumors having claudin-7 and claudin-8 expression have a considerably longer survival time; on the other hand, patients with tumors with claudin-5 expression have a drastically shorter survival. However, the exact mechanism of claudin-7 overexpression and their function in GC is unclear (Johnson et al. 2005). Expression of Claudin-11 mRNA was observed in all normal gastric mucosal tissues and cell lines whereas it is silenced in case of GC. However, promoter region of claudin-11 is hypermethylated in GC tissues and cell lines. Whereas, downregulation of claudin-11 mediated through siRNA in GC phenotype particularly elevates cell motility and invasiveness and is considered a probable target of epigenetic inactivation in GC (Agarwal et al. 2009). Claudin-18 is downregulated in GC (Hagen et al. 2018). The expression of its isoform 2 (Claudin-18.2) is confined to differentiated epithelial cells of the gastric mucosa as well as in early GC (Sahin et al. 2008).

The association of tight junctions to the cytoskeleton is maintained by three membrane-linked proteins. They are zonula occludens (ZO)-1, ZO-2, and ZO-3 having molecular weight 220-kDa (Morita et al. 1999), and they perform a crucial role in tight junctions and are expressed in all normal epithelial cells and not downregulated in advanced GC. ZO-1 is a submembrane molecule directly linked with occludin, claudins, junctional adhesion molecules (Itoh et al. 1999), and also to actin at its C-terminal domain, and thereby maintains contact with neighboring cells (Fanning et al. 2002). Reduced expression of ZO-1 has been observed during invasion and de-differentiation in gastrointestinal cancers (Kimura et al. 1997). ZO-1 also causes severe barrier defects exclusively by *H. pylori* through increased expression of tyrosine phosphorylation and decreased expression of ZO-1 (Martin and Jiang 2009). Phosphorylation within crucial domains of ZO-1 is directly implicated in the binding with occludins. Alterations in such domains may result in detachment of ZO-1 from tight junction proteins, thereby making the epithelial barriers weak and helping in the entry of pathogen like *H. pylori* (Ribet and Cossart 2010). Epithelial cells lacking occludin display a strong network of tight junction strands, implicating the importance of occludin in tight junction strand formation (Tsukita et al. 2001).

Gap Junction

CX32, a gap junction protein, is normally found in the gastrointestinal tract epithelium. Modification of localization or alteration of its function could develop GC

(Jee et al. 2011). C-terminal of connexins another gap junction protein is a significant one for protein trafficking. Research suggested that phosphorylation of some amino acids at the tail region can also modify the half-life of the protein and thereby gap junction assembly (Johnstone et al. 2012).

Adherens Junction

Along with the cell cytoskeleton, adherens junctions are principal elements for the establishment and maintenance of the tissue architecture. Alterations in cell-to-cell and cell-to-matrix interactions result in the migration of cancer cells across normal tissue barrier and metastasize (Pignatelli and Vessey 1994). Abnormalities in the expression and function of E-cadherin, the principal constituent of the adherens junction, are involved in a number of gastric cell lines. Immunohistochemical studies on GC tissues have shown abnormal E-cadherin expression (Matsuura et al. 1992). Further, there is an inverse correlation between E-cadherin expression and invasive growth (Jawhari et al. 1997). E-cadherin mutations are reported in 50% of diffuse-type tumors (Berx et al. 1998). Although E-cadherin is said to be responsible for determining the growth characteristics of gastric carcinomas, the biological differences between intestinal and diffuse types of gastric carcinoma cannot be altogether explained by the expression levels of E-cadherin. Few human cancer cells may display abnormal E-cadherin-mediated cell adhesiveness by declining α-catenin expression (Shiozaki et al. 1994).

Crosstalk Between of MMPs and Cell Junction Proteins

Interrelation between MMPs and cell junction proteins is very crucial for cancer progression. MMPs are produced in the vicinity of cancer cells, and the imbalance of expression of MMPs can lead to the degradation of ECM and basement membrane which are held tightly close together by specialized structures like tight junction, adherens junctions, and gap junctions. Cross-talks between MMPs and Different cell junction proteins are discussed below.

