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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Unraveling a New Role for Claudins in Gastric Tumorigenesis

Gastric cancer pathogenesis is a multistep process that is associated with *Helicobacter pylori* infection as an important risk factor. The progression of mucosal pathology through the Correa cascade[1] begins with acute gastritis, which is followed by chronic active gastritis, atrophic gastritis, intestinal metaplasia/dysplasia, and then gastric cancer. A high prevalence of gastric cancer remains; there were more than 1 million new cases in 2018 worldwide, and the mortality rates of gastric cancer among all cancers are third for men and fourth for women.[2] Despite *H pylori* eradication therapy and improved surveillance, pockets of high incidence and mortality still occur in Asia, South and Central America, and Eastern Europe.[2] Furthermore, mortality rates worldwide have not improved much in the past 20 years despite our growing knowledge of the factors regulating gastric cancer pathogenesis, including the biology of *H pylori*, environmental factors including diet and toxins, and epithelial factors including oxidative damage. One emerging area providing new insights into gastric cancer pathogenesis is tight junction dysfunction, which contributes to neoplasia development during *H pylori* infection.[3] Advances in animal models and in molecular techniques have facilitated the discovery of important new ideas about tight junction dysfunction in the stomach and its link to gastric tumorigenesis.

Tight junction dysfunction occurs in the gastrointestinal tract when the barrier is no longer selective and tissue homeostasis is disrupted as a result of dysfunction of transporters that depend on ion gradients. The main contributors to selective permeability at tight junctions are claudins, a family of membrane-bound, tetraspanning, and pore-forming proteins. There are currently 27 known members of the human claudin gene family, each thought to confer unique selectivity to the passage of charged and uncharged solutes. Claudin expression defines paracellular permeability, and expression of specific family members varies between tissues. The major claudin expressed in stomach is claudin-18 (*CLDN18A2.1*; the *CLDN18A1.1* is expressed primarily in lung). Patients with gastric cancer showed claudin-18 loss (both lung and stomach isoforms) early in the Correa cascade,[4] and claudin-18 loss was an independent predictor of poor prognosis in patients with gastric cancer.[5] Knockout of *Cldn18A2.1* in mice (st*Cldn18*-knockout [KO]) increased apical to basolateral H^+-flux and caused atrophic gastritis despite compensatory *Cldn18A1.1* expression at tight junctions.[6] In contrast, studies using mice deficient in both *Cldn18A2.1* and *Cldn18A1.1* recently showed that claudin-18 loss drives neoplasia and tumor formation in the absence of *H pylori* infection, which provides mechanistic insight into effectors that participate in proliferation, stem cell homeostasis, neoplasia development, and tumorigenesis.[7]

In the current issue of *Cellular and Molecular Gastroenterology and Hepatology*, a study by Suzuki et al[8] added another important piece to the puzzle. They dissected pathways regulating the transition to metaplasia and then tumor development in young (8 weeks after birth), middle-aged (40 weeks after birth), and aged (>60 weeks after birth) st*Cldn18*-KO mice. Suzuki et al[8] found that active gastritis in young st*Cldn18*-KO mice became chronic active gastritis by the time the mice were middle aged. This transition was accompanied by altered cytokine profiles and increased signal transducer and activator of transcription 3 and nuclear factor-κB signaling. Pharmacologic blockade of C-C motif chemokine ligand 28, a mucosa-associated epithelial chemokine, reduced nuclear factor-κB activity, suggesting that C-C motif chemokine ligand 28 contributed to the transition from acute to chronic active gastritis. The investigators assessed spasmolytic polypeptide-expressing metaplasia (SPEM), a preneoplastic lesion in the mouse stomach. Proliferative SPEM cells in aged mice were positive for trefoil factor 2 and pepsinogen C, showed high levels of CD44 variants, and expressed stem cell markers including Ascl2, Sox2, and matrix metallopeptidase 7. The presence of intestinal markers, such as villin, indicated that aged mice had intestinalized proliferative SPEM. By 100 days after birth, invasive submucosal glands and tumors were present in 20% to 30% of mice. Expression of Wnt1a, which can regulate CD44, C-X-C motif chemokine ligand 5, and matrix metallopeptidase 7 expression, was increased in stomach tissues from mice older than 40 days. To assess this further, st*Cldn18*-KO mice, with transgenic Wnt1a overexpression, were generated. These mice developed gastric tumors more rapidly than st*Cldn18*-KO mice, suggesting that at least 1 effector, C-X-C chemokine ligand 5, is a tumor initiator in this model. Analysis of tissues from gastric cancer patients showed that some, but not all, of the changes identified in st*Cldn18*-KO mice were present.

Future studies of Cldn18 KO mice should be used to understand how claudin-18 contributes to gastric homeostasis and how its loss leads to neoplasia. One idea, proposed in this work and by Hayashi et al,[6] is that acid back-diffusion causes mucosal injury that over time results in inflammation and mucosal injury. One challenge to this idea is that claudin-18A2.1 is not localized to tight junctions per se, even though it is billed as a tight junction protein. Instead it is concentrated on basolateral membranes beneath tight junctions.[7] It therefore remains unclear whether claudin-18 participates directly in the regulation of mucosal barrier function and this remains to be determined. Although the current work showed reduced inflammation and delayed carcinogenesis after cimetidine treatment, it is not clear if this reflects reduced H^+ back-diffusion and mucosal injury from leaky tight junctions or the effects of

cimetidine on cell types other than parietal cells (eg, by blocking histamine/histamine H2 receptors). Whether cimetidine-sensitive immune or other cells are present in the gastric mucosa or cancers and how these cells may impact the tumor environment remains a potential topic for future studies. The work presented by Suzuki et al[8] in this issue triggers thought-provoking and far-reaching ideas that suggest important new studies that will expand our understanding of gastric carcinogenesis further.

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