A Molecular Role for Lysyl Oxidase in Breast Cancer Invasion

Dawn A. Kirschmann, Elisabeth A. Seftor, Sheri F. T. Fong, Daniel R. C. Nieva, Colleen M. Sullivan, Elijah M. Edwards, Pascal Sommer, Katalin Csiszar, and Mary J. C. Hendrix

ABSTRACT

We identified previously an up-regulation in lysyl oxidase (LOX) expression, an extracellular matrix remodeling enzyme, in a highly invasive/metastatic human breast cancer cell line, MDA-MB-231, compared with MCF-7, a poorly invasive/nonmetastatic breast cancer cell line. In this study, we demonstrate that the mRNA expression of LOX and other LOX family members [lysyl oxidase-like (LOXL), LOXL2, LOXL3, and LOXL4] was observed only in breast cancer cells with a highly invasive/metastatic phenotype but not in poorly invasive/nonmetastatic breast cancer cells. LOX and LOXL2 showed the strongest association with invasive potential in both highly invasive/metastatic breast cancer cell lines tested (MDA-MB-231 and Hs578T). To determine whether LOX is directly involved in breast cancer invasion, LOX antisense oligonucleotides were transfected into MDA-MB-231 and Hs578T cells, and found to inhibit invasion through a collagen IV/α-laminin/gelatin matrix in vitro compared with LOX sense oligonucleotide-treated and untreated controls. In addition, treatment of MDA-MB-231 and Hs578T cells with β-aminopropionitrile (an irreversible inhibitor of LOX enzymatic activity) decreased invasive activity. Conversely, MCF-7 cells transfected with the murine LOX gene demonstrated a 2-fold increase in invasiveness that was reversible by the addition of β-aminopropionitrile in a dose-dependent manner. In addition, endogenous LOX mRNA expression was induced when MCF-7 cells were cultured in the presence of fibroblast conditioned medium or conditioned matrix, suggesting a role for stromal fibroblasts in LOX regulation in breast cancer cells. Moreover, the correlation of LOX up-regulation and invasive/metastatic potential was additionally demonstrated in rat prostatic tumor cell lines, and human cutaneous and uveal melanoma cell lines. These results provide substantial new evidence that LOX is involved in cancer cell invasion.

INTRODUCTION

In 2002, breast cancer is predicted to account for 31% of all of the diagnosed cancers in women, more than twice that of the second most common cancer (lung cancer; Ref. 1). Because metastasis is a major challenge in cancer management, it is critical to determine molecular markers that definitively distinguish tumors of nonmetastatic potential from those with metastatic potential. To identify such markers, a clearer understanding of the metastatic progression in breast cancer is required. To this end, we identified an up-regulation in LOX expression in invasive/metastatic breast cancer cell lines compared with poorly invasive/nonmetastatic breast cancer cell lines (2).

LOX is a copper-dependent amine oxidase that initiates the covalent cross-linking of collagens and elastin in extracellular matrices (reviewed in Refs. 3, 4). It is secreted as a M₆ 50,000 glycosylated proenzyme, which is proteolytically processed by procollagen C proteinase (bone morphogenetic protein-1) into a mature, biologically active M₄ 32,000 form (3, 4). The formation of collagen/elastin cross-links by LOX leads to an increase in tensile strength and structural integrity, and is essential for normal connective tissue function, embryonic development, and wound healing (3, 5). Consequently, aberrant LOX expression or enzymatic activity leads to disease. Decreases in LOX expression or activity have been associated with such heritable connective tissues disorders as Ehler-Danlos syndrome, cutis laxa, and Menkes’ syndrome (6–10). Increases in LOX expression contribute to the development of fibrotic diseases such as arteriosclerosis, scleroderma, and liver cirrhosis, diseases that involve connective tissue remodeling (11–14).

Although the ECM maturation activity of LOX has long been thought to be its sole function, more recent evidence implicates the involvement of LOX in many important biological functions other than collagen/elastin cross-linking. LOX has been shown to induce motility and migration in monocytes, vascular smooth muscle cells, and fibroblasts (15–17). In addition, LOX may play a role in cell growth/differentiation as its expression is up-regulated by a number of growth factors and steroids (3, 4, 18). Moreover, a role for LOX in transcriptional gene regulation and cellular transformation has also been implicated as evidenced by localization of LOX protein and enzymatic activity to cell nuclei (19), potential utilization of histone H1 as a substrate (20), activation of the collagen III α1 promoter (21), and a putative tumor suppressor in nontumorigenic revertants of ras-transformed fibroblasts (reviewed in Ref. 3).