MMP and Adherence Junction Proteins

MMP-3 and MMP-7 are known to cleave E-cadherin (Lynch et al. 2010). Clinical data suggested abnormal E-cadherin expression is associated with MMP-7 upregulation in gastric carcinoma compared to normal gastric tissue (Lee et al. 2006). E-cadherin alteration by MMP-7 instigates a proliferative pathway to enhance Rho A activity and enhance cyclin D1 expression and bypasses p27 (Lynch et al. 2010). In GC, upregulation of MMP-9 and VEGF and downregulation of E-cadherin were found as markers for malignancies (Gao et al. 2017). However, in gastric

carcinoma cells, macrophage infiltration induces α- and β-catenin expression by AKT/ERK pathway which is also directly linked with MMP-9 levels (Wu et al. 2015).

MMPs and Tight Junction Proteins

In most gastric intestinal-type adenocarcinomas, ZO-1 expression is observed along with upregulation of MMP-14 (Resnick et al. 2005). The elevation of MMP-10 expression in *H. pylori*-induced GC is related with downregulation of ZO-1 expression (Lv et al. 2019). Further, claudin-4 level was considerably associated with MMP-2 and MMP-9 expressions. Overexpression of claudin-4 enhances cell invasion as well as migration, suggesting that claudin-associated invasion may be intervened by activation of MMPs. Therefore, changes in claudin-4 level may take part in the invasiveness of GC, by regulating the barrier function of tight junctions or by mediating MMP-2 and MMP-9 activities (Hwang et al. 2014). Again it was reported that expression of claudin-3, claudin-4, and claudin-7 were found elevated in late stage GC with detectable MMP-9 upregulation (Hewitt et al. 2006). *H. pylori* also modulate expression of claudin-7 via MMP-9 mediated pathway (Wroblewski et al. 2015). Claudin-6 helps in MMP-2 activation, promoting cell migration and invasiveness during GC progression (Torres-Martinez et al. 2017). In GC, Claudin-18 expression has promising prognostic value, but its expression is poorly correlated with MMP activity (Sanada et al. 2006). Upregulation of MMP-9 and MMP-2 is also related to altered homeostasis of occludin protein (Turksen and Troy 2011).

MMPs and Gap Junction Proteins

In lymph node metastasis of GC, the expression of connexion Cx-43 was found downregulated with poor TIMP-3 activity (Zhu et al. 2018). Upregulation of gap junction β-4 (GJB4) in GC patients is associated with increased Wnt/CTNNB1 signaling and its downstream MMP-7 expression resulting in poor survival of patients (Liu et al. 2019). Downregulation of connexion 32 (Cx-32) and connexion 43 (Cx-43) with increased expression of multiple MMPs was found in stomach mucosal cell line (CES-1) (Wu et al. 2007). Pathogenic interaction with gap junction proteins is of great interest in GC progression. Gap junction proteins are used as excellent experimental tools to understand the mechanisms of GC development. Decoding of gap junctional signaling pathways in gastric carcinogenesis with their involvement on metalloproteinases and their inhibitors would provide a new avenue for disease diagnosis.

Conclusion and Future Directions

In the treatment of both local and metastatic GC, chemotherapy is known to play a vital role, but its efficacy remains limited by intrinsic or acquired chemoresistance, which is again associated with tumor cells and tumor microenvironment. The cause

behind chemoresistance could be either genetic or epigenetic, such as expression of drug resistance genes and altered signaling pathways in cancer stem cells. A large number of GC patients develop recurrence despite surgery; majority of them develop distant metastases. Therefore, early detection methods and multimodality approaches for treatment should be adopted for the prevention and recurrences of GC.

