Differential Expression and Function of Caveolin-1 in Human Gastric Cancer Progression

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Abstract

Caveolin-1 is a scaffolding protein of caveolae that acts as a tumor modulator by interacting with cell adhesion molecules and signaling receptors. The role of caveolin-1 in the pathogenesis of gastric cancer (GC) is currently unknown. We show by confocal immunofluorescence microscopy and immunohistochemistry of biopsies from GC patients (n = 41) that the nonneoplastic mucosa expressed caveolin-1 in foveolar epithelial cells and adjacent connective tissue. GC cells of only 3 of 41 (7%) patients expressed caveolin-1 and were all of the intestinal type. Quantitative PCR and Western blotting confirmed that, compared with nonneoplastic tissue, the overall caveolin-1 mRNA was decreased in 14 of 19 (74%) GC patients and protein in 7 of 13 (54%), respectively. Strong caveolin-1 reactivity was found in the nonepithelial compartment (myocytes, fibroblasts, perineural, and endothelial cells) in both tumor-free and GC samples. In a series of human GC cell lines, caveolin-1 expression was low in cells derived from a primary tumor (AGS and SNU-1) but was increased in cell lines originating from distant metastases (MKN-7, MKN-45, NCI-N87, KATO-III, and SNU-5). Ectopic expression of caveolin-1 in AGS cells decreased proliferation but promoted anchorage-independent growth and survival. RNAi-mediated knockdown of endogenous caveolin-1 in MKN-45 cells accelerated cell growth. These data indicate that caveolin-1 exhibits a stage-dependent differential expression and function in GC and may thereby contribute to its pathogenesis. [Cancer Res 2007;67(18):8519–26]

Introduction

Despite its decreasing trend in incidence, gastric cancer (GC) is still one of the most frequent causes of cancer-related deaths worldwide and, due to its very poor prognosis, remains a great clinical challenge (1). More than 90% are adenocarcinomas and classified into diffuse and intestinal types. GC is assumed to originate from a sequence of molecular and genetic events that accumulate on transition from chronic or atrophic gastritis to intestinal metaplasia, dysplasia, and cancer (2). Our understanding of the disease was revolutionized by the discovery of Helicobacter pylori (3) being associated with increased risk of GC, indicating that both genetic and microbial factors are of importance in its pathogenesis (4).

Caveolae are vesicular invaginations of the plasma membrane abundant in differentiated cells of epithelial and mesenchymal origin (5). Caveolae facilitate cellular transport, protein sorting, and cholesterol efflux. Caveolin-1 is an essential structural protein that forms oligomers (with caveolin-2) and interacts with cholesterol and glycolipids in lipid rafts. Caveolin-1 is also a scaffold protein that directly interacts with signaling molecules (receptors, kinases, adhesion molecules, and G-proteins) and controls their subcellular distributions and activation status. This checkpoint function of caveolin-1 explains its effects on diverse signaling pathways regulating cell proliferation, differentiation, apoptosis, adhesion, and invasion. Therefore, perturbations in caveolin-1 expression and/or function were hypothesized to play an important part in the pathogenesis of human diseases, such as cancer (6, 7). Several studies implicate that caveolin-1 fulfills a tumor-suppressor role in vitro and in vivo (8–10). However, others reported an increased expression of caveolin-1 in the more advanced stages of cancers (11–13). These conflicting results possibly reflect the complex function of caveolin-1 in cell transformation.

Chronic infection of the gastric mucosa with H. pylori is a major risk factor for the pathogenesis of GC in humans (3, 14). Bacterial virulence factors (vacA and cagA) are internalized by host cells and act as intracellular effectors, leading to disruption of the gastric epithelial barrier and promoting inflammation and proliferation. Interestingly, cagA and vacA bind to lipid rafts to facilitate their uptake into human gastric carcinoma AGS and HeLa cells (15–18). Recently, caveolin-1 was reported to colocalize with Na+/K+ ATPase and vascular cell adhesion molecule-1 in the human gastric carcinoma cell lines HGT-1 and SNU-5, respectively (19, 20). However, the expression and function of caveolin-1 in the stomach and in the pathogenesis of GC are thus far unknown.