In this study, we test the hypothesis that LOX expression contributes to cellular invasive ability. The data demonstrate that LOX and other LOXL family members are specifically expressed by invasive/metastatic cancer cells compared with poorly invasive/nonmetastatic cancer cells, and that modulation of LOX expression and function in breast cancer cells affects in vitro cellular invasive activity.

MATERIALS AND METHODS

Cells and Culture Conditions. MCF-7 cells were kindly supplied by Dr. F. Miller (Karmanos Cancer Institute, Detroit, MI), and MDA-MB-231, 47TD, and Hs578T cell lines were obtained from the American Type Culture Collection (Manassas, VA). The cutaneous melanoma A375P and C8161 cell lines were kind gifts from Drs. I. J. Fedler (M.D. Anderson Cancer Center, University of Texas, Houston, TX) and F. L. Meyssenguins, Jr. (University of California, Irvine Cancer Center, Orange, CA), respectively. The uveal melanoma cell line OCM-1 was kindly provided by Dr. J. Kan-Mitchell (Karmanos Cancer Institute), and M619 and C918 uveal melanoma cell lines were a kind gift from Dr. K. Daniels (University of Iowa, Iowa City, IA). Human Rb foreskin fibroblasts were a generous gift from Dr. Gregory Goldberg (Washington University, St. Louis, MO). Rat prostate cancer cell lines (5P, 5A, and 5B) were derived and established from the R-3327 Dunning tumor in our laboratory. Cell lines were maintained as described previously (22) and were harvested when cultures were ~80% confluent.

RNA Isolation. Total RNA was isolated from breast cancer cell lines using TRizol RNA isolation reagent (Invitrogen), according to manufacturer’s spec-
ifications. Polyadenylated RNA was isolated from total RNA by binding to oligodeoxynucleotide cellulose (Becton Dickinson, Bedford, MA), as described previously (23).

Semiquantitative RT-PCR Analysis. Reverse transcription of total RNA from breast, prostate, and melanoma cancer cell lines was performed using the Advantage PCR kit according to manufacturer's instructions (BD Clontech, Palo Alto, CA). PCR amplification was performed with LOX- and LOXL2-specific primers: hLOX (accession number S78694 forward: 5'-GATCCGTCGATCT-CGGGACA-3' (bases 500–520); reverse: 5'-GGGACCCGTACTG-GAAGTGAGCAGT-3' (bases 843–868); rat LOX (accession number U11038 forward: 5'-CAAACCGGAATTACATTAACTGACAGTGGT-3' (bases 1376–1405); reverse: 5'-CCTCCTCCAGCACAAGTGTACCTC-3' (bases 1986–1950); and hLOXL2 (accession number NM_002518 forward: 5'-GGGACCCC-GCACGCTGATCT-3' (bases 2093–2110); reverse: 5'-CCCAGGTTGCTG-TGATGCCAGCCC-3' (bases 2752–2774)). Annealing temperature and number of amplification cycles were optimized at 64°C and 30 cycles for LOX, and 68°C and 27 cycles for LOXL2, respectively in a Robocycler gradient 96 thermocycler (Stratagene, La Jolla, CA) under the following conditions: 1 cycle at 94°C for 1 min; 27 or 30 cycles at 94°C for 1 min, 64°C or 68°C for 2.5 min, 72°C for 1 min; and 1 cycle at 72°C for 5 min. GAPDH primers (BD Clontech) were used as controls for PCR amplification. PCR fragments were ligated into the pCR2.1-TOPO sequencing vector as per manufacturer's instructions (Invitrogen). Plasmid DNA was isolated and subjected to DNA sequence analysis using fluorescent Sanger-based dideoxy sequencing on an ABI 373A Automated Sequencer (University of Iowa DNA Facility). Two plasmids were sequenced, and each showed 100% identity to the reported LOX DNA sequences.