In order to reduce the mortality rate, development of specific, targeted, and personalized therapy is required and hence identification of specialized biomarkers is of high priority for early diagnosis, prognosis, and treatment. In support mutant E-cadherin is a promising biomarker for diagnosis owing to its specificity for diffuse-type GC (Lee et al. 2006). We speculate, connexion-43 as one of the major proteins that can be used for target-based therapeutics for gastric carcinoma. In spite of large number of literature on MMPs in the progression of GC, there are only a few studies which confirm the candidature of MMPs as prognostic biomarkers. Although serum MMPs-7, 8, and 14 along with TIMP-1 may prove useful potential biomarkers in the prognosis of GC, nonetheless, additional studies are required for better understanding the influence of certain MMPs on specific stages of GC to use specific inhibitors of MMPs in cancer therapy.

References

Agarwal R, Mori Y, Cheng Y, Jin Z, Olaru AV (2009) Silencing of claudin-11 is associated with increased invasiveness of gastric cancer cells. PLoS One 4(11):e8002. https://doi.org/10.1371/journal.pone.0008002

Akter H, Park M, Kwon OS, Song EJ, Park WS, Kang MJ (2015) Activation of matrix metalloproteinase-9 (MMP-9) by neurotensin promotes cell invasion and migration through ERK pathway in gastric cancer. Tumour Biol 36:6053–6062

Alpízar-Alpízar W, Laerum OD, Christensen IJ, Ovrebo K, Skarstein A, Høyer-Hansen G, Ploug M, Illemann M (2016) Tissue inhibitor of metalloproteinase-1 is confined to tumor-associated myofibroblasts and is increased with progression in gastric adenocarcinoma. J Histochem Cytochem 64:483–494

Berx G, Becker KF, Hofler H, van Roy F (1998) Mutations of the human E-cadherin (CDH1) gene. Hum Mutat 12:226–237

Chen YJ, Liang L, Li J, Wu H, Dong L, Liu TT, Shen XZ (2020) IRF-2 inhibits gastric cancer invasion and migration by down-regulating MMP-1. Dig Dis Sci 65:168–177

Chu D, Zhang Z, Li Y, Zheng J, Dong G, Wang W, Ji G (2010) Matrix metalloproteinase-9 is associated with disease-free survival and overall survival in patients with gastric cancer. Int J Cancer 129(4):887–895

Elkouby-Naor L, Ben-Yosef T (2010) Functions of claudin tight junction proteins and their complex interactions in various physiological systems. Int Rev Cell Mol Biol 279:1–32

Fanning AS, Ma TY, Anderson JM (2002) Characterization of actin binding region in the tight junction protein ZO-1. FASEB 16:1835–1837

Farquhar MG, Palade GE (1963) Junctional complexes in various epithelia. J Cell Biol 17:375–412

Fedwick JP, Lapointe TK, Meddings JB, Sherman PM, Buret AG (2005) *Helicobacter pylori* activates myosin light-chain kinase to disrupt claudin-4 and claudin-5 and increase epithelial permeability. Infect Immun 73:7844–7852

Gao M, Li W, Wang H, Wang G (2013) The distinct expression patterns of claudin-10, -14, -17 and E-cadherin between adjacent non-neoplastic tissues and gastric cancer tissues. Diagn Pathol 8:205

Gao H, Lan X, Li S, Xue Y (2017) Relationships of MMP-9, E-cadherin, and VEGF expression with clinicopathological features and response to chemosensitivity in gastric cancer. Tumor Biol 39:1010428317698368

Hagen SJ, Ang LH, Zheng Y, Karahan SN, Wu J, Wang YE, Caron TJ, Gad AP, Muthupalani S, Fox JG (2018) Loss of tight junction protein claudin 18 promotes progressive neoplasia development in mouse stomach. Gastroenterology 155:1852–1867

Hewitt KJ, Agarwal R, Morin PJ (2006) The claudin gene family: expression in normal and neoplastic tissues. BMC Cancer 6:186. https://doi.org/10.1186/1471-2407-6-186

