FoxM1 is Overexpressed in Helicobacter pylori–Induced Gastric Carcinogenesis and Is Negatively Regulated by miR-370

Yimin Feng1, Lixiang Wang1,2, Jiping Zeng1,3, Li Shen1, Xiuming Liang1, Han Yu1, Shili Liu1, Zhifang Liu1,3, Yundong Sun1, Wenjuan Li1, Chunyan Chen1, and Jihui Jia

Abstract
Helicobacter pylori (H. pylori) infections are strongly implicated in human gastric mucosa–associated diseases. Forkhead box M1 (FoxM1), a key positive regulator of cell proliferation, is overexpressed in gastric cancer. MicroRNAs are important post-transcriptional regulators of gene expression. In this study, the effects of H. pylori infection on FoxM1 expression and possible mechanisms of carcinogenesis were explored. The expression of FoxM1 was gradually increased in human gastric specimens from inflammation to cancer. FoxM1 upregulation was time- and concentration-dependent in gastric epithelial-derived cell lines infected with H. pylori. CagA, a key virulence factor of H. pylori, was associated with increased FoxM1 expression. H. pylori and CagA inhibited the expression of p27Kip1 (CDKN1B) and promoted cell proliferation by upregulating FoxM1. The expression of miR-370 was decreased in human gastritis and gastric cancer. FoxM1 was directly downregulated by miR-370 in gastric cell lines. H. pylori and CagA inhibited miR-370 expression, which led to overexpression of FoxM1 and cell proliferation. Furthermore, the overexpression of FoxM1 and reduced expression of miR-370 was confirmed in H. pylori–infected C57BL/6J mice. H. pylori infection and CagA upregulated FoxM1 expression, dependent on miR-370, altered the expression of p27Kip1, and promoted proliferation in gastric cells.

Implications: These findings delineate the mechanisms governing FoxM1 regulation and the role of H. pylori in the process of gastric carcinogenesis. Mol Cancer Res; 11(8); 834–44. ©2013 AACR.

Introduction
Gastric cancer is the fourth diagnosed cancer and the second most common cause of cancer-related death worldwide, especially in developing countries (1, 2). Most patients are diagnosed at an advantaged stage because of lack of early specific symptoms, so prognosis remains poor even after extensive surgery and adjuvant therapy.

Gastric carcinogenesis is a complex, multistep, and multifactorial event. Helicobacter pylori (H. pylori) infection is involved in the early stage of gastric cancer pathogenesis by inducing chronic gastritis (3–6). This chronic gastritis can persist for decades and may result in nonresolving inflammation, which is a major driver of gastric cancer (6), and the interaction of host–pathogen contributes to this carcinogenesis (7). The protein CagA of H. pylori is closely associated with gastric cancer and can intervene in signal pathways in cells (8). To date, however, the underlying molecular mechanisms of carcinogenesis induced by H. pylori remain to be elucidated.

Forkhead box M1 (FoxM1), a member of the Fox transcription factor family (9), is a key positive cell-cycle regulator in cell proliferation. Aberrant expression of FoxM1 is involved in several tumor types, including hepatocellular carcinoma, basal cell carcinoma, breast cancer, lung cancer, prostate cancer, glioblastomas, and gastric cancer (10–18), which implies an oncogene role in carcinogenesis. We previously reported that FoxM1 is upregulated in gastric cancer, and its inhibition leads to cellular senescence (18), but the relevance of H. pylori infection and FoxM1 expression associated with the pathogenesis of gastric cancer remains undefined.

miRNAs, a family of small noncoding RNAs, are important negative regulators of posttranscriptional gene expression by directly targeting the 3' untranslated regions (3'UTR) of target mRNAs, eventually promoting the degradation or translation suppression of target mRNAs.
miRNAs are frequently deregulated in many types of human cancers and play critical roles in tumorigenesis, serving as tumor suppressors or oncogenes (21, 22). Recent studies have shown that several miRNAs, such as miR-146a, miR-155, and miR-21, are involved in H. pylori-induced infection (23–25). MiR-370 has been verified as a tumor suppressor in bladder cancer and cholangiocarcinoma cell lines (26, 27). Furthermore, FoxM1 is predicted as a putative target of miR-370 by bioinformatics.

