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Could Down-Regulation of Muscle-Specific MircoRNAs Provoke Functional Dyspepsia in *Helicobacter pylori*-Infected Stomach?

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Summary

Pathogenesis of functional dyspepsia has not been well-established and it's treatment is frequently not satisfactory. Recently Saito et al[1] suggested that dysfunctional gastric emptying could be induced by down-regulation of muscle-specific mircoRNAs (miRNAs) in *Helicobacter pylori* (*H. pylori*)-infected mice (C57BL/6) for 40 weeks. They demonstrated that miRNAs, which are associated with myogenic regulation such as *miR-1* and *miR-133*, were significantly down-regulated, and histone deacetylase 4 and serum response factor, which are reported to be target genes of miRNAs, were increased in the muscular layers of stomach in the *H. pylori*-infected mice. Muscular hypertrophy was observed as a result of this effect on posttranscriptional level induced by *H. pylori* infection, and gastric emptying was accelerated in *H. pylori*-infected mice. In addition, down-regulation of *miR-1*, *miR-133*a and *miR-133b* and increased cell proliferation were observed in C2C12 mouse myoblast cells after coculture with *H. pylori*.[1] Furthermore, *miR-1* and *miR-133* were also significantly decreased in patients with *H. pylori* infection.[1]

The authors concluded that chronic infection with *H. pylori* down-regulated the expression of muscle-specific miRNAs and up-regulated expression of histone deacetylase 4 and serum response factor. These changes might cause hyperplasia in the muscular layer of the stomach and dysfunction in gastric emptying.

Comment

H. pylori has been regarded as one of the major causes in functional dyspepsia and this view has been supported by several epidemiologic studies.[2,3] However, the pathogenesis of functional dyspepsia caused by *H. pylori* was not clearly illuminated so far. Numerous studies have been conducted for evaluation of the association between chronic *H. pylori* infection and gastric motility or perception. In regard to gastric dysmotility, it's type has not been established well. Heterogeneous type of abnormal gastric motility was suggested in the pathognomic mechanism of functional dyspepsia such as delayed gastric emptying, accelerated gastric emptying, antral hypomotility with altered intestinal mo-

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tility, and dysfunctional gastric accommodation.[4,5] Actually, delayed gastric emptying was associated with functional dyspepsia in various studies. However, gastric emptying was not influenced by chronic *H. pylori* infection.[6] In addition, no solid data has been introduced until now regarding the association of dyspeptic symptoms with dysfunctional gastric emptying.[4,5]

MicroRNAs are small non-coding RNAs that regulate gene expression at the post-transcriptional level via translational inhibition or mRNA degradation.[7] This post-transcriptional role has been suggested to influence cellular development and maturation.[7] Various researches suggested that miRNAs had inhibitory effect on translation, and dysregulation of miRNAs was considered as the pathogenesis in various disorders or carcinogensis.[8,9] Zhang et al[9] recently demonstrated that *miR-21* was over-expressed in specimens of gastric cancer and *H. pylori*-infected stomach, and suggested the relationship between miRNAs and gastric carcinogenesis. The *miR-1* and *miR-133* used in this study were muscle specific miRNAs, which are essential for normal myoblast differentiation and proliferation.[7,8] Also, these miRNAs have been implicated in the pathogenesis and treatment of skeletal and cardiac muscular disorders.[8] In this study, Saito et al[1] firstly showed the role of *miR-1* and *miR-133* in gastric muscular layer and dysfunctional gastric emptying in chronic *H. pylori*-infected mice.

However, the critical problem of this study is a mismatch with human clinical studies as the authors also mentioned. In most of human studies for functional dyspepsia, *H. pylori* did not show influence on gastric emptying.[4-6] That is, *H. pylori* was not associated with delayed gastric emptying. Instead functional dyspepsia was associated with accelerated gastric emptying or dysfunctional gastric accommodation.[10,11] Furthermore, accelerated gastric emptying was observed in the stomach with chronic *H. pylori* infection especially in pediatric study.[12] Therefore, further human studies are necessary to validate the association between aberrant expression of muscle-specific miRNAs and the gastric motility disorder associated with chronic *H. pylori* infection. In spite of this limitation, this article has provided a valuable insight into the molecular pathogenesis of gastric motility disorders, including functional dyspepsia.

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