RNA Hybridization Analysis. Northern blot analysis was used to determine LOXL, LOXL2, and LOXL4 expression in breast cancer cell lines, as described previously (2). 32P-labeled LOXL- (24), LOXL2- (25), LOXL3-, (1.2 kb of the 5' region), and LOXL4-specific (26) cDNA were used as probes. Blots were exposed to a phosphor screen for 12–36 h and then scanned using a PhosphorImager SI (Molecular Dynamics, Sunnyvale, CA). No cross-hybridization between LOXL family members was observed.

Stable and Transient Transfections. A mammalian expression vector containing the mLOX gene (27) was stably transfected into MCF-7 cells using LipofectAMINE reagent according to manufacturer’s instructions (Invitrogen). Transient transfections with phosphorothioate-modified LOX-specific antisense (5'-CCAGGGCAAGCGCATAC-3') or sense (5'-GTGATGCCCT-TGCCCTGG-3') oligonucleotides (Integrated DNA Technologies, Coralville, IA) were performed using LipofectAMINE reagent according to manufacturer’s specifications. Briefly, breast cancer cell lines (5 × 10^5 cells/well) were seeded onto six-well tissue culture plates. Cells were washed with Opti-MEM medium (Invitrogen) and incubated with 1 μg sense or antisense oligonucleotide/LipofectAMINE complexes or with LipofectAMINE alone. After 5 h, serum containing medium was added and cultures were incubated an additional 24 h at 37°C, 5% CO₂, before harvesting. RT-PCR

In Vitro Invasion Analysis. Analysis and quantitation of the in vitro invasive phenotype of breast cancer cell lines was performed using the MICS as described previously (28). Where indicated, breast cancer cells were pretreated with 100 or 200 μM βAPN (Sigma, St. Louis, MO) for 24 h before and during invasion analysis. Statistical significance was evaluated by ANOVA using Microsoft Excel 2000 spreadsheets.

Immunofluorescence. mLOX-FLAG-transfected MCF-7 cells (5 × 10^4 cells/well) were seeded onto 12-mm round glass coverslips in a 24-well tissue culture plate. Cells were fixed with ice-cold methanol for 5 min and blocked with PBS (pH 7.4) containing 1% BSA (Sigma) for 1 h at room temperature. Anti-FLAG M2 antibody (20 μg/ml; Sigma) was added to fixed cells for 1 h at room temperature. A rhodamine-conjugated goat antinmouse IgG secondary antibody (ICN Pharmaceuticals, Aurora, OH) was added and incubated at room temperature for 1 h. Between each step, cells were gently washed three times with PBS. Coverslips were mounted onto glass slides for analysis by fluorescence microscopy.

Cm and CmEx. Cm from MCF-7 cells and Rb fibroblasts were harvested from ~1 × 10^6 cells grown in complete medium for 3 days. The cm was centrifuged (2000 rpm, 10 min), filtered (0.22 μm) to remove residual cells and cellular debris, and stored at −20°C until use. Conditioned matrices were generated by coating six-well tissue culture plates with 122 μg of rat tail collagen I (BD Bioscience) and polymerizing with 100% ethanol for 5 min at room temperature. Matrices were rehydrated with 1 ml of PBS for 5 min at room temperature, and 5 × 10^4 Rb fibroblasts were added to each well in complete medium and cultured for 3 days at 37°C, 5% CO₂. Wells were treated with 20 μM NH₄OH for 10 min at room temperature to remove the cells and subsequently washed three times with sterile water and two times with PBS. MCF-7 cells (5 × 10^5 cells/well) were then added to conditioned matrices for an additional 3 days. Total RNA was harvested by adding 1 ml of TRIzol reagent to each well.

RESULTS

LOX Expression in Breast Cancer Cell Lines. Using differential display analysis, we identified previously an up-regulation in LOX mRNA expression in MDA-MB-231 (highly invasive/metastatic) compared with MCF-7 (poorly invasive/nonmetastatic) breast cancer cell lines (2). Here we confirm, by RT-PCR analysis using LOX-specific primers, that LOX expression is up-regulated specifically in breast cancer cell lines with a highly invasive/metastatic potential (Hs578T and MDA-MB-231) and not in poorly invasive/nonmetastatic breast cancer cell lines (T47D and MCF-7; Fig. 1A), suggesting a putative role for LOX in breast cancer cell invasive and metastatic potential.