Here, we aimed to identify the role of FoxM1 in H. pylori infection and the pathogenesis of gastric cancer and regulation by miR-370 in vitro and in vivo.

Materials and Methods

Patients and tissue specimens

Resected tissues from 25 patients with gastric cancer were harvested at surgery. Gastritis species were collected from 34 patients undergoing gastroscopy. All these patients underwent surgery at Qilu Hospital, Shandong University (Jinan, PR China) from 2009 through 2011. None of the patients had received adjuvant chemotherapy before surgery. The diagnosis of all gastric cancer and gastritis was histopathologically confirmed. General information about patients is given in Supplementary Table S1. The study was approved by the Ethics Committee of Shandong University School of Medicine (Jinan, PR China).

Experimental animals

C57BL/6J mice were purchased from the Experimental Animal Center of Shandong University and maintained in the Animal Center in Shandong University School of Medicine. Male mice aged 6 weeks were used in all experiments. We randomly divided 40 mice into 2 groups for treatment: infection (n = 24) and control (n = 16). The infection group received by intragastric gavage 10^9 colony-forming units of H. pylori (SS1, a standard strain of H. pylori adapted to the murine stomach.) after 12-hour fasting every other day for 3 times. The control group received 1 mL PBS each time in the same way. At 8 months, mice were killed, and stomach tissue samples underwent hematoxylin and eosin staining and immunohistochemical (IHC) assay. All animal care and experimental protocols were approved by the Ethics Committee of Shandong University School of Medicine.

H. pylori and bacterial culture

The standard strains of H. pylori (NCTC 11637, 26695, and SS1) were kindly provided by Dr. Jianzhong Zhang (Chinese Disease Control and Prevention Center; Beijing, China). All strains were cultured in Brucella broth with 5% FBS under microaerobic conditions (5% O2, 10% CO2, and 85% N2) at 37°C. The strains were harvested at exponential amplification phases by centrifugation and added to gastric cell lines at different bacteria-to-cell ratios and times.

Cell lines and cell culture

The gastric epithelial-derived cell lines, AGS and BGC-823, were obtained from China Academia Sinica Cell Repository (Shanghai, China). AGS cells were cultured in F12 medium supplemented with 10% FBS. BGC-823 cells were cultured in RPMI-1640 medium supplemented with 10% FBS. Both cell lines were incubated in a humidified atmosphere containing 5% CO2 at 37°C without antibiotics.

Plasmid construction and transfection

The sequence fragment of 212 bp incorporating the whole length of pre-miR-370 was amplified from normal human genomic DNA with the primers sense, 5’-AAAGGAGTCTACTTGGAGGGATGCGATA-3’; and antisense, 5’-TCAAGGTCCTCCGGAGCTCTGGTTAGTAC-3’. The amplified fragment was cloned into the specific vector pSilencer3.1-H1 (Ambion) to construct the pSilencer-miR-370 expression plasmid. Likewise, for constructing the anti-miR-370 interfering plasmid, the miR-370 complementary sequence was synthesized as DNA oligonucleotides and cloned into the pSuper vector (Oligoengine) after annealing. Firefly luciferase reporter vectors with the intact putative miR-370 recognition sequence of the wild-type (pGL3-FoxM1-wild-3’UTR) and mutant (pGL3-FoxM1-mutant-3’UTR) were cloned from the FoxM1 3’UTR. The authenticity of DNA sequences was confirmed by sequencing. All plasmids were transfected into cell lines by the Lipofectamine 2000 method (Invitrogen). The si-FoxM1 oligonucleotides were also transfected with Lipofectamine 2000, with final concentration 100 nmol/L.

