Transcription of the Vascular Endothelial Growth Factor Gene in Macrophages Is Regulated by Liver X Receptors*

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Macrophages are an important source of angiogenic activity in wound healing, cancer, and chronic inflammation. Vascular endothelial growth factor (VEGF), a cytokine produced by macrophages, is a primary inducer of angiogenesis and neovascularization in these contexts. VEGF expression by macrophages is known to be stimulated by low oxygen tension as well as by inflammatory signals. In this study, we provide evidence that Vegfa gene expression is also regulated by activation of liver X receptors (LXRs). VEGF mRNA was induced in response to synthetic LXR agonists in murine and human primary macrophages as well as in murine adipose tissue in vivo. The effects of LXR ligands on VEGF expression were independent of hypoxia-inducible factor HIF-1α activation and did not require the previously characterized hypoxia response element in the VEGF promoter. Rather, LXR/retinoid X receptor heterodimers bound directly to a conserved hormone response element (LXRE) in the promoter of the murine and human VEGF genes. Both LXRα and LXRβ transactivated the VEGF promoter in transient transfection assays. Finally, we show that induction of VEGF expression by inflammatory stimuli was independent of LXRs, because these effects were preserved in LXR null macrophages. These observations identify VEGF as an LXR target gene and point to a previously unrecognized role for LXRs in vascular biology.

Vascular endothelial growth factor (VEGF),¹ also known as vascular permeability factor, is the founding member of a family of closely related cytokines that exert critical functions in angiogenesis and lymphangiogenesis. A ligand for the tyrosine kinase receptors VEGFR1 (Flk-1/KDR) and VEGFR2 (Flt-1), VEGF triggers a variety of effects on vascular endothelial cells. VEGF elicits a strong angiogenic response in several models, including the chick chorioallantoic membrane (1, 2) and rabbit cornea (3). Inhibition of VEGF signaling results in extensive apoptotic changes in the vasculature of the neonatal mouse (4). VEGF mRNA is also up-regulated in many solid tumors. Inhibition of VEGF activity in endothelial cells of tumor-associated blood vessels results in tumor regression, indicating that VEGF is a major initiator of tumor angiogenesis (5, 6). In addition to its decisive role in vessel formation, VEGF affects maturation of bone marrow-derived cell populations. First, VEGF treatment enhances colony formation by mature subsets of granulocyte macrophage and erythroid progenitor cells that have been pre-stimulated with colony-stimulating factor in vitro (7). Second, VEGF administration induces a rapid mobilization of hematopoietic stem cells and circulating endothelial precursor cells (8). Finally, VEGF-deficient bone marrow cells fail to repopulate lethally irradiated hosts in bone marrow transplantation experiments (9).

Several independent pathways have been described to regulate Vegfa gene expression. Among these, hypoxia and hypoglycemia play a major role, both in vitro and in vivo. Hypoxia-induced regulation of VEGF mRNA is mediated by direct binding of a heterodimeric helix-loop-helix transcription factor known as hypoxia-inducible factor 1 (HIF-1) to a response element in the proximal VEGF promoter (10, 11). Under normoxic conditions, the HIF-1 complex is actively targeted for proteasomal degradation by a ubiquitin-ligase complex that relies on the VHL protein (12). In addition to hypoxia, numerous cytokines and growth factors, including endothelial growth factor, transforming growth factor α, transforming growth factor β, keratinocyte growth factor, insulin-like growth factor 1, fibroblast growth factor, platelet-derived growth factor, interleukin 1, and interleukin 6 can regulate VEGF expression in different cell types (13–16). Cell differentiation status also plays an important role in the regulation of VEGF expression. VEGF is up-regulated during adipocyte differentiation of 3T3-L1 cells and during myogenic differentiation of C2C12 cells (17). Conversely, VEGF transcription is repressed during neuronal differentiation of pheochromocytoma PC12 cells.

