Expression of Class A Scavenger Receptor Inhibits Apoptosis of Macrophages Triggered by Oxidized Low Density Lipoprotein and Oxysterol

Hai-Sun Liao, Tatsuhiko Kodama, Yong-Jian Geng

Abstract—The class A macrophage scavenger receptor (MSR-A) is a multifunctional trimeric glycoprotein involved in innate immune response as well as the development of lipid-laden foam cells during atherosclerosis. The MSR ligand, oxidized low density lipoprotein (oxLDL), is known to be cytotoxic to macrophages and other cell types. This study examined whether MSR mediates or modulates oxLDL-induced apoptosis. Treatment with oxLDL and its cytotoxic oxysterol, 7-ketocholesterol (7-KC), reduced viability and increased DNA fragmentation in human THP-1 cells, Chinese hamster ovary cells, and mouse peritoneal macrophages. However, cell death and DNA fragmentation were markedly diminished in the phorbol ester–differentiated MSR-expressing THP-1 cells and Chinese hamster ovary cells, with stable expression of MSR-AI after cDNA transfection when exposed to the same concentrations of oxLDL and 7-KC. Moreover, treatment with oxLDL and 7-KC induced much greater death and DNA fragmentation in MSR-A–deficient peritoneal macrophages compared with wild-type macrophages. Thus, MSR-A does not act as a receptor responsible for the apoptotic effect of oxLDL, and instead, expression of this receptor confers resistance of macrophages to the apoptotic stimulation by oxLDL and its cytotoxic lipid component. These results suggest that by preventing apoptosis, MSR-A may contribute to the long-term survival of macrophages and macrophage-derived lipid-laden foam cells in atherosclerotic lesions. (Arterioscler Thromb Vasc Biol. 2000;20:1968-1975.)

Key Words: macrophages ■ scavenger receptors ■ atherosclerosis ■ lipoproteins ■ cell death

Atherosclerosis is a chronic arterial disease with 2 life-threatening complications, myocardial and cerebral infarcts. The long-lasting process of atherogenesis involves dramatic alterations in cellularity, extracellular matrix, and lipid components of the arterial wall, resulting in intimal thickening, vessel lumen narrowing, and increased susceptibility to thrombosis. Cell proliferation has been traditionally regarded as a key factor that increases the number of cells in the arterial intima. However, analysis of proliferative markers has revealed a low degree of cell replication.1 On the other hand, recent studies have documented that deregulation of apoptosis, a form of genetically programmed cell death, occurs in atherosclerotic lesions.2,3 Imbalance between cell survival and death may contribute to dramatic alterations in cellularity of the arterial wall with atherosclerosis.

Formation of lipid-laden foam cells from macrophages and, to a less extent, from smooth muscle cells represents a landmark for atherosclerosis. The development of foam cells is mainly due to overloading of lipids, particularly cholesterol and cholesterol ester, into the cells through a scavenger receptor–mediated process. It is believed that the lipids within the foam cells largely come from the lipid-rich proteins in blood, particularly LDLs, which enter the cells after chemical modification, such as oxidation and converting to the ligand for macrophage scavenger receptors (MSRs). Three different classes of MSR have been identified.4 Among them, the class A MSR (MSR-A) is the first one to be cloned and characterized for its ligand binding specificity and capacity.5 Its expression is limited to differentiated or mature mononuclear cells and is thus characterized for the monocyte-to-macrophage differentiation. Our previous studies have shown that circulating monocytes elaborate MSR-A at undetectable levels but that when the cells differentiate into tissue macrophages, they express high levels of MSR-A.6,7

The MSR ligand, oxidized LDL