Hollande F, Lee DJ, Choquet A, Roche S, Baldwin GS (2003) Adherens junctions and tight junctions are regulated via different pathways by progastrin in epithelial cells. J Cell Sci 116: 1187–1197

Hwang TL, Changchien TT, Wang CC, Wu CM (2014) Claudin-4 expression in gastric cancer cells enhances the invasion and is associated with the increased level of matrix metalloproteinase-2 and -9 expression. Oncol Lett 8:1367–1371

Isaacson KJ, Jensen MM, Subrahmanyam NB, Ghandehari H (2017) Matrix-metalloproteinases as targets for controlled delivery in cancer: an analysis of upregulation and expression. J Control Release 259:62–75

Itoh M, Furuse M, Morita K, Kubota K, Saitou M, Tsukita S (1999) Direct binding of three tight junction-associated MAGUKs, ZO-1, ZO-2, and ZO-3, with the COOH termini of claudins. J Cell Biol 147:1351–1363

Jawhari A, Jordan S, Poole S, Browne P, Pignatelli M, Farthing MJ (1997) Abnormal immunoreactivity of the E-cadherin catenin complex in gastric carcinoma: relationship with patient survival. Gastroenterology 112:46–54

Jee H, Nam KT, Kwon HJ, Han SU, Kim DY (2011) Altered expression and localization of connexion 32 in human and murine gastric carcinogenesis. Dig Dis Sci 56:1323–1332

Jiang XJ, Lin J, Cai QH, Zhao JF, Zhang HJ (2019) CDH17 alters MMP-2 expression via canonical NF-κB signalling in human gastric cancer. Gene 682:92–100

Johnson AH, Frierson HF, Zaika A, Powell SM, Roche J, Crowe S, Moskaluk CA, El-Rifai W (2005) Expression of tight-junction protein Claudin-7 is an early event in gastric tumorigenesis. Am J Pathol 167(2):577–584

Johnstone SR, Billaud M, Lohman AW, Taddeo EP, Isakson BE (2012) Posttranslational modifications in connexins and pannexins. J Membr Biol 245:319–332

Kimura Y, Shiozaki H, Hirao M (1997) Expression of occludin, tight-junction-associated protein, in human digestive tract. Am J Pathol 151:45–54

Kwon MJ (2013) Emerging roles of claudins in human cancer. Int J Mol Sci 14:18148–18180

Lauren P (1965) The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. Acta Pathol Microbiol Scand 64:31–49

Lee KH, Shin SJ, Kim KO, Kim MK, Hyun MS, Kim TN, Jang BI, Kim SW, Song SK, Kim HS, Bae SH, Ryoo HM (2006) Relationship between E-cadherin, matrix metalloproteinase-7 gene expression and clinicopathological features in gastric carcinoma. Oncol Rep 16(4):823–830

Li LH, Wu GY, Lu YZ, Chen XH, Liu BY, Zheng MH, Cai JC (2017) P 21-activated protein kinase 1 induces the invasion of gastric cancer cells through c-Jun NH2-terminal kinase-mediated activation of matrix metalloproteinase-2. Oncol Rep 38:193–200

Lian PL, Liu Z, Yang Y, Zhao R, Zhang ZY, Chen YG, Zhuang ZN, Xu KS (2016) Integrin αvβ6 and matrix metalloproteinase 9 correlate with survival in gastric cancer. World J Gastroenterol 22:3852–3859

Liu GY, Pang Y, Zhang Y, Fu H, Xiong W, Zhang Y (2019) GJB4 promotes gastric cancer cell proliferation and migration via Wnt/CTNNB1 pathway. Onco Targets Ther 12:6745–6755

Lochhead P, El-Omar E (2008) Gastric cancer. Br Med Bull 85:87–100. https://doi.org/10.1093/bmb/ldn007

Lv YP, Cheng P, Zhang JY et al (2019) *Helicobacter pylori*-induced matrix metallopeptidase-10 promotes gastric bacterial colonization and gastritis. Sci Adv 5(4):eaau6547. https://doi.org/10.1126/sciadv.aau6547