Macrophages play a key role in the induction of angiogenesis under fibroproliferative conditions, including wound healing, rheumatoid arthritis, and solid tumor development. Although resting monocytes and macrophages exhibit a nonangiogenic phenotype under normoxic conditions, hypoxia, elevated lactate levels, and inflammation strongly stimulate VEGF production (18). Treatment with bacterial lipopolysaccharide (LPS) or with CD40L stimulates VEGF production in human primary macrophages (19). This effect has been reported to be NFκB-dependent, because it is sensitive to the overexpression of the inhibitory protein, IκBα (20). In mouse peritoneal macrophages, LPS induces only a modest increase in VEGF expression, however this effect is strongly enhanced by co-treatment with adenosine A2A receptor agonists (21).
The liver X receptors (LXRα and LXRβ) are members of the nuclear hormone receptor family that form obligate heterodimers with the retinoid X receptor (RXR). LXR/RXR heterodimers bind to DR-4-type sequence elements known as LXR response elements (LXREs) in their target genes. Oxidized derivatives of cholesterol (oxysterols), such as 22(R)-hydroxycholesterol or 24(S),25-epoxycholesterol have been described as endogenous ligands for LXR (22, 23). LXRα is highly expressed in tissues rich in lipid metabolism, such as white adipose tissue, liver, intestine, and macrophages, whereas LXRβ is ubiquitously expressed (23). The endogenous functions of the two LXRs appear to overlap significantly. In liver, where LXRα is very highly expressed, this receptor appears to play a particularly important role in the control of genes linked to cholesterol and fatty acid metabolism such as Srebp-1c and Cyp7a1 (24, 25). In macrophages, where both receptors are abundantly expressed, target genes such as Abca1, Abcg1, and apoE are equivalently induced by both receptors (26, 27). In the present study, we identified the Vegfa gene as a direct target for regulation by LXR. These observations point to a previously unrecognized role for LXRs in vascular biology.

**MATERIALS AND METHODS**

**Cell Culture and Transfections**—Murine peritoneal macrophages were obtained from thioglycolate-injected mice as described by Venkateswaran et al. (28) and plated in 6-well dishes in RPMI 1640 medium containing 10% fetal bovine serum. Nonadherent cells were removed by repeated washing with RPMI 1640 medium. Human primary monocytes/macrophages were obtained as described previously (28) and were maintained in Iscove’s modified Dulbecco’s medium containing 10% fetal bovine serum. HepG2 cells were grown in minimal Eagle’s medium containing 10% fetal bovine serum. For serum-free treatments, adherent cells were incubated for 24 h in RPMI 1640 medium supplemented with 0.2% bovine serum albumin and subsequently washed three times with this same medium. RPMI 1640 medium (0.2% bovine serum albumin) was used for treatments in serum-free medium (see legends to Figs. 1, 2, and 6).

**RNA Analysis**—Total RNA was isolated using TRIzol reagent (Invitrogen). 10 μg of RNA was separated by 1% agarose/formaldehyde gel electrophoresis and transferred to a nylon membrane (Hybond), and the latter was hybridized with [α-32P]dCTP-radiolabeled DNA probes as described by the manufacturer. The blots were normalized using cDNA probes to 36B4 and quantitated by PhosphorImager (Amersham Biosciences) analysis.

**Real Time Quantitative PCR**—Assays were performed using an Applied Biosystems 7700 sequence detector. Briefly, 1 μg of total RNA was...
reverse transcribed with random hexamers using the Taqman reverse transcription reagent kit (Applied Biosystems) according to the manufacturer’s protocol. Each Taqman reaction (50 μl) contained 50 ng of cDNA, 900 nM forward primer, 900 nM reverse primer, 100 nM dual-labeled fluorogenic probe (IDT), and 25 μl of Universal PCR Master mix (Qiagen). PCR thermocycling parameters were 95 °C for 10 min, 40 cycles of 95 °C for 15 s, and 60 °C for 1 min. All samples were analyzed for 36B4 expression in parallel. The quantitative expression values were extrapolated from standard curves for VEGF or 36B4. Each sample was run in duplicate and was normalized to 36B4. The replicates were then averaged and fold induction was determined. Statistical analysis of mRNA expression data in white adipose tissue was performed by using the two-tailed, homoscedastic t test. Probe and primer sequences are available on request.