In this study, we show that caveolin-1 is differentially expressed in the normal stomach compared with primary GC. In human GC cell lines, caveolin-1 is low in cells originating from a primary tumor but abundant in cell lines derived from distant metastases. Caveolin-1 reduces the proliferation rate of adherent GC cells, indicating that early down-regulation of caveolin-1 may contribute to gastric carcinogenesis. Conversely, caveolin-1 provides survival signals under anchorage-independent conditions, which may represent an acquired phenotype in metastatic GC.

Materials and Methods

Subjects and immunohistochemistry. Tissue specimens were obtained by surgical resection from 60 patients (38 male, 22 female) with GC, with a
mean age of 63.2 years (range, 27–84 years), from the tumor and a tumor-free location that was at least 2 cm distant from the tumor and confirmed by histology to be without any tumor cell infiltration. GC was classified according to Lauren into diffuse type (25 patients), intestinal type (34 patients), and undifferentiated type (1 patient). Immediately after surgery, tissue samples were frozen in liquid nitrogen and stored at −80°C until use. This study was approved by the Ethics Committee of the Technical University of Munich. Immunohistochemistry was done as described before (21) with a mouse monoclonal antibody directed against caveolin-1 [immunoglobulin G1 (IgG1), clone 2297, BD Transduction Laboratories].

DNA constructs. The cDNA of mouse caveolin-1 was inserted into pCMV3.1 (Invitrogen GmbH). The RNAi oligonucleotides against human caveolin-1 and controls were designed using software from OligoEngine. The RNAi oligonucleotides against human caveolin-1 were transfected with Lipofectamine 2000 as recommended by the manufacturer (Invitrogen). For generation of stable clones, AGS and MKN-45 cells were transfected with Lipofectamine 2000 as recommended by the manufacturer (Invitrogen). Transfectants were selected for 3 weeks and single clones were picked and subcultivated in 24-well plates for 4 weeks at 250 μg/mL G418 (Life Technologies/Invitrogen). Western blotting of cell lysates was done as published (24) with anti–caveolin-1 (mouse monoclonal IgG1, clone 2297, BD Transduction Laboratories), anti–caveolin-1 (rabbit polyclonal, sc-894, α-isoform only), and anti–β-actin (clone AC-74, Sigma).

Immunofluorescence microscopy. Cells were processed as described (24) with the following modifications. Caveolin-1 was detected with a 1:50 antibody dilution (clone 2297, BD Transduction Laboratories) in immunofluorescence buffer [PBS with 0.1% (v/v) Triton X-100, 1% (w/v) saponin, and 3% bovine serum albumin (w/v)] followed by a 2:250 dilution of goat anti-mouse IgG-Alexa 488 conjugate (Invitrogen). Actin was stained with a 1:250 dilution of phalloidin-Alexa 594 (Invitrogen). Nuclei were visualized with a 4′,6-diamidino-2-phenylindole–containing mounting medium (Vectorshield, Vector Laboratories). Slides were photographed with an Axiowert 200M microscope (Carl Zeiss MicroImaging GmbH) using Axiowision software (release 4.4). Mucosal biopsies (1 mm × 3 mm) were gained under routine endoscopy and immediately fixed in 4% (w/v) PBS-buffered paraformaldehyde. The tissue was permeabilized and blocked in immunofluorescence buffer and stained overnight at 4°C for caveolin-1 (as above) followed by an incubation with Alexa 488 conjugate (1:250), phalloidin-Alexa 594 (1:500), and TOPRO-3 (1:1,000; Invitrogen) for 2 h at room temperature. Samples were mounted on a SuperFrost glass slide and visualized by confocal microscopy (Axiowert 40) with LSM510 software (both from Zeiss). Three-dimensional reconstruction of z-stacked xy sections was done using Velocity software (Improvision).

Cellular assays. Cell cycle analysis was done using asynchronously growing cells (1 × 10^6/mL) that were fixed in 70% ethanol for 1 h at 4°C,
treated for 3 h with 0.5 μg/mL RNase A (Sigma), and stained with 50 μg/mL propidium iodide (Sigma). The DNA content was analyzed by propidium iodide staining and flow cytometry (FACSCalibur, BD Biosciences) in the FL2A channel after FL2W/FL2A gating. Proliferation and viability of adherent cells was measured by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) conversion (Roche Diagnostics) and anchorage-independent growth was determined by colony formation in soft agar as described (25). Anoikis assays were done on bacteriologic plastic dishes coated with poly(2-hydroxyethyl methacrylate) (poly-HEMA; Sigma) according to a previously published procedure (26).