In addition, the up-regulation of LOX mRNA expression observed in highly invasive/metastatic breast cancer cells does not appear to be limited to just LOX but is observed with other members of this growing amine oxidase family. As shown in Fig. 1B, mRNA expression of LOXL, LOXL2, and the newest identified members of the
LOX family, LOXL3 (29) and LOXL4 (26), was also observed in the invasive/malignant cell lines but not in the poorly invasive cell lines. However, their expression was somewhat disparate between the invasive/malignant cell lines (Hs578T and MDA-MB-231). These results suggest that LOX and LOXL2 have the strongest association with an invasive/malignant phenotype in the breast cancer cell lines tested.

Transfection of Antisense LOX Oligonucleotides Inhibits Invasion. To directly test whether LOX expression is involved in cellular invasion of an ECM, LOX-specific sense and antisense oligonucleotides were transiently transfected into MCF-7, T47D, Hs578T, and MDA-MB-231 cell lines, and their 
\textit{in vitro} invasive potential was assessed. As shown in Fig. 2A, LOX antisense oligonucleotides but not LOX sense oligonucleotides were capable of significantly inhibiting Hs578T and MDA-MB-231 invasive ability \textit{in vitro}. No appreciable effect on invasive potential was observed with either LOX sense or antisense oligonucleotide-treated MCF-7 and T47D cells. These results suggest that LOX expression has an effect on cellular invasion.

\textbf{\beta}APN Inhibition of LOX Activity Inhibits Invasion. To determine whether LOX enzymatic activity is required for cellular invasion, breast cancer cells were treated with increasing concentrations of \betaAPN (a specific irreversible inhibitor of LOX enzymatic activity; Ref. 30), and their 
\textit{in vitro} invasive potential was assessed. It is important to note that the inhibition of LOX enzymatic activity by \betaAPN is never complete and that \~{}20\% of enzyme activity still remains under \textit{in vitro} conditions (31). A significant inhibition in invasive ability was observed with the addition of \betaAPN to Hs578T and MDA-MB-231 cells (Fig. 2B). The inhibition in Hs578T and MDA-MB-231 invasion by \betaAPN could not be attributed to \betaAPN toxicity, as no difference in the percentage of viability was detected by trypan blue exclusion (data not shown). Moreover, addition of \betaAPN to MCF-7 and T47D cells (which do not express LOX) had no effect on invasion compared with untreated controls (Fig. 2B). These results demonstrate that LOX enzymatic activity is required for breast cancer cell invasion of an ECM \textit{in vitro}.

\textbf{Expression of LOX in MCF-7 Cells Increases Invasive Potential.} To determine whether the induction of LOX expression can increase invasive potential, poorly invasive/noninvasive MCF-7 cells were stably transfected with a mammalian expression vector containing the mLOX-FLAG fusion protein. The mLOX mature protein has a 94\% amino acid identity to the hLOX mature protein. Furthermore, the copper binding (aa 280–290) and active sites (aa 352–368) in mLOX have 100\% and 99\% amino acid identity to hLOX (aa 286–290 and aa 358–374), respectively, suggesting that mLOX functions similarly to hLOX. In addition, the mLOX-FLAG protein is enzymatically active in 3T6–5 fibroblasts (27). Immunofluorescence staining of mLOX-FLAG-expressing MCF-7 cells with an anti-FLAG antibody demonstrated punctate LOX-FLAG fusion protein expression that localized to the cytoplasm (Fig. 3A). Localization of LOX-FLAG was similar to that observed in 3T6–5 fibroblasts (data not shown).

As is shown in Fig. 3B, stable transfection of mLOX in MCF-7 cells significantly increased their \textit{in vitro} invasive potential by 2-fold compared with untransfected MCF-7 cells. The invasive phenotype induced by mLOX expression in MCF-7 cells was reversible, in a dose-dependent manner, by addition of \betaAPN demonstrating that the increase in invasion was mediated by catalytically active LOX. These results show that LOX expression can potentiate cellular invasion; however, other genes are apparently necessary to obtain an invasive potential similar to Hs578T and MDA-MB-231 cells.