**Mobility Shift Assays—**In vitro translated RXR and LXR were generated from pCMX-RXR and pCMX-hLXR plasmids by using the Tnt quick-coupled transcription/translation system (Promega). Gel-shift assays were performed as described (29) by using in vitro translated proteins and the following oligonucleotides (only one strand is shown): human VEGF wt, 5’-caggaaaagtgAGGTTAcgtgCAGACAgggtctaaga-3’; human VEGF mut, 5’-caggaaagtgAGGTTAcgtgCAAGACAgggtctaaga-3’; mouse VEGF wt, 5’-cagggagatgAGGTTATagtCAGACAgggtctaga-3’; mouse VEGF mut, 5’-cagggagtgtAGGTTATagtCAGACAgggtctaga-3’; human LXR, 5’-gatctgtctgccGGGTCActggTGGTCActtca-3’; mouse ApoE, 5’-gatctgtctgccGGGTCActggCAGACActgg-3’.

**RESULTS**

We have described previously the use of Affymetrix cDNA arrays to identify LXR target genes in macrophages (30). These studies led to the identification of VEGF as a potential LXR-regulated gene (data not shown). To confirm these results, we examined the ability of synthetic LXR agonists to regulate expression of VEGF in primary murine and human macrophages. As VEGF expression is known to be responsive to a number of signaling pathways including factors present in serum, we investigated the regulation of VEGF expression in macrophages cultured in serum-free medium. Thioglycolate-elicted murine peritoneal macrophages were cultured in a medium supplemented with bovine serum albumin (0.2%) and treated for 24 h with one of two structurally unrelated synthetic LXR agonists, GW3965 or T1317. VEGF mRNA expression was determined by real time quantitative PCR (Taqman) assays (Fig. 1A) or Northern blotting (Fig. 1B). Both GW3965 and T1317 led to a moderate, 2–3-fold induction in VEGF mRNA expression. Co-treatment with the RXR selective agonist LG268 (31, 32) resulted in a more prominent 6–18-fold increase. Induction of VEGF by LXR was particularly dependent on the combined presence of RXR agonist (Fig. 1). The maximal expression of VEGF mRNA induced by LXR and RXR agonists in fetal bovine serum and serum-free conditions was similar; however, the fold induction by ligand was greater in the absence of serum because of lower levels of basal expression (data not shown). In contrast to the results obtained with LXR agonists, treatment of murine or human macrophages with high affinity ligands for PPARα (GW7647), PPARβ (GW1516), or PPARγ (GW7845) had no effect on VEGF mRNA (Fig. 2).

To determine whether the ability of synthetic LXR ligands to modulate VEGF expression was dependent on the expression of LXR, we examined their effects in peritoneal macrophages derived from wild type mice or mice lacking LXRα, LXRβ, or both receptors. Peritoneal macrophages were cultured in vitro in the presence or absence of LXR and/or RXR agonists. T1317, GW3965, and LG268 were effective inducers of VEGF expression in wild type cells (Fig. 3A). Induction by LXR and RXR ligand was unaltered in cells lacking LXRα, reduced in cells lacking LXRβ, and essentially lost in LXRαβ double knockout cells. VEGF expression appears to be somewhat more sensitive to loss of LXRβ expression than the established LXR target genes Abca1 and Abcg1, because induction of Abca1 and Abcg1 is reduced only in double knockout cells (Fig. 3, B and C). Nev-
Nevertheless it is clear that both LXR\(\alpha\)/H9251 and LXR\(\alpha\)/H9252 are competent to mediate ligand induction of VEGF expression in macrophages. We next investigated the possibility that the \(\text{Vegfa}\) gene was a direct transcriptional target of LXR/RXR heterodimers. Sequence analysis of the human and murine VEGF promoters led to the identification of a conserved DR-4-like motif located in the human and murine VEGF promoters. Underlined positions were mutated in the luciferase reporter vector. A, the human VEGF LXRE binds the LXR/RXR heterodimer in the electrophoretic mobility shift analysis assays. A previously characterized LXRE, derived from the human LXR promoter, served as a control. C and D, 10-, 50-, or 200-fold molar excess of the unlabeled oligonucleotide (hVEGF LXRE, mVEGF LXRE, or MUT LXRE) was used as a competitor for LXR/RXR binding to the human VEGF LXRE.