**Statistical analysis.** Student's t test, Spearman's rank correlation, and Fisher's exact test were used to determine statistical difference. All tests were two sided, and P < 0.05 was considered statistically significant. All analyses were done using GraphPad InStat 3.0 software.

**Results**

Reduced expression of caveolin-1 mRNA and protein in GC tissue compared with the nonneoplastic stomach. Nineteen patients with GC were studied for caveolin-1 mRNA expression in gastric tissue samples from 13 randomly selected patients. Both the 24-kDa α-isof orm and the 21-kDa β-isof orm of caveolin-1 were expressed (Fig. 1A). Caveolin-1 protein phosphorylated at Tyr14 was also readily detectable in the adjacent connective tissue surrounding the glands (Supplementary Fig. S2B). Unspecific staining (dotted, green) was observable from surface mucus and in lumina of the glands. In contrast, the specimen of a diffuse, undifferentiated type of GC did not exhibit regular gland structures or caveolin-1 staining in the epithelial cells, indicating a loss of caveolin-1 in GC cells in this tumor type (Supplementary Fig. S2C and D). Immunohistochemistry on a larger series of samples corroborated that caveolin-1 was detected in the GC cells of only 3 of 41 (7%) patients, all being of the intestinal type. In each case, <10% of

caveolin-1 gene, which has been reported to occur in 16% of human breast cancers. However, we did not find the P132L mutation in GCs, matching nonneoplastic gastric tissues and GC cell lines (data not shown).

**Differential compartmentalization of caveolin-1 in normal gastric mucosa, intestinal metaplasia, and GC.** Because the latter methods do not differentiate between stroma and tumor cells, we carried out immunohistochemistry on 41 randomly selected patients. Immunostaining for caveolin-1 was found in each of the 41 specimens tested. Caveolin-1 was expressed in the normal gastric foveolar epithelium and in the gland region (GL) of tumor-free gastric mucosa (Supplementary Fig. S1A). A strong reactivity was also evident in the connective tissue (CT) between the gastric foveolar (Supplementary Fig. S1B). Interestingly, the metaplastic intestinal epithelium (IM) expressed caveolin-1 at the apical pole in 5 of 10 patients (Supplementary Fig. S1C). The three-dimensional reconstruction of z-stacked xy sections from confocal immunofluorescence microscopy corroborated the expression of caveolin-1 in the normal mucous epithelial cells within gastric pits (Supplementary Fig. S2). On the surface of the gastric mucosa, the "honeycomb"-like caveolin-1 staining (green) colocalized (yellow) with the basolateral staining of the actin cytoskeleton (red) in the cell periphery, whereas the centers of the cells were filled with laser-intransparent dark mucus and the nuclei (blue) were arranged basally marking the lumen of the gastric gland (Supplementary Fig. S2A). Caveolin-1 (green) was also readily detectable in the adjacent connective tissue surrounding the glands (Supplementary Fig. S2B). Unspecific staining (dotted, green) was observable from surface mucus and in lumina of the glands. In contrast, the specimen of a diffuse, undifferentiated type of GC did not exhibit regular gland structures or caveolin-1 staining in the epithelial cells, indicating a loss of caveolin-1 in GC cells in this tumor type (Supplementary Fig. S2C and D).

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the GC cells expressed caveolin-1. A weak cytoplasmic staining was present in two patients (Fig. 2A) and staining of the apical cell membrane facing signet-ring-like structures was found in the third patient (Fig. 2B). In all other specimens, caveolin-1 expression was limited to the nonepithelial compartment. Caveolin-1 was mainly found in the perineurium (Fig. 2C), smooth muscle of vessel walls (Fig. 2C), and submucosal muscle layers (Fig. 2D) and in the connective tissue (not shown). Caveolin-1–positive cells were myocytes (100% of the cases), endothelial cells (80%), fibroblasts (76%), adipocytes (68%), and perineural cells (44%). Caveolin-1 was more frequently expressed in the nonepithelial compartment of well-differentiated tumors than in undifferentiated GCs. These data indicate that caveolin-1 levels correlate with the differentiation status of the gastric mucosa and that down-regulation of caveolin-1 in primary gastric tumors is a frequent event.

