Histone Methyltransferase hSETD1A Is a Novel Regulator of Metastasis in Breast Cancer

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Abstract

Epigenetic alteration is a hallmark of all cancers. Such alterations lead to modulation of fundamental cancer-related functions, such as proliferation, migration, and invasion. In particular, methylation of Histone H3 Lysine 4 (H3K4), a histone mark generally associated with transcriptional activation, is altered during progression of several human cancers. While the depletion of H3K4 demethylases promotes breast cancer metastasis, the effect of H3K4 methyltransferases on metastasis is not clear. Nevertheless, gene duplications in the human SETD1A (hSETD1A) H3K4 methyltransferase are present in almost half of breast cancer cell lines and clinical tumor specimens. Ablation of hSETD1A in breast cancer cells led to a decrease in migration and invasion in vitro and to a decrease in metastasis in nude mice. Furthermore, a group of matrix metalloproteinases (including MMP2, MMP9, MMP12, MMP13, and MMP17) were identified which were downregulated upon depletion of hSETD1A and demonstrated a decrease in H3K4me3 at their proximal promoters based on chromatin immunoprecipitation analysis. These results provide evidence for a functional and mechanistic link among hSETD1A, MMPs, and metastasis in breast cancer, thereby supporting an oncogenic role for hSETD1A in cancer.

Implications: This study reveals that hSETD1A controls tumor metastasis by activating MMP expression and provides an epigenetic link among hSETD1A, MMPs, and metastasis of breast cancer. Mol Cancer Res. 13(3): 461–9. ©2014 AACR.

Introduction

Breast cancer is the second leading cause of cancer-related deaths among women in the United States (1). While the prognosis is favorable for patients diagnosed with localized or regional disease, there is only an approximately 24% chance of 5-year survival for patients diagnosed with metastatic breast cancer (1). As metastasis is the primary reason for cancer-related deaths, understanding mechanisms that control metastatic activity is critical for designing novel interventional strategies and improving disease outcomes.

Genetic mutations and anomalous epigenetic alterations, such as aberrant DNA methylation and/or posttranslational histone modifications are commonly linked to abnormal gene expression patterns that underlie tumorigenic initiation and progression (2–8). Dysregulated expression and activities of histone-modifying enzymes have recently emerged as a mechanism responsible, at least in part, for cancer-associated changes within the epigenome (4, 6). As epigenetic alterations are in theory reversible, pharmacologic targeting of epigenetic modulators is an attractive strategy to restore normal gene expression patterns as a means to treat cancer (2, 6, 8). Several histone-modifying enzymes have been linked to breast tumorigenesis including Ezh2 H3K27 methyltransferase (9–11), LSD1 H3K4 demethylase (12), HDAC6 histone deacetylase (13), UTX H3K27 demethylase (14), and JMD2C H3K9/H3K36 demethylase (15). While such enzymes are promising targets for therapeutic intervention, a more thorough understanding of their impact on tumor phenotype is required. For example, trimethylation of Histone H3 at the Lysine 4 residue (H3K4me3) is a well-characterized histone mark that is enriched at gene transcriptional start sites (TSS) and is associated with transcriptionally active genes (16–19). Levels of H3K4me3 are globally and locally altered during different developmental stages of cancer, and can serve as a predictor for disease recurrence (20–26). It was also recently documented that increased H3K4me3 and decreased H3K27me3 is important for activation of genes linked to proliferation and invasion of breast cancer such as matrix metalloproteinases (MMP), ERBB3, Six1, Cyclin A1, Pim-1, and CSPG4 (14).