**Fig. 4.** Identification of an LXRE in the human and murine VEGF promoters. A, the LXR binding site (LXRE) and the HIF-1 binding site (HRE, hypoxia response element) are highly conserved between mouse and human VEGF promoters. Underlined positions were mutated in the luciferase reporter vector. B, the human VEGF LXRE binds the LXR/RXR heterodimer in the electrophoretic mobility shift analysis assays. A previously characterized LXRE, derived from the human LXR promoter, served as a control. C and D, 10-, 50-, or 200-fold molar excess of the unlabeled oligonucleotide (hVEGF LXRE, mVEGF LXRE, or MUT LXRE) was used as a competitor for LXR/RXR binding to the human VEGF LXRE.

**Fig. 5.** The VEGF promoter is activated by LXR\(\alpha\) and LXR\(\beta\) in transient transfection assays. Sequences ranging from the position -984 to +1 relative to the transcriptional start site on the human VEGF promoter were cloned into a luciferase reporter vector. The wild type construct (WT) or constructs containing specific mutations in the LXRE (LXRE mut), the hypoxia response elements (HRE mut), or both (DBL mut) were used in transient transfection experiments in HepG2 cells. Assays were performed in triplicate, and luciferase activity was normalized to an internal \(\beta\)-galactosidase control.

We next investigated the possibility that the \(\text{Vegfa}\) gene was a direct transcriptional target of LXR/RXR heterodimers. Sequence analysis of the human and murine VEGF promoters led to the identification of a conserved DR-4-like motif located...
downstream of the hypoxia response element (Fig. 4, HRE). In vitro expressed LXRs bound to this element in a heterodimeric complex with RXRα as revealed by electrophoretic mobility shift assays (Fig. 4B and data not shown). The previously identified LXR response element from the human LXRα gene served as a control. The complex formed on the VEGF-derived LXRE was sequence-specific, as judged by the ability of an excess of unlabeled murine or human VEGF LXRE to compete for its formation (Fig. 4C). In contrast, oligonucleotides carrying point mutations in the LXRE (indicated schematically in Fig. 4A) did not compete (Fig. 4D).

To investigate whether the LXRE in the VEGF promoter was functional, we constructed a luciferase reporter containing sequences from -984 to +1 of the human VEGF gene. Fig. 5 demonstrates that cotransfection of the hVEGF-luc reporter into HepG2 cells along with expression vectors for LXRα/RXRα led to a ligand-dependent increase in reporter activity. Similar results were obtained when an LXRα expression vector was used. Mutation of the previously identified hypoxia response element in the hVEGF promoter had minimal effect on the LXR-dependent induction (Fig. 5, HRE mut), indicating that the effects of LXR are independent of HIF-1α. In contrast, mutation of the LXRE in the promoter completely abolished the response to LXRα and LXRβ (Fig. 5, LXRE mut). The activity of the double mutant construct (Fig. 5, DBL mut) was not different from that of the LXRE mutant. Taken together, the results of Figs. 4 and 5 demonstrate that the VEGF promoter is a direct target for regulation by LXR and that LXR regulation is independent of the hypoxia response element.

Hypoxia is a key physiologic regulator of VEGF expression. Therefore, we investigated the ability of LXR ligands to modulate VEGF expression under both normoxic and hypoxic conditions. As expected, incubation of murine peritoneal macrophages under conditions of low oxygen tension (1% O2) led to a strong induction in VEGF mRNA compared with normoxia (21% O2) (Fig. 6A). Treatment of the cells with LXR agonist further induced VEGF expression under both normoxic and hypoxic conditions. These observations suggest that the regulation of VEGF expression by LXRs is additive to that of the hypoxia response pathway.

Macrophage expression of VEGF has also been reported to be responsive to various inflammatory stimuli (18). Treatment of peritoneal macrophages with LPS stimulates the expression of numerous inflammatory genes including iNOS (Fig. 6B). Consistent with previous work, treatment of peritoneal macrophages with the LXR agonist, GW3965, inhibited LPS-induced iNOS expression. The pattern of VEGF expression following treatment with inflammatory stimuli and LXR ligand, however, is distinct from that of iNOS and other highly NFκB-responsive inflammatory genes. LXR ligand induces VEGF expression, although repressing iNOS expression in the same cell (Fig. 6, B and C). LPS alone is a very weak inducer of VEGF expression in mouse peritoneal macrophages; however, the effect of LPS is strongly enhanced by co-treatment with the adenosine A2A receptor agonist NECA (Fig. 6C) (21). Although the induction by LXR ligands is lost in LXR-deficient macrophages (Fig. 3), both wild type and LXR null cells are equally responsive to a combined treatment with low doses of LPS and NECA. Thus, the induc-