Expression of caveolin-1 correlates with the origin of GC cell lines from primary tumors or distal metastases. In a series of human GC cell lines, we identified caveolin-1 mRNA by quantitative RT-PCR (Fig. 3A). In adherent, epithelial AGS cells and in spherical, suspended SNU-1 cells, both of which are derived from primary GC, the expression of caveolin-1 mRNA was very low. In contrast, in cell lines derived from distant metastases, caveolin-1 was moderate (NCI-N87 liver and KATO-III pleural effusion) to very high (MKN-45 liver, SNU-5 ascites, and MKN-7 lymph node) and independent of the adherent, suspended, or mixed growth properties and morphology of the cell line. This expression pattern was also evident on the protein level by Western blotting of cell lysates (Fig. 3B). Both the 24-kDa α-isoform and the 21-kDa β-isoform of caveolin-1 were expressed in MKN-7, MKN-45, and SNU-5, whereas caveolin-1α was mainly expressed at lower levels in KATO-III and NCI-N87. Phosphorylated caveolin-1 was only detectable in MKN-7 cells. Because hypermethylation of the caveolin-1 promoter has been associated with the loss of caveolin-1 expression in prostate cancer (27), we treated AGS and NCI-N87 cells with the demethylation agent 5-aza-2′-deoxycytidine. However, no apparent difference in the mRNA levels was observed, indicating that the caveolin-1 promoter is not subjected to hypermethylation in these GC cell lines (data not shown).

Caveolin-1 is targeted to the perinuclear Golgi region and lipid rafts in GC cells. To elucidate the functional consequences of an altered caveolin-1 status in GC cells, we selected a caveolin-1–negative GC cell line (AGS) in which ectopic caveolin-1 was overexpressed (Fig. 4A) and a caveolin-1–positive GC cell line (MKN-45) in which endogenous caveolin-1 expression was knocked down by stable RNAi transfection (Fig. 4B). Immunofluorescence microscopy in stably transfected AGS/cav1 clones confirmed that caveolin-1 was evenly distributed in vesicular structures within the cytosol and in the typical “dotted” pattern of lipid rafts at the plasma membrane (Fig. 4C, left). Isolation of low-density, Triton X-100–insoluble membrane domains by sucrose gradient equilibrium density centrifugation, as done by us before (11, 24), corroborated that in AGS transfectants caveolin-1 is mainly localized in Golgi and cytosolic fractions, as evidenced by cofractionation with the marker proteins furin and heat shock protein 90, but is also targeted to the lipid raft fractions (data not shown). In MKN-45 cells, caveolin-1 was expressed in the periphery of the spherical cell aggregates, whereas this localized staining was lost on stable RNAi knockdown (Fig. 4C, right). We then analyzed the AGS and MKN-45 clonal cell lines with modified caveolin-1 status for their growth properties and resistance to stress.

Caveolin-1 reduces proliferation of adherent GC cells. Representative clones of AGS/cav1 and MKN-45 transfectants were
cultivated for 2 to 7 days under two-dimensional adherent conditions and assayed for their proliferation rate by MTT-assay. AGS/cav1 cells exhibited an approximately 30% to 40% reduced proliferation rate compared with empty vector–transfected control cells (Fig. 5A). Conversely, RNAi-mediated knockdown of endogenous caveolin-1 in MKN-45 enhanced proliferation by 1.3- to 2-fold compared with cells transfected with empty vector or control RNAi (Fig. 5B). Flow cytometric cell cycle analysis corroborated that in AGS/cav1 cells, a higher proportion of cells is in the G0/G1 stage compared with empty vector–transfected cells (Fig. 5C). Vice versa, in MKN-45 cells with knocked down caveolin-1, a higher proportion of cells accumulated in the S and G2-M stages compared with cells transfected with empty vector or control RNAi (Fig. 5D). These data suggested that caveolin-1 inhibits proliferation of adherent GC cells.