Dynamic methylation and demethylation of H3K4 is primarily facilitated by the trithorax (TrxG) members of histone methyltransferases (HMT) termed SETD1A/B and MLL1–4 (27), and the histone demethylases LSD1/2 (28) and JARID1A-D (29–32). hSETD1A mainly catalyzes H3K4me3 and is thus an important coactivator of gene transcription (27). We previously showed that H3K4me3 and hSETD1A are both upregulated in colorectal cancer cell lines and primary colorectal tumors (26). We also documented that hSETD1A positively impacts the transcription of...
A potential role for hSETD1A in promoting metastasis has not been studied. However, a recent study demonstrated that TGFβ-induced epithelial–mesenchymal transition (EMT) led to a global increase in H3K4me3 and dramatic decrease in the transcriptionally repressive H3K9me2 histone mark (25). EMT is an embryonic process in which epithelial cells lose polarity and acquire motility and invasive potential (34). In the context of cancer, activation of EMT is a critical phenotypic event that promotes metastatic behavior (34–36). Depletion of the H3K4 demethylases LSD1 or JARID1B in breast cancer cells promoted metastasis in animal models (37, 38). These findings suggest that downregulation of H3K4 HMTs could conversely suppress breast cancer metastasis. Consistent with this idea, gain in hSETD1A gene copy number is detected in approximately 45% of breast tumors (39). Finally, increased MMP activity is commonly observed in breast cancer cells and promotes a variety of cellular activities including proliferation, migration, and invasion (33, 40–43). Taken together, these facts prompted us to investigate a possible link between hSETD1A, H3K4me3, MMP expression, and metastatic breast cancer phenotype. We found that hSETD1A is overexpressed in metastatic human breast cancer cell lines and patient specimens. Depletion of hSETD1A in breast cancer cells was associated with downregulation of several MMPs and led to a decrease in the metastatic phenotype, indicating an important role of hSETD1A and its H3K4 HMT activity in regulation of breast cancer progression.

Materials and Methods

Cell culture and reagents

Human cell lines were purchased from ATCC unless otherwise indicated. All cells were obtained from ATCC, authenticated, and maintained in early passages, no more than 6 months after receipt from ATCC. SUM159 were obtained from Dr. David Reisman (University of Florida). Cells were cultured in a humidified 5% CO2 environment at 37°C. HEK293FT, MDA-MB-231, MCF7, BT549, and SUM159 cell lines were maintained in DMEM supplemented with 10% FBS and 1% penicillin–streptomycin (Invitrogen). The human mammary epithelial cell lines MCF10A and HMEC were obtained from Dr. Jianrong Lu (University of Florida, Gainesville, FL), and were cultured in DMEM/F-12 medium (Cellgro) supplemented with 5% horse serum (Sigma), 30 ng/mL EGF, 10 µg/mL insulin, and 0.5 µg/mL hydrocortisone (Sigma).

shRNA-mediated knockdown of hSETD1A

A pLKO.1-TRC vector encoding shRNA sequence specific for hSETD1A (clone ID: TRCN0000152242) was obtained from the UP Health Cancer Center shRNA library (Thermo Scientific). pCI/pZ vectors encoding hSETD1A-specific shRNA sequences (shSETD1A #1, Clone ID: V2LHS_119184, shSETD1A #2, Clone ID: V3LHS_316055) were purchased from Thermo Scientific. Lentiviruses were generated by cotransfecting shRNA constructs along with viral packaging plasmids pMD2.G and psPax2 (Addgene) into HEK293FT cells using a calcium phosphate transfection method (Promega). Indicated lines were transduced with lentivirus for 48 hours and selected using 1 µg/mL puromycin (Calbiochem). Polyclonal cell populations were used for indicated experiments.

Antibodies

hSETD1A antibody was purchased from Bethyl Laboratories (A300-289A), anti-α-tubulin from Sigma (T6199), anti-histone H3 from Abcam (Ab1791), anti-H3K4me3 (MC315) and anti-H3K27me3 (07-449) from Millipore, and anti-H3K27Ac from Cell Signaling Technology (#8173).

Western blotting

Cell lysates were prepared by resuspending cell pellets in RIPA buffer (140 mmol/L NaCl, 0.5% Triton X-100, 1% sodium deoxycholate, 0.025% sodium azide, 10 mmol/L Tris, pH 8.0) containing proteinase inhibitors followed by short sonication. Protein samples were subjected to SDS-PAGE and subsequently electrotransferred onto polyvinylidene difluoride membrane. Next, membranes were sequentially probed with indicated primary antibody, horseradish peroxidase–conjugated secondary antibody, and immunoreactive bands visualized by chemiluminescence (ECL, Pierce) and autoradiography.