RNA extraction and qRT-PCR

Total RNA was extracted by use of Trizol reagent (Invitrogen). For detection of miR-370, RNA was converted into cDNA with use of the TaqMan MicroRNA Reverse Transcription Kit, then real-time PCR (RT-PCR) was conducted with specific primers (TaqMan MicroRNA Assay) and TaqMan Universal PCR Master Mix (Applied Biosystems). For detecting FoxM1 and P27Kip1, 1 μg RNA was converted into cDNA by the MMLV Reverse Transcription System (Promega) and RT-PCR involved use of the SYBR Premix Ex Taq system (TaKaRa). All PCRs were run on an ABI 7500 sequence detector (Applied Biosystems). U6 snRNA or β2-microglobulin was used as an endogenous control. All RT-PCR reactions were conducted in triplicate, and relative quantification was calculated by the ΔΔCt method (95% confidence interval) with calibration to the corresponding endogenous control. Primers for RT-PCR were for H. pylori, sense, 5’-TGCAAGCTAGGGATGTTAATCTCC-3’, and antisense, 5’-GGAGCCCGACCTCATCAGAACC-3’; and for P27Kip1, sense, 5’-ATGTCACAACTGGCAGTGCTAAC-3’, and antisense, 5’-TTACGTTCAGTCTCTTCGAGG-3’.

Luciferase assay

The P27Kip1 reporter plasmid, constructed to harbor the P27Kip1 promoter sequence (–1358/+132), and control TK plasmid were added into cells by use of Lipofectamine 2000. Cells were infected with H. pylori by the ratio 1:100.
Expression of FoxM1 is upregulated in human gastritis and primary gastric cancer

We investigated the expression of FoxM1 in gastric specimens at different disease stages, including 20 normal, 12 superficial gastritis, 12 atrophic gastritis associated with intestinal metaplasia (AG/IM), and 20 primary gastric cancer tissues (Supplementary Table S1). The mRNA expression of FoxM1 gradually increased from gastritis to cancer as compared with the control (Fig. 1A), so upregulation of FoxM1 was an early event in human gastric carcinoma. This overexpression was confirmed by IHC assay, which showed FoxM1 expressed in superficial gastritis tissue (21.7% positive cells), AG/IM tissue (36.4% positive cells), and gastric cancer tissue (89.2% positive cells) as compared with noncancerous gastric tissues (6.7% positive cells; \( P < 0.01 \); Fig. 1B and C). FoxM1 expression was not associated with patient age or sex (Supplementary Table S1).

Results

Expression of FoxM1 is upregulated in human gastritis and primary gastric cancer

Statistical analysis

Quantitative data are expressed as mean ± SEM. Statistical analysis involved SPSS 13.0 (SPSS Inc.) with 2-tailed Student’s t test or 1-way ANOVA for analysis of more than 2 subgroups. Statistical significance was set at \( P < 0.05 \).

For 6 hours, Luciferase activity was determined with the Dual Luciferase Reporter Assay system (Promega), and the P27\(^{kip1} \) promoter-driven firefly luciferase activity was normalized to that of TK Renilla. For luciferase assays of miRNA target validation, pSilencer-miR-370, wild-type or mutant 3\(^\prime\)UTR of FoxM1, and TK plasmids were cotransfected into AGS cells. After 48 hours, cells were lysed in passive lysis buffer and luciferase activity was determined.

Western blot analysis and IHC assay

According to standard Western blot procedures, proteins were separated by 10% SDS-PAGE and then transferred to PVDF membrane (Bio-Rad), which were blocked in 5% nonfat milk, then incubated with the primary antibodies FoxM1 (1:500), P27\(^{kip1} \) (1:200), and \( \beta \)-actin (1:500) for 1 to 2 hours under room temperature, then horseradish peroxidase-labeled goat-anti-mouse or goat-anti-rabbit immunoglobulin G antibody (1:5,000, all Santa Cruz Biotechnology). Protein levels were detected by use of enhanced chemiluminescence (Pierce) and visualized on X-ray film. FoxM1 levels in tissue specimens were determined by IHC staining with primary antibody (FoxM1, 1:250) incubation at 4°C overnight. Negative controls were treated without the primary antibody.

Colony formation assay

AGS cells were infected with \( H. \) pylori standard strain 26695 or transfected with FoxM1 siRNA and pSilencer-miR-370 for corresponding time, and then seeded into 6-well plates (300 cells/well) for 10 to 14 days. Plates were stained with Giemsa, and the number of colonies with more than 50 cells were counted.

Statistical analysis

Quantitative data are expressed as mean ± SEM. Statistical analysis involved SPSS 13.0 (SPSS Inc.) with 2-tailed Student’s t test or 1-way ANOVA for analysis of more than 2 subgroups. Statistical significance was set at \( P < 0.05 \).