\textbf{Up-Regulation of Endogenous LOX and LOXL2 Expression in MCF-7 Cells.} To determine whether endogenous LOX expression could be up-regulated in MCF-7 cells by either soluble factors or “cues” obtained from the ECM, MCF-7 cells were cultured for 3 days with either Rb fibroblast cm or on a Rb fibroblast cmtx. As is shown in Fig. 4A, endogenous LOX expression in MCF-7 cells was dose-dependently up-regulated when cultured with increasing concentrations of Rb fibroblast cm but not in MCF-7 cm. Similarly, endogenous LOX expression was up-regulated in MCF-7 cells that were cultured on a Rb fibroblast cmtx. The up-regulation in LOX expression could not be attributed to carry over of LOX RNA or DNA from Rb fibroblasts, as no LOX expression was detected in Rb cmtx alone. Furthermore, endogenous LOX expression was not induced in MCF-7 cells cultured on a collagen I matrix alone (data not shown). In addition, LOXL2 expression was also up-regulated in MCF-7 cells cultured on a Rb fibroblast cmtx (Fig. 4B). These results suggest that fibroblasts and possibly stromal cells in general can contribute to LOX and LOXL2 regulation in breast cancer cells.

\textbf{LOX and LOXL2 Expression in Other Cancers.} To determine whether the up-regulation of LOX and LOXL2 expression was unique to breast cancer, other cancer cell lines that are well characterized in our laboratory were analyzed (32, 33). As shown in Fig. 5, A and C, expression of LOX mRNA was absent in poorly invasive cutaneous (A375P) and uveal (OCM-1A) human melanoma cell lines compared
with their highly invasive counterparts C8161 and M619, C918, respectively. Similarly, no expression of rat LOX was observed in a poorly invasive rat prostate cancer cell line (5\textsuperscript{H}11032\textsuperscript{B}) compared with highly invasive cell lines 5\textsuperscript{H}11032\textsuperscript{P} and 5\textsuperscript{H}11032\textsuperscript{A} (Fig. 5, B and D). However, similar trends in up-regulation of LOXL2 was only observed in aggressive uveal melanoma cell lines M619 and C918 compared with poorly aggressive OCM-1A. These results suggest that the up-regulation of LOX mRNA expression, and to a limited extent LOXL2, is associated with an invasive phenotype in different cancer cell types.

**DISCUSSION**

It is now widely accepted that the progression of a non-neoplastic cell to a hyperplastic cell and eventually to one that is capable of metastasis requires the stepwise accumulation of many genetic alterations (34). The molecular mechanisms contributing to breast cancer invasion and metastasis are poorly understood; however, the perception is that additional genetic alterations are required from those involved in tumorigenesis (35).

We identified an up-regulation in LOX expression in invasive/metastatic breast cancer cells compared with poorly invasive/non-metastatic breast cancer cells. Furthermore, we demonstrate that an inhibition of LOX expression and enzymatic activity in invasive/metastatic breast cancer cell lines reduced their invasive potential. Conversely, experimental up-regulation of LOX expression in a poorly invasive/nonmetastatic breast cancer cell line increased invasive potential, which is reduced on inhibition of LOX enzymatic activity. These results are consistent with our hypothesis that LOX enzymatic activity contributes to cellular invasive ability.

At first glance our results appear to contradict published literature regarding LOX expression in tumor cell lines; however, an in-depth
analysis shows some interesting consistencies. For example, LOX was first identified as a “ras recognition gene” in normal cells transformed by LTR-c-H-ras. LOX expression was reduced greatly in ras-transformed NIH 3T3 fibroblasts, and was restored to high levels in cells reverted by IFN treatment (36, 37). Other reports confirm the loss of LOX expression in transformed cells (38–41), in which a decrease in LOX activity was noted in malignant cell lines including fibrosarcoma, rhabdomyosarcoma, and choriocarcinoma (42). Csiszar et al. (43) demonstrate a decrease in LOX expression in colon tumors and Ren et al. (44) demonstrate a progressive reduction of LOX expression with the transition from normal prostate epithelium to malignant prostate epithelium. Consistent with these reports, poorly invasive/nonmetastatic breast cancer, uveal and cutaneous melanoma, and rat prostate cancer cell lines used in our study express little to no LOX.