Real-time PCR

Total RNA was isolated from frozen tissues by TRIzol extraction (Ambion) according to the manufacturer’s instructions. Total RNA was isolated from cell lines using the RNeasy Mini Kit (Qiagen) according to the manufacturer’s instructions. cDNA was synthesized from 2 µg of RNA using a Superscript II Reverse Transcriptase kit (Invitrogen). Real-time PCR was performed on cDNA templates with a CFX Real-Time PCR Detection System (Bio-Rad), using SYBR Green. All real-time PCR assays were performed in triplicate using GAPDH or β-actin as an internal control. Quantitative reverse transcription polymerase chain reaction (qRT-PCR) primer sequences are listed in Supplementary Table S1.

Growth assays

Cell proliferation was measured by seeding cells at a density of 2 × 10^4 cells in 10 cm culture dishes. Viable cells were counted using Trypan Blue every other day and assays were carried out on duplicated cultures.

Migration and invasion assays

To measure cell migration, hSETD1A knockdown and control MDA-MB-231 (5 × 10^4) or BT549 (5 × 10^4) cells were harvested, resuspended in 500 µL complete growth medium, and placed onto 24-well plate with inserts containing membranes with 8 µm pores (BD Biosciences). Inserts were placed inside wells (24-well plate) containing 700 µL of complete DMEM medium. After 24 hours, nonmigrating cells remaining on top of the membranes were removed with a cotton swab. Cells that had migrated through the membrane onto the underside surface were fixed and stained with crystal violet and photos taken using light microscopy. Each experiment was carried out in 3 to 5 replicates and repeated at least twice.

To measure cell invasion, hSETD1A knockdown and control MDA-MB-231 cells (1 × 10^4) or BT549 cells (2 × 10^4) were suspended in 500 µL serum-free medium and seeded onto basement membrane Matrix-coated invasion inserts (BD Biosciences). The insert is covered with a membrane containing 8 µm pores and is coated with Matrigel. Cells were allowed to invade the Matrigel membrane for 24 hours, after which invaded cells were counted.
by light microscopy. Each experiment was carried out in 2 to 5 replicates and repeated at least twice.

**Wound-healing assay**

hSETD1A knockdown and control MDA-MB-231 or BT549 cells were cultured in monolayer to near confluence (>90%) in 6 cm tissue culture dishes. MDA-MB-231 cells were cultured with 2% FBS to eliminate proliferation. Using a sterile pipette tip, the monolayer was wounded with a pipette tip, rinsed with PBS, and medium was added to the dish. Cells were fixed by immersion in 100% ethanol and subsequently stained with crystal violet. Photomicrographs of the wound were taken at the indicated time points. Wound healing was quantified by normalizing after injury wound width (48–72 hours) to wound width immediately after injury (time 0).

**Patient samples**

Deidentified primary breast tumor and metastatic cancer samples were obtained from the Cooperative Human Tissue Network (CHTN) at the University of Alabama at Birmingham (Birmingham, AL). Samples were obtained with the approval of the Institutional Animal Care and Use Committee of the University of Florida.

**Chromatin immunoprecipitation**

ChIP was conducted as previously described (26). Briefly, cells were crosslinked with 1% formaldehyde and 1.5 mmol/L ethylene glycol bis[succinimidylsuccinate] at room temperature. Crosslinked chromatin was subsequently harvested, sheared, and precipitated with antibodies against H3K4me3, hSETD1A, H3K27Ac, H3K27me3, or nonspecific IgG. Fold enrichment of precipitated DNA over input chromatin was determined in duplicates or triplicate via real-time PCR assays. PCR were designed to amplify DNA over input chromatin was determined in duplicates or triplicate via real-time PCR assays.

**Results**

hSETD1A and H3K4me3 are upregulated in breast cancer

We previously showed that hSETD1A and H3K4me3 are upregulated in colorectal carcinoma, and regulate canonical Wnt signaling and cellular proliferation (26). Available evidence suggested that hSETD1A may also function in breast tumorigenesis as gain in human SETD1A gene copy number was detected in 45% (352/782) of breast cancer cases compared with only 6.8% loss in gene copy (53/782; ref. 39). These observations suggested that...
increased levels of hSETD1A expression and activity occur in breast cancer. To test this we examined the levels of hSETD1A protein as well as H3K4me3 in breast cancer compared with mammary epithelial cell lines by Western blot analysis. As shown, hSETD1A and H3K4me3 levels were coordinately elevated in the breast cancer cell lines MCF7, MDA-MB-231, BT549, and SUM159 compared with the mammary epithelial cells MCF10A and HMEC (Fig. 1A and B).