\( H. \) pylori and its key virulence factor CagA promote FoxM1 expression in gastric epithelial cell lines

Next, we determined whether infection with \( H. \) pylori (standard strain 26695) could affect FoxM1 expression in 2 gastric epithelial cell lines: poorly differentiated AGS and undifferentiated BGC-823 cells. Both the mRNA and protein levels of FoxM1 were significantly upregulated with \( H. \) pylori infection time and dose dependently (Fig. 2A–D). Furthermore, to evaluate whether overexpression of FoxM1 by \( H. \) pylori infection was strain specific, AGS and BGC-823 cell lines were infected with \( H. \) pylori strains 26695, 11637, and SS1 (1:100) for 12 hours. FoxM1 expression was substantially elevated after infection by all of the 3 strains as compared with the control (Fig. 2E and G). To determine which virulence factor was responsible for the increased FoxM1 expression, we treated cells with CagA (CagA full-length plasmid), VacA (centrifugation of \( H. \) pylori liquid medium), and lipopolysaccharide (LPS; hot inactivation of \( H. \) pylori; ref. 28) and examined FoxM1 expression.
cells. CagA promoted the mRNA and protein levels of FoxM1, with almost no impact with other treatments (Fig. 2F and H). These results were confirmed in cells with CagA overexpression (Fig. 2I and J). Thus, upregulation of FoxM1 may have been induced by *H. pylori* infection through its component CagA.
H. pylori and CagA were involved in cell proliferation by suppressing P27\(^{kip1}\) expression mediated by FoxM1

We previously reported that P27\(^{kip1}\) expression was suppressed by FoxM1 in gastric cancer cell lines (18). Hence, we examined whether H. pylori infection could inhibit P27\(^{kip1}\) expression by upregulating FoxM1. Both the mRNA and protein levels of P27\(^{kip1}\) were significantly inhibited in AGS and BGC-823 cell lines after H. pylori infection and CagA transfection, separately (Figs. 3A and B). Furthermore, both H. pylori and CagA treatment reduced the luciferase activity of P27\(^{kip1}\) promoter and P27\(^{kip1}\) expression in AGS cells with H. pylori (1:100) infection [Hp] for 12 hours, control siRNA transfection for 48 hours (Cs), and FoxM1 silencing with specific siRNA for 48 hours (Fs). Luciferase activity was normalized to that of Renilla of the TK plasmid. *, \(P < 0.01\) versus con; #, \(P < 0.05\) versus H. pylori infection. F and G, the foci number of AGS cells after H. pylori (MOI 1:100) infection for 12 hours and FoxM1 silencing. *, \(P < 0.01\) versus con and #, \(P < 0.01\) versus H. pylori infection. Data are mean ± SEM of 3 independent experiments.

FoxM1 is a direct target of has-miR-370

We used computer-aided algorithmic programs [TargetScanHuman (http://www.targetscan.org), PicTar (http://pictar.mdc-berlin.de), and miRBase (http://www.mirbase.org)] to predict FoxM1 as a putative target of has-miR-370 (Fig. 5A). The mRNA level of miR-370 was gradually decreased from superficial gastritis, AG/IM to gastric cancer samples, which indicates the importance of...
miR-370 during gastric cancer progression (Fig. 5B). The effect of miR-370 on FoxM1 expression was evaluated with effective overexpressing and interfering plasmids of miR-370 (Fig. 5C). Both AGS and BGC cell lines transfected with pSilencer-miR-370 expression plasmid showed reduced mRNA and protein levels of FoxM1 (Fig. 5D and E). Meanwhile, FoxM1 was upregulated after plasmid knockdown of miR-370 (Fig. 5D and E). Next, we validated FoxM1 as a target of miR-370 by dual luciferase reporter assay. AGS cells were cotransfected with pSilencer-miR-370 and FoxM1 wild-type or mutant-type 3'UTR plasmids. Cotransfection of hsa-miR-370 and wild-type 3'UTR plasmid reduced the luciferase activity by approximately 80% relative to the control, whereas mutant 3'UTR cotransfection almost restored the luciferase activity (Fig. 5F). Thus, miR-370 directly targeted the binding site located at FoxM1 3'UTR and FoxM1 may be a direct target of miR-370.
MiR-370–FoxM1 pathway mediates *H. pylori*-induced cell proliferation