**Fig. 6.** LXR-mediated induction of VEGF occurs under both normoxia and hypoxia. VEGF induction by inflammatory stimuli is independent of LXR. A, mouse peritoneal macrophages were cultured in medium supplemented with a lipoprotein-deficient serum and either of the two synthetic LXR ligands (1μM). Cells were grown for 8 h either in normoxic (21% O2) or in hypoxic (1% O2) conditions. VEGF and 36B4 mRNAs were measured by real time PCR. B, peritoneal macrophages were treated for 24 h with LPS (100 ng/ml) and/or 1μM GW3965. Expression of iNOS and VEGF was determined by real time PCR. C, peritoneal macrophages were treated for 24 h with LPS (100 ng/ml) alone or in combination with the purinergic agonist, NECA (1μM). DMSO, dimethyl sulfoxide. WT, wild type.
Expression of Vegfa gene expression by these inflammatory stimuli is independent of LXR.

Finally, we endeavored to address whether expression of VEGF could be modulated by LXR agonists in vivo. Because adipose tissue is highly vascularized and it has been shown previously to express VEGF in a differentiation-dependent manner and because both LXRα and LXRβ are expressed in fat, we examined the ability of LXR ligand to regulate VEGF expression in adipose tissue. C57BL/6 mice (8 animals/group) were treated for 3 days with 20 mg/kg body weight of the LXR agonist, GW3965. RNA was extracted from inguinal fat pads. VEGF and 36B4 expression was quantified by real time PCR. Circles indicate data points, and black bars indicate averages.

DISCUSSION

VEGF is primarily known as an inducer of angiogenesis, but this cytokine also has roles in vascular permeability and hematopoietic cell development and differentiation (33). VEGF is important in both inflammation and repair and is critical for the resolution of injury and the process of wound healing. Macrophages are a major source of VEGF in wound healing, chronic inflammation, and cancer (34–36). Two independent pathways, namely hypoxia and inflammation, have been described as mediators of VEGF expression under these conditions (21, 37). In this report, we provide evidence that VEGF expression in macrophages is also regulated by LXR. VEGF mRNA expression in murine peritoneal macrophages was potently induced (up to 18-fold) by combined treatment with synthetic agonists for LXR and RXR. We further showed that LXR/RXR heterodimers bound to and activated a conserved element in the VEGF promoter. Finally, the ability of LXR agonists to regulate VEGF expression was compromised in macrophages derived from LXRβ or LXRαβ null mice. These observations suggest that the LXR signaling pathway may modulate VEGF expression in response to lipid mediators in settings of inflammation and repair.

In macrophages, uptake of oxidized low density lipoprotein results in an increased cellular concentration of oxidative derivatives of cholesterol. Activation of LXR by such compounds has been shown to lead to the induction of target genes involved in reverse cholesterol transport such as Abca1, Abcg1 and apoE (26, 38, 39). Our study suggests that activation of LXR in this context may also lead to increased production of VEGF. Previous studies from several authors suggest that VEGF expression in macrophages is regulated by components of oxidized low density lipoprotein, which are ligands for the nuclear receptor PPARγ (40–42). However, these studies employed high concentrations of compounds that are rather poor PPARγ agonists, such as 15-deoxy-delta12,14-prostaglandin J2 and ciglitazone. It is now recognized that these agents also target other pathways because many of their effects are preserved in PPARγ-deficient cells (43). In our hands, none of the highly selective PPAR agonists altered expression of VEGF when used at appropriate concentrations in mouse or human macrophages (Fig. 2).

Because reduced oxygen tension is a major physiologic signal for induction of VEGF expression, we investigated whether LXR could contribute to VEGF induction under hypoxic conditions. VEGF expression was increased by LXR agonists under both normoxic and hypoxic conditions, and the LXR effect was additive to the HIF-1-dependent pathway. Similarly, VEGF induction, by inflammatory signals such as LPS and the purinergic receptor agonist NECA, is also independent of LXR as it occurs to the same extent in both wild type and LXR-deficient macrophages (Fig. 5). We have also demonstrated that LXR agonist administration results in a significant increase in VEGF mRNA expression in the white adipose tissue in mice. Thus, the LXR pathway may impact VEGF expression in other cell types as well.