In addition, qRT-PCR was next used to examine mRNA levels of hSETD1A in primary and metastatic human breast tumors (Fig. 1C). This analysis revealed that relative to transcript levels measured in normal breast tissue and primary breast neoplasms, levels of hSETD1A mRNA were elevated in metastatic breast tumors suggesting a potential role for hSETD1A in breast cancer metastasis. On the other hand, mRNA levels of Ash2L, the homolog of MLL1 and the TrxG core subunit with a weak H3K4 methyltransferase activity, did not show significant change among normal and malignant breast tissues (Supplementary Fig. S1A and S1B). Nevertheless, transcript levels of the closely related hSETD1B gene were elevated in breast cancer samples (Supplementary Fig. S1C).

Effect of hSETD1A depletion on breast cancer cell growth and invasiveness

We previously showed that hSETD1A knockdown negatively impacts growth of cultured colon cancer cells (26). To assess the effect of hSETD1A on proliferation of breast cancer cells, we stably knocked down hSETD1A in the human breast cancer lines MDA-MB-231 and BT549 using lentiviral-encoded shRNAs (Fig. 2A and Supplementary Fig. S2A). We subsequently observed that, similar to our previous findings in colorectal cancer lines, hSETD1A knockdown consistently reduced cellular proliferation, although the extent of reduction varied (Fig. 2B and Supplementary Fig. S2B).

Invasion and migration are critical functions acquired by metastatic cells. Therefore, we sought to investigate the effect of hSETD1A on these cellular processes in breast cancer cells. We first assessed the effect of hSETD1A knockdown on directional cell motility using a wound-healing assay. Results clearly indicated that over time BT549 and MDA-MB-231 cells migrated slower in the absence of hSETD1A compared with the control cells (Fig. 3A). Quantification of the wound width at the indicated time post-injury revealed that knockdown of hSETD1A decreased healing 4- and 2-fold in MDA-MB-231 and BT549 cells, respectively, compared with control cells (Fig. 3A, bottom). Second, we tested the impact of hSETD1A on cell migration using a commercially available Transwell chamber, in which migration is assessed by the ability of cells to pass through a porous membrane. Comparatively fewer hSETD1A knockdown MDA-MB-231 or BT549 cells migrated through the pores, further supporting that loss of hSETD1A challenged the migratory capacity of these breast cancer cell lines (Fig. 3B and Supplementary Fig. S2D and S2E).

Cellular invasiveness was tested using modified Boyden chamber assays. Knockdown of hSETD1A in both MDA-MB-231 and BT549 cells led to a statistically significant decrease in cell invasion measured by counting cells that invaded through the Matrigel and porous supporting membrane (Fig. 3C and Supplementary Fig. S2C). Both pLKO.1 and pGIPZ vectors carrying hSETD1A shRNAs showed consistent results in inhibiting breast cancer cell invasion. In sum, the results of these experiments indicate that hSETD1A promotes both cellular motility and invasiveness in cultured breast cancer cells.

hSETD1A knockdown reduces metastasis in nude mice

To determine the impact of depleted hSETD1A on breast cancer cell metastasis, we utilized a tail vein injection mouse model. Specifically, injection of MDA-MB-231 cells directly into the blood stream of immunocompromised mice results primarily in the development of pulmonary metastases (44). Fewer metastatic lung nodules were detected in mice that were injected with the hSETD1A knockdown MDA-MB-231 cells compared with mice injected with control MDA-MB-231 cells (all mice were sacrificed at the same time point after injection; Fig. 4A). When counted, we measured a significant (P = 0.0255 by the Wilcoxon signed-rank test) decrease in the number of lung nodules present in mice injected with hSETD1A knockdown cells when compared with mice that were injected with control cells (Fig. 4B). Interestingly, Kaplan–Meier analysis revealed an association between elevated mRNA levels of
hSETD1A and hSETD1A-components WDR82 and HCF1 with reduced relapse-free survival in lymph node–positive (Supplementary Fig. S3A) but not lymph node–negative (Supplementary Fig. S3B) breast cancer (http://www.kmplot.com; ref. 45). These results together further support an active role for the hSETD1A complex in progression of breast cancer and suggest that hSETD1A could serve as a useful biomarker for increased metastatic potential in patients with breast cancer.