Lynch CC, Vargo-Gogola T, Matrisian LM, Fingleton B (2010) Cleavage of E-cadherin by matrix metalloproteinase-7 promotes cellular proliferation in nontransformed cell lines via activation of RhoA. J Oncol. https://doi.org/10.1155/2010/530745

Martin TA, Jiang WG (2001) Tight junctions and their role in cancer metastasis. Histol Histopathol 16:1183–1195

Martin TA, Jiang WG (2009) Loss of tight junction barrier function and its role in cancer metastasis. Biochim Biophys Acta 1788:872–891

Matsuura K, Kawanishi J, Fujii S (1992) Altered expression of E-cadherin in gastric cancer tissues and carcinomatous fluid. Br J Cancer 66:1122–1130

Morita K, Furuse M, Fujimoto K, Tsukita S (1999) Claudin multigene family encoding four-transmembrane domain protein components of tight junction strands. Proc Natl Acad Sci U S A 96:511–516

Mullin JM (1997) Potential interplay between luminal growth factors and increased tight junction permeability in epithelial carcinogenesis. J Exp Zool 279:484–489

Naz A, Obaid A, Awan FM, Ikram A, Ahmad J, Ali A (2017) Petri net-based model of *Helicobacter pylori* mediated disruption of tight junction proteins in stomach lining during gastric carcinoma. Front Microbiol 8:168. https://doi.org/10.3389/fmicb.2017.01682

Pignatelli M, Vessey CJ (1994) Adhesion molecules: novel molecular tools in tumor pathology. Hum Pathol 25:849–856

Quintero-Fabián S, Arreola R, Becerril-Villanueva E, Torres-Romero JC, Arana-Argáez V, Lara-Riegos J, Ramírez-Camacho MA, Alvarez-Sánchez ME (2019) Role of matrix metalloproteinases in angiogenesis and cancer. Front Oncol 9:1370. https://doi.org/10.3389/fonc.2019.01370

Rawla P, Barsouk A (2019) Epidemiology of gastric cancer: global trends, risk factors and prevention. Gastroenterol Rev 14:26–38

Raychaudhary S, Ghosh S, Roy A, Swarnakar S (2019) Protective role of black tea flavonoids against ethanol-induced gastropathy via matrix metalloproteinase pathway. Ind J Clin Biochem 34:379–394

Reinmuth N, Parikh AA, Ahmad SA, Liu W, Stoeltzing O, Fan F, Takeda A, Akagi M, Ellis LM (2003) Biology of angiogenesis in tumors of the gastrointestinal tract. Microsc Res Tech 60:199–207

Resnick MB, Gavilanez M, Newton E, Konkin T, Bhattacharya B, Britt DE, Sabo E, Moss SF (2005) Claudin expression in gastric adenocarcinomas: a tissue microarray study with prognostic correlation. Hum Pathol 36:886–910

Ribet D, Cossart P (2010) Pathogen-mediated posttranslational modifications: a re-emerging field. Cell 143:694–702

Rosenthal R, Milatz S, Krug SM, Oelrich B, Schulzke JD, Amasheh S (2010) Claudin-2, a component of the tight junction, forms a paracellular water channel. J Cell Sci 123:1913–1921

Sahin U, Koslowski M, Dhaene K, Usener D, Brandenburg G, Seitz G, Huber C, Tureci O (2008) Claudin-18 splice variant 2 is a pan-cancer target suitable for therapeutic antibody development. Clin Cancer Res 14:7624–7634

Sanada Y, Oue N, Mitani Y, Yoshida K, Nakayama H, Yasui W (2006) Down-regulation of the claudin-18 gene, identified through serial analysis of gene expression data analysis, in gastric cancer with an intestinal phenotype. J Pathol 208:633–642