In AGS and BGC-823 cells, the expression of hsa-miR-370 was inhibited by *H. pylori* infection and transfection of CagA full-length plasmid, respectively, which suggests that suppression of hsa-miR-370 by *H. pylori* may play an important role in gastric carcinogenesis (Fig. 6A and B). Next, we examined whether the miR-370–FoxM1 pathway was involved in *H. pylori*-induced gastric cancer cell proliferation. miR-370 could inhibit FoxM1 expression and suppress *H. pylori* and CagA-induced upregulation of FoxM1 in AGS cells (Fig. 6C and D), which implies the existence of a miR-370–FoxM1 pathway in *H. pylori*-induced cell proliferation.

Furthermore, the results were confirmed by colony-formation assay, which showed that miR-370 significantly inhibited *H. pylori* and CagA-induced cell proliferation (*P* < 0.01; Fig. 6E and F).

**FoxM1 is involved in *H. pylori*-induced gastritis in vivo**

The validation of our mouse model of gastritis induced by *H. pylori* infection was confirmed by hematoxylin and eosin staining (Fig. 7A). After administration of *H. pylori* for 8 months, 90% (18/20) of mice were validated as gastritis models in the *H. pylori* infection group as compared with 13% (2/15) in the control group (Supplementary Table S2). FoxM1 protein level was more in the model than the control on IHC assay (Fig. 7A and B; *P* < 0.01). In addition, the
mRNA level of mmu-miR-370 was reduced and that of FoxM1 increased in mucosal epithelial samples of \textit{H. pylori}-induced gastritis (Fig. 7C and D; $P < 0.01$). The results in vivo revealed the involvement of FoxM1 and miR-370 in \textit{H. pylori}-induced gastritis.

**Discussion**

In this study, we found overexpression of FoxM1 and reduced expression of hsa-miR-370 in human gastritis and gastric cancer. \textit{H. pylori} and its key virulent factor CagA induced the expression of FoxM1 by inhibiting that of hsa-miR-370, which directly targeted FoxM1, resulting in cell proliferation for gastric carcinogenesis by reducing P27Kip1 promoter activity and its expression (Supplementary Fig. S1).

Gastric carcinomas may occur on the background of chronic gastric inflammation caused by persistent infection of \textit{H. pylori} (29). Accumulating studies indicate that \textit{H. pylori} may be involved in superficial gastritis formation, which might later progress into AG/IM, or even gastric cancer. The chronic inflammatory status over decades increases the risk of gastric cancer with \textit{H. pylori} considered a Group 1 human carcinogen (30). Studies have focused on the mechanism by which \textit{H. pylori} induces carcinogenesis, such as bacterium products that cause gastric mucosal damage (31), generation of oxidative stress (32), and favoring the formation of mutagenic substances (33). Moreover, \textit{H. pylori} may inhibit apoptosis and promote proliferation, invasion, and angiogenesis of cancer cells via CagA, the key virulence factor of \textit{H. pylori} (34).

Despite the importance of \textit{H. pylori}, a susceptible host is also required in gastric tumorigenesis. Some typical pathways have been verified in \textit{H. pylori} infection-related gastric cancer and include NF-κB and Wnt/β-catenin signaling.
However, the involvement of the transcription factor FoxM1, shown upregulated in gastric cancer samples in our previous studies (18), remained unknown. As a typical cell-cycle–related transcription factor, one of the key roles of FoxM1 in carcinogenesis is to promote tumor proliferation (9). In addition, upregulation of FoxM1 is a frequent event in different tumor types, and FoxM1 deficiency triggers reduced cellular proliferation or even growth arrest (10–14), which suggests that FoxM1 may play an important role in tumorigenesis and progression. Our results revealed that overexpression of FoxM1 occurred from gastritis to gastric cancer progression and H. pylori-induced FoxM1 expression in vivo and in vitro, so FoxM1 might take part in the early stage of gastric cancer. Because of the genetic heterogeneity present within H. pylori genomes, infection outcomes vary for different H. pylori strains and their virulence factors, such as CagA, VacA, and LPS.