hSETD1A is required for expression of numerous MMP genes

Our results thus far indicated that hSETD1A is overexpressed in breast cancer and affects metastasis. We next investigated the underlying mechanism by which hSETD1A promotes metastatic behavior. MMPs are enzymes which catalyze degradation of extracellular matrix components and are secreted by cells within the tumor microenvironment and/or by the tumor cells themselves. This activity promotes cancer cell invasion, migration, and proliferation, and associates with poorer survival in breast cancer (33, 40–43). Epigenetic mechanisms play a central role in regulating expression of MMPs in breast cancer, most notably MMP9 (46, 47). We previously determined that hSETD1A-mediated H3K4me3 regulated MMP7 expression in colorectal cancer (26), compelling us to examine whether hSETD1A and corresponding H3K4me3 are recruited to MMP promoters for their expression in breast cancer cells. ChIP assays showed that increased enrichment of hSETD1A
Mol Cancer Res; 13(3) March 2015

Salz et al.

Second, we conducted ChIP assays using hSETD1A antibodies to examine binding of hSETD1A to proximal promoters adjacent to the TSS of these MMPs. hSETD1A levels were enriched at promoters of MMP2 compared with a negative control region at the 3′ITR of the MYC gene and relative to nonspecific IgG, in MDA-MB-231 cells (Fig. 5C). These data indicate that hSETD1A directly binds MMP promoters.

Subsequently, we examined the effect of hSETD1A on local H3K4me3. To that end, we conducted ChIP assays using antibodies against H3K4me3 in the hSETD1A knockdown and control MDA-MB-231 cells. We observed a significant decrease in H3K4me3 levels in regions surrounding the TSS of numerous MMP genes analyzed (i.e., MMP2, 9, 12, 17, 13) compared with IgG and MYC 3′ITR controls in the hSETD1A knockdown MDA-MB-231 cells compared with the control cells (Fig. 5D). Consistent with decrease in H3K4me3 enrichment at the MMP promoters, hSETD1A occupancy at the MMP promoter was also significantly reduced upon hSETD1A knockdown (Supplementary Fig. S4B). Of note, levels of H3K4me3 at the TSS of MMP11 remained unchanged in response to hSETD1A knockdown. This observation is consistent with continued expression of MMP11 gene following hSETD1A suppression (Fig. 5A).

In addition to the decrease in H3K4me3 levels in the hSETD1A knockdown cells, we observed increased levels of the repressive mark H3K27me3 in all tested MMP promoters, but no significant changes in levels of H3K27Ac with the exception of MMP17 (Fig. 5E). Taken together, these results indicate that hSETD1A is important for maintaining the promoter activity and transcription of MMPs in breast cancer cells and provide a potential mechanism by which hSETD1A can promote metastatic behavior.

Discussion

Compelling evidence indicating alterations in histone modification patterns during cancer initiation, progression, and metastasis has fueled speculation concerning the role of histone-modifying enzymes in tumorigenesis (25, 35, 52). H3K4me3 is enriched at the TSS of transcriptionally active genes (16–19), although whether this modification is a passive mark for active transcription or plays an active role in promoting transcription is currently under debate. Nevertheless, our group and others have observed both global and local changes in H3K4me3 at promoters of genes with cancer-promoting activity, in cancer cells (14, 25, 26, 53, 54). Methylation of H3K4 is primarily catalyzed by TrxG members, with the modification of H3K4me3 chiefly catalyzed by hSETD1A (26, 27, 55–58). Here, we showed increase in both global H3K4me3 and hSETD1A protein levels in cultured breast cancer cell lines (Fig. 1A and B). hSETD1A mRNA levels were also upregulated in human breast cancer samples, particularly in metastatic lesions (Fig. 1C). These observations may be attributed to SETD1A gene duplication commonly detected in breast cancer (39), although we cannot rule the possibility that other mechanism(s) may drive hSETD1A overexpression in this tumor type.