Still other studies show an up-regulation in LOX expression in some malignant tumors (45), some osteosarcoma cell lines (46), and all conventional (clear cell) renal cell carcinoma tumors analyzed (47). In addition, Stassar et al. (48) demonstrate that LOX expression is significantly associated with a higher staging in clear cell renal carcinoma tissues. Furthermore, Ren et al. (44) reported that in two of three mouse prostate cancer cell lines derived from primary tumors and their matched lung metastasis, LOX expression was decreased in the metastatic lesions compared with primary tumors. However, one of the primary tumors did not express LOX whereas its matched metastases did (44). Taken together these reports also support our observations of LOX up-regulation in aggressive cancer cell lines.

Where is there such disparity in the literature regarding LOX expression in various cancers? One possibility may be differences in cell types such as cell origin or differentiation status. Fibrosarcoma, osteosarcoma, rhabdomyosarcoma, and renal cell carcinoma originate from the mesoderm, whereas breast adenocarcinoma cells, melanoma cells (neural crest), and choriocarcinoma cells originate from the ectoderm, and prostate carcinoma cells originate from the endoderm. However, the observation of LOX expression in renal cell carcinoma and some osteosarcoma cell lines, and a lack of LOX expression in choriocarcinoma blurs these delineations between mesoderm versus ecto/endoderm. Another plausible explanation of the disparity in LOX expression may be that an up-regulation in LOX expression is a consequence of an epithelial to mesenchymal transition in aggressive carcinoma cells or a mesenchymal to epithelial transition in aggressive melanoma cells. We have shown previously that cancer cells demonstrating an “interconverted” phenotype in which cells display both cytokeratin and vimentin intermediate filaments have an increased invasive and metastatic potential (32, 49, 50). In the cell lines that we have tested, there is a 100% correlation with LOX expression and an interconverted phenotype. However, transfection of MCF-7 cells with LOX did not induce a phenotypic epithelial to mesenchymal transition, as shown in Fig. 3A, suggesting that other genes are necessary for this process (51).

Alternatively, LOX expression could be the result of global genetic differences, with respect to the availability of LOX substrates, between normal cells and tumor cells. For instance, disparities in gene function in different cellular contexts have been noted in microcell-mediated chromosomal transfer experiments (reviewed in Ref. 35). Hence, the loss of LOX in a cell that normally expresses LOX or the gain of LOX in a cell that normally does not express LOX may confer tumorigenic and invasive properties, respectively. This premise indicates a complex role for LOX in cancer requiring additional investigation.

In vivo, Peyrol et al. (52, 53) report that LOX is associated with an extracellular stromal reaction in breast carcinoma and bronchopulmonary carcinoma. They demonstrated that in breast tissues, LOX expression was most strongly associated with myoepithelial cells, myofibroblasts, and ECM in the newly formed stroma around carcinomatous ducts rather than tumor cells. Because myofibroblasts and initiated stromal cells are known to potentiate tumor progression (54, 55), we investigated the contribution of fibroblasts to the induction of LOX expression in a poorly invasive/nonmetastatic breast cancer cell line. Indeed, we observed an increase in endogenous LOX expression in MCF-7 cells cultured in the presence of fibroblast-cm, as well as a fibroblast-cm. Because exogenous LOX expression in MCF-7 cells has been shown to induce cellular invasion and motility, these results suggest that soluble factors as well as molecular signals left in the ECM by fibroblasts have the potential to influence tumor progression. Whether these processes are recapitulated in vivo remains to be investigated.

Although not the primary focus of the current study, we also identified an association between the expression of other members of the LOX family and the invasive phenotype of breast cancer cells. In particular, LOXL2 demonstrated a similar expression pattern to LOX in breast cancer cells and was similarly induced in MCF-7 cells cultured on a fibroblast-cm. There is extensive sequence homology between LOXL2 and LOX with regards to the copper binding and catalytic domains, suggesting similar biological functions. Saito et al. (56) demonstrate that LOXL2 is highly expressed in astrocytoma, fibrosarcoma, and cervical adenocarcinoma cell lines. However, subsequent analysis is needed to determine the role of LOXL2 in breast cancer invasion and metastasis.

In addition to invasive/metastatic breast cancer cell lines, LOX expression was up-regulated in highly invasive human uveal and cutaneous melanoma, and rat prostate cancer cell lines. The expression of LOX in several different types of invasive cancer cell lines may suggest a general mechanistic role for this gene in cell-cell and cell-matrix interactions. These new observations raise the possibility of using LOX expression in tumor cells as a predictive/prognostic indicator for cancer staging and progression.

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