In this study, we found that all 3 H. pylori strains, 26695, 11637, and SS1, increased the expression of FoxM1 in different gastric cells, further indicating the key role of FoxM1 in H. pylori-induced pathologic process. However, only CagA was able to promote FoxM1 upregulation. Microdissection and microarray were used to determine the differentially expressed mRNA levels with progression of superficial gastritis, AG/IM, and gastric cancer; data analysis revealed the involvement of FoxM1 in this process (data not shown). In short, we found that upregulation of FoxM1 existed in the early stage of gastric cancer associated with H. pylori infection, which suggests an important role of FoxM1 in this progress.

Cell-cycle checkpoint genes play a pivotal role in gastric carcinogenesis (36). P27Kip1, the negative regulator of cell cycle, is commonly downregulated in gastric cancer. It has been considered a tumor suppressor and could serve as a candidate molecular marker for early gastric carcinoma (37). In the diffuse gastric cancer subtype, P27Kip1-negative–C-MYC–positive was the most frequent combination and was associated with more pathogenic H. pylori strains (38). Furthermore, transcription of P27Kip1 was verified to be inhibited by CagA via a PI3K/Akt1 pathway (39). In agreement with these observations, we found inhibited P27Kip1 mRNA and protein levels with H. pylori CagA...
treatment by upregulating FoxM1 expression, which decreased P27Kip1 promoter activity in AGS and BGC-823 cells. However, P27Kip1 inhibition and colony number were only partially reversed after knockdown of FoxM1 by its specific siRNA, which suggests other molecules involved in this process. One study showed that H. pylori decreased P27Kip1 expression through delta opioid receptor–mediated inhibition of histone acetylation within the P27Kip1 promoter (40). Other research confirmed the involvement of cytoplasmic mislocalization of P27Kip1 induced by H. pylori in gastric cancer (41). These findings also link low gastric P27Kip1 expression with gastric carcinogenesis induced by H. pylori infection. Also, they could explain why P27Kip1 expression could not be completely reversed by FoxM1 silencing: H. pylori-induced FoxM1 may be a critical but not the only way for downregulation of P27Kip1 for cell proliferation. Two oncogenes, c-myc and human telomerase reverse transcriptase (hTERT), can be induced by H. pylori and are the direct target genes of FoxM1 (9, 42). We also found substantial induction of the protein levels of c-myc and hTERT in vivo and in vitro after H. pylori infection (data not shown), which further indicates that FoxM1 plays a key role in gastric tumorigenesis induced by H. pylori infection. We failed to induce gastric cancer after 8 months of H. pylori infection in animal models. However, we elucidate that H. pylori and its key virulent factor CagA take part in inflammation-related gastric cancer through upregulation of FoxM1.

miRNAs are important negative regulators of posttranscriptional gene expression and involved in several biologic processes, including tumorigenesis, by regulating tumor suppressors or oncogenes. Numerous deregulated miRNAs are involved in gastric cancer and include miR-146a, miR-155, miR-21, miR-27a, miR-106–93–25, miR-221–222 clusters, and the miR-200 family (23–25, 43–46). A growing number of studies also suggest the involvement of miRNAs in various steps of gastric carcinogenesis: from gastritis to metastatic disease (47). In this study, we found reduced hsa-miR-370 expression in different disease stages, and the expression could be downregulated by H. pylori infection and CagA treatment in gastric cell lines. Moreover, FoxM1 was validated as a direct target of miR-370. Overexpression of hsa-miR-370 inhibited the cell proliferation induced by H. pylori infection or CagA treatment by silencing FoxM1, which suggested a tumor-suppressive role of miR-370 in H. pylori-induced gastritis toward gastric cancer.

In summary, our study shows that the miR-370–FoxM1 pathway is involved in the progress of gastritis toward gastric cancer induced by H. pylori infection by affecting the expression of P27Kip1, which suggests potential application in early intervention and treatment of gastric cancer.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: Y. Feng, L. Wang, J. Zeng, J. Jia
Development of methodology: L. Wang, J. Jia
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Y. Feng, L. Wang, J. Zeng, L. Shen, X. Liang, H. Yu
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y. Feng, J. Zeng, L. Shen, X. Liang, H. Yu, S. Liu, Z. Liu, Y. Sun, W. Li, C. Chen
Writing, review, and/or revision of the manuscript: Y. Feng, L. Wang, J. Zeng, J. Jia
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L. Wang, J. Jia
Study supervision: J. Jia

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