Our study focused on the potential effect of hSETD1A on breast cancer phenotype. Depletion of hSETD1A in both MDA-MB-231 and BT549 breast cancer cells resulted in altered rates of proliferation, motility, and invasiveness in vitro (Figs. 2 and 3 and Supplementary Fig. S2). Furthermore, using an in vivo model, we observed significantly reduced metastatic potential in MDA-MB-231 cells following hSETD1A knockdown (Fig. 4). These findings
are in clear agreement with other studies demonstrating that additional critical epigenetic modifiers, such as Ezh2, LSD1, JARID1, SLIZ12, SET8, and various HDACs exhibit prominent effects on cancer cell proliferation, invasion, migration, angiogenesis, or metastatic activity (37, 38, 59–63). In sum, current evidence firmly supports the conclusion that H3K4me3 and other epigenetic modifications exert a critical impact on cancer cell phenotype and behavior.

To better understand how hSETD1A impacts the invasive behavior of breast cancer cells we examined gene expression following knockdown of hSETD1A. MMPs are widely known as critically important in promoting cancer cell migration and invasion by degrading extracellular matrix proteins (33, 40–43). As previous work from our group indicated that hSETD1A was required for MMP7 expression in colorectal tumor lines (26), we examined a number of MMP genes that could be potentially affected by hSETD1A knockdown in breast cancer cells. This work identified downregulation of several MMPs, known to be involved in breast cancer, upon depletion of hSETD1A, including MMP2, MMP9, MMP12, MMP13, and MMP17 (Fig. 5A). Moreover, hSETD1A directly binds the promoters of these MMPs and regulates H3K4me3 levels as noted by ChIP analysis of selected MMP promoters in breast cancer cells (Fig. 5C, Supplementary Fig. S4A) and by the decrease in H3K4me3 at TSS of each gene upon hSETD1A knockdown (Fig. 5D). Elevated H3K27me3 levels upon knockdown of hSETD1A further supports the suppression of these promoters in the absence of hSETD1A (Fig. 5E). Together, these data indicate that hSETD1A-mediated H3K4me3 is important in promoting the expression of MMPs, and provide a potential mechanism for how hSETD1A promotes breast cancer.
metastasis. In further support of the importance of hSETD1A in promoting breast tumorigenesis, we observed that increased expression of hSETD1A is significantly associated with reduced relapse-free survival among lymph node–positive, but not lymph node–negative, patients with breast cancer (Supplementary Fig. S3). The full spectrum of genes controlled by hSETD1A in breast tumor cells remains to be determined and may provide further insight into the functions of this protein and H3K4me3 in this disease.

In the colorectal cancer line HCT116, we observed that knockdown of hSETD1A resulted in diminished global H3K4me3 abundance (26). In contrast, we did not observe decreased H3K4me3 abundance in either MDA-MB-231 or BT549 cells expressing reduced levels of hSETD1A (Fig. 5B). While we are unsure how global levels of H3K4me3 are maintained following hSETD1A knockdown in breast cancer, the contribution of other TrxG family member(s), such as hSETD1B and MLL1–5, to the maintenance of H3K4me3 in breast cancer cells could be significant (14, 27, 64). In support of this possibility, we observed a significant increase in the transcript levels of hSETD1B in primary and metastatic breast cancer samples (Supplementary Fig. S1C). Therefore, it is possible that, along with hSETD1A, hSETD1B is also responsible for the elevated H3K4me3 level that occurs in breast cancer cells.

In conclusion, we showed that hSETD1A and H3K4me3 levels are increased in advanced breast cancer. Data support our conclusion that hSETD1A promotes breast cancer metastasis by positively regulating expression of numerous MMP genes. Patient survival data also support the notion that hSETD1A is associated with poor breast cancer patient survival and has a potential use as a prognostic biomarker. In sum, our study highlights a previously undetermined role for hSETD1A in promoting breast cancer invasiveness and metastasis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: T. Salz, Y. Qiu, S. Huang

Development of methodology: T. Salz, D. Siemann, S. Huang

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): T. Salz, C. Deng, C. Pampo, D. Siemann

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): T. Salz, C. Deng, Y. Qiu, K. Brown, S. Huang

Writing, review, and/or revision of the manuscript: T. Salz, C. Deng, Y. Qiu, K. Brown, S. Huang

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): T. Salz, C. Deng

Study supervision: S. Huang

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