Shan YQ, Ying RC, Zhou CH, Zhu AK, Ye J, Zhu W, Ju TF, Jin HC (2015) MMP-9 is increased in the pathogenesis of gastric cancer by the mediation of HER2. Cancer Gene Ther 22:1–7

Shiozaki H, Iihara K, Oka H, Kadowaki T, Matsui S, Gofuku J (1994) Immunohistochemical detection of alpha-catenin expression in human cancers. Am J Pathol 144:667–674

Soler AP, Miller RD, Lauglin KV, Carp NZ, Klurfeld DM, Mullin JM (1999) Increased tight junction permeability is associated with the development of colon cancer. Carcinogenesis 20:1425–1431

Torres-Martinez AC, Gallardo-Vera JF, Lara-Holguin AN, Montano LF, Rendon-Huerta EP (2017) Claudin-6 enhances cell invasiveness through claudin-1 in AGS human adenocarcinoma gastric cancer cells. Exp Cell Res 350(1):226–235

Tsukita S, Furuse M, Itoh M (2001) Multifunctional strands in tight junctions. Nat Rev Mol Cell Biol 2:285–293

Turksen K, Troy TC (2011) Junctions gone bad: claudins and loss of the barrier in cancer. Biochim Biophys Acta 1816:73–79

Van Itallie CM, Balda MS, Anderson JM (1995) Epidermal growth factor induces tyrosine phosphorylation and reorganization of the tight junction protein in ZO-1 in A431 cells. J Cell Sci 108:1735–1742

Verma S, Kesh K, Ganguly N, Jana S, Swarnakar S (2014) Matrix metalloproteinases and gastro-intestinal cancers: impacts of dietary antioxidants. World J Biol Chem 5:355–376

Weinstein RS, Merk FB, Alroy J (1976) The structure and function of intercellular junctions in cancer. Adv Cancer Res 23:23–89

Wroblewski LE, Piazuelo MB, Chaturvedi R, Schumacher M, Aihara E, Feng R, Noto JM, Delgado A, Israel DA, Zavros Y, Montrose MH, Shroyer N, Correa P, Wilson KT, Peek RM Jr (2015) Helicobacter pylori targets cancer-associated apical-junctional constituents in gastroids and gastric epithelial cells. Gut 64:720–730

Wu J, Zhou HF, Wang CH, Zhang B, Liu D, Wang W, Sui GJ (2007) Decreased expression of Cx32 and Cx43 and their function of gap junction intercellular communication in gastric cancer. Zhonghua Zhong Liu Za Zhi 29(10):742–747

Wu MH, Lee WJ, Hua KT, Kuo ML, Lin MT (2015) Macrophage infiltration induces gastric cancer invasiveness by activating the β-Catenin pathway. PLoS One 10(7):e0134122. https://doi.org/10.1371/journal.pone.0134122

Yang L, Sun X, Meng X (2018) Differences in the expression profiles of claudin proteins in human gastric carcinoma compared with nonneoplastic mucosa. Mol Med Rep 18:1271–1278

Zhang M, Zhu GY, Gao HY, Zhao SP, Xue Y (2011) Expression of tissue levels of matrix metalloproteinases and tissue inhibitors of metalloproteinases in gastric adenocarcinoma. J Surg Oncol 103:243–247

Zheng H, Takahashi H, Murai Y, Cui Z, Nomoto K, Niwa H, Tsuneyama K, Takano Y (2006) Expressions of MMP-2, MMP-9 and VEGF are closely linked to growth, invasion, metastasis and angiogenesis of gastric carcinoma. Anticancer Res 26:3579–3584

Zheng L, Li D, Xiang X, Tong L, Qi M, Pu J, Huang K, Tong Q (2013) Methyl jasmonate abolishes the migration, invasion and angiogenesis of gastric cancer cells through down-regulation of matrix metalloproteinase 14. BMC Cancer 13:74

Zhu T, Hu X, Wei P, Shan G (2018) Molecular background of the regional lymph node metastasis of gastric cancer. Oncol Lett 15(3):3409–3414