The physiological relevance of LXR-dependent VEGF regulation is not clear at present. It is unlikely that the LXR pathway is a primary regulator of angiogenesis, because LXR null mice show no obvious defects in vascularization.2 However, it is possible that activation of LXR in macrophages in contexts such as inflammation or wound healing may be important for modulation of VEGF activity. Recently, we demonstrated that in addition to controlling genes involved in lipid metabolism, LXR negatively regulates a number of inflammatory pathways in macrophages. Treatment of murine macrophages with LXR ligands inhibits the expression of numerous NFκB target genes, such as TNFα, iNOS, and COX-2 (30). Surprisingly, VEGF does not follow this same pattern. VEGF mRNA expression is up-regulated by LXR agonists both in the presence and absence of LPS. Although VEGF has been reported to be responsive to NFκB activation (19, 20), it is also regulated by many other pathways. Unlike iNOS, VEGF expression in murine macrophages is not highly dependent on NFκB (Fig. 6). The unique response of VEGF compared with other inflammatory genes is most likely explained by the observation that it is a direct target for regulation by LXR.

How do these observations relate to recent work on the functions of LXRs in atherosclerosis? In addition to its angiogenic activity, VEGF has been shown to regulate the survival and maturation of hematopoietic stem cells and to increase the mobilization of myeloid cells from bone marrow into the circulation. VEGF has also been shown to enhance recruitment of inflammatory cells into atherosclerotic lesions (44). Recent studies have implicated VEGF in plaque neovascularization and plaque progression (45). However, targeted suppression of VEGF signaling by blocking antibodies for either Flt-1 or Flk-1 showed very little effect on angiogenesis in atherosclerotic lesions (46). Macrophages play both positive and negative roles in the context of the atherosclerotic lesion. The scavenging of oxidized lipids and the removal of cholesterol through reverse cholesterol transport is beneficial. However, once overwhelmed

2 R. Walczak, S. B. Joseph, B. A. Laffitte, A. Castrillo, L. Pei, and P. Tontonoz, unpublished observations.
by their lipid load, macrophages elaborate inflammatory mediators, induce smooth muscle cell proliferation, and contribute to plaque instability through production of matrix metalloproteinases. Although the regulation of VEGF expression by LXR in macrophages might be predicted to be proatherogenic, it is well established that the net effect of LXR activation is antiatherogenic. Synthetic LXR agonists reduce lesion formation in murine models of atherosclerosis (47), whereas loss of bone marrow LXR expression increases lesion formation (48). LXR activation also inhibits basal and cytokine-inducible expression of the matrix metalloproteinase (MMP-9), which is expressed in its active form in atherosclerotic lesions and is believed to play an important role in vascular remodeling and plaque instability (49). Further research will be needed to understand the role of LXR-dependent VEGF regulation in both physiologic and pathophysiologic contexts.

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REFERENCES

1. Leung, D. W., Cuchianes, G., Kuang, W. J., Goeddel, D. V., and Ferrara, N. (1989) Science 246, 1306–1309
2. Plouet, J., Schilling, J., and Gospodarowicz, D. (1989) EMBO J. 8, 3801–3806
3. Phillips, G. D., Stone, A. M., Jones, B. D., Schultz, J. C., Whitehead, R. A., and Ward, R. A. (1989) EMBO J. 8, 261–265
4. Forsey, J. A., Jiang, B. H., Iyer, N. V., Agani, F., Leung, S. W., Koos, R. D., Brill, J. W., and Tontonoz, P. (2002) Proc. Natl. Acad. Sci. U. S. A. 99, 18570–18575
5. Castrillo, A., Joseph, S. B., Marathe, C., Mangelsdorf, D. J., and Tontonoz, P. (2003) J. Biol. Chem. 278, 35217–35222
6. Castrillo, A., Joseph, S. B., Marathe, C., Mangelsdorf, D. J., and Tontonoz, P. (2003) Nature 428, 1547–1549
7. Castrillo, A., Joseph, S. B., Marathe, C., Mangelsdorf, D. J., and Tontonoz, P. (2003) Proc. Natl. Acad. Sci. U. S. A. 99, 11086–11091
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