Caveolin-1 regulates anchorage-independent growth and survival in GC cells. In contrast, under nonadherent conditions, using soft agar as a three-dimensional growth matrix, AGS/cav1 cells were able to form a greater number and diameter of colonies than empty vector–transfected cells (Fig. 6A), emphasizing a protective role for caveolin-1 in providing survival/growth signals under anchorage-independent conditions. We then carried out additional stress resistance experiments by exposing adherent cells to matrix-denial and measured detachment-induced apoptosis (anoikis). Clones of AGS (Fig. 6B) and MKN-45 (Fig. 6C) were seeded on either poly-HEMA–coated dishes or regular tissue culture dishes for control and were incubated in suspension for 48 h before determination of the survival rate by MTT assay. In contrast to their characteristic (prismatic) epithelial morphology under adherent conditions, AGS cells on poly-HEMA rounded up and formed multicellular aggregates that floated in the medium. Despite their slower growth rate under adherent conditions and higher survival in soft agar, AGS/cav1 cells exhibited a similar 40% to 50% reduced survival rate after detachment like empty vector–transfected cells (Fig. 6B). These data indicate that caveolin-1 provides protective survival signals in conditions of matrix-dependent growth but not during growth in suspension. MKN-45 cells also formed multicellular clusters on detachment but did not suffer at all from anoikis, which may be due to their origin from a distal metastasis. Instead, in cells with caveolin-1 knockdown, a significant increase in survival compared with control cells was observed (Fig. 6C). In summary, these results underline the role(s) of caveolin-1 as a proliferation inhibitor and prosurvival factor, and that its expression may be reacquired during cancer progression. In future, the molecular mechanisms that underlie these functions of caveolin-1 in GC have to be elucidated.

Discussion

In our study, we show for the first time that caveolin-1 is expressed in the normal stomach and may exert a role as a tumor modulator in the pathogenesis of human GC. Caveolin-1 mRNA was detected both in healthy stomach tissue and GC by quantitative RT-PCR. However, the overall caveolin-1 mRNA levels were markedly decreased in the GC samples as compared with the tumor-free tissue. Reduced caveolin-1 expression was also reported for sarcomas and (adeno)carcinomas of the lung, colon, breast, cervix, and ovary (6, 9, 28). Hayashi et al. (23) identified a sporadic dominant-negative mutation of caveolin-1 in human breast cancers (P132L), which leads to Golgi retention, degradation of endogenous caveolin-1, and oncogenic transformation. In quest of the molecular mechanism(s) for caveolin-1 down-regulation, we were unable to find this mutation in our series of GCs. Engelman et al. (8) described methylated CpG islands in the 5′-promoter region as a cause for absence of caveolin-1 in human breast cancer cells. However, we did not gain evidence for promoter methylation in GCs, emphasizing that other genetic silencing mechanisms exist for the down-regulation and/or functional inactivation of caveolin-1 in GC. For example, repression of the caveolin-1 promoter can be mediated by oncogenic myc (29) and ras via the mitogen-activated protein kinase signaling cascade (30). The transcription factors p53, E2F/DP-1, SP1, and sterol-regulatory element binding protein also

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Figure 4. Caveolin-1 expression and localization in genetically modified GC cells. Western blotting of whole-cell lysates: A, parental AGS (negative control), MKN-7 (positive control), and AGS/cav1 cells (stably transfected with caveolin-1); B, MKN-45 transfectants with stable RNAi-mediated knockdown of endogenous caveolin-1 and controls; C, immunofluorescence of caveolin-1 (green), actin (red), and nuclei (blue). Original magnification, ×400. Bar, 10 μm.
inhibit the caveolin-1 promoter within the S and M phases of the cell cycle (31, 32). The latter mechanisms may therefore be candidates that contribute to the down-regulation of caveolin-1 on gastric carcinogenesis.

In line with results on other human adenocarcinomas (6) and sarcomas (10), we detected both the 24-kDa α-isofrom and the 21-kDa β-isofrom of caveolin-1 by Western blotting. However, both isofroms were expressed at lower levels in GC tissue than in the adjacent normal gastric mucosa. Because the nonepithelial tissue is greatly increased in cancer tissues, the caveolin-1 expression therein may thus derive from nonepithelial cells. This assumption was supported by our immunohistochemical analysis, where caveolin-1 was abundantly expressed among myocytes, endothelial cells, fibroblasts, adipocytes, and perineural cells, a finding consistent with reports on different cancer tissues (10, 12, 13).

Our data thus propose that down-regulation of caveolin-1 in the epithelial and connective tissue compartments of the stomach is a frequent event in gastric carcinogenesis and supports a role for caveolin-1 as a tumor suppressor in the nonneoplastic stomach. Caveolin-1 knockout mice exhibit an enhanced susceptibility toward chemically induced carcinogenesis (7) and hyperplasia of stem cell niches in the small intestine (33) and the mammary gland (34). Therefore, loss of caveolin-1 in the proliferative zone of the gastric foveolar neck region may as well allow clonal expansion and tumor formation in the stomach.

This early loss of caveolin-1 in primary tumors is in sharp contrast to findings that show a regain of caveolin-1 expression in advanced-stage cancers such as of colon (35), breast (13), prostate (13), bladder, esophagus, and thyroid (6). For prostate cancer, reduced caveolin-1 was reported in normal epithelium, in contrast to increased frequency of caveolin-1–positive cells in primary tumors (27) and related lymph node metastases (13). Caveolin-1 was thus proposed as a negative prognostic factor in patients with advanced metastatic prostate cancer (36). A similar differential caveolin-1 expression was observed by us in GC cell lines, which was low in cell lines derived from primary tumors (AGS and SNU-1) but high in those originating from distal metastases (NCI-N87, KATO-III, SNU-5, MKN-7, and MKN-45). This biphasic pattern may be explained by the role of caveolin-1 as a tissue and stage-specific tumor modulator (6), where it acts as an inhibitor or promoter of tumor formation and progression depending on its protein interaction partners such as growth factor receptors or cell adhesion molecules.

Caveolin-1 arrests fibroblasts in the G0-G1-phase of the cell cycle through a p53/p21–dependent pathway (37) and inhibits Wnt signaling in epithelial cells (38). Caveolin-1 also interacts with integrins that mediate cell-matrix interactions toward the basal membrane (39) and with cadherins that organize cell-cell contacts at adherens junctions in epithelial cells (40). Thus, its presence is likely to be critical in maintaining homeostasis and barrier functions in the epithelium of the gastric mucosa (41). In line with these modes of action, ectopic caveolin-1 slowed proliferation of adherent epithelial AGS cells and enhanced their survival during anchorage-independent growth, whereas in metastatic MKN-45 cells, loss of endogenous caveolin-1 accelerated growth at any
condition. These findings propose that caveolin-1 functions as a tumor suppressor in normal adherent gastric epithelial cells, is down-regulated on transformation allowing clonal expansion in the primary GC, and then regained in GC cells undergoing detachment from the basal membrane and metastasis into the underlying stroma. The selection process of isolated metastases on breakage of the gastric barrier may finally favor reexpression of caveolin-1 to exert certain prosurvival functions (6). For example, caveolin-1 protects human prostate cancer cells from androgen deprivation-induced apoptosis (42) and breast adenocarcinoma cells from anoikis via activation of the insulin-like growth factor-I protein kinase B/Akt survival pathway (26). Interestingly, the strong expression of caveolin-1 in AGS cells does not promote resistance to detachment-induced apoptosis (anoikis). C, RNAi-mediated knockdown of caveolin-1 in MKN-45 cells accelerates growth in suspension on detachment. B, c-met, caveolin-1 in AGS cells does not promote resistance to detachment-induced apoptosis (anoikis). Columns, absorbance values (in triplicates) from conversion of MTT, expressed as percent proliferation on regular tissue culture (TC) or poly-HEMA (PH)-coated dishes compared with empty vector-transfected cells (n = 5 independent experiments); bars, SE. *, P < 0.05, poly-HEMA versus tissue culture clonotype.

Although further studies are required to assess the functional role of caveolin-1 in GC, we conclude that caveolin-1 is frequently lost in primary GC tissue and may contribute to the maintenance of the epithelial barrier in the stomach. Its expression in the nonepithelial compartment may indicate a role in the formation of or interaction with the extracellular matrix, thereby indirectly contributing to tumorigenesis. In future, therapeutic interference with caveolin-1 functions may constitute novel strategies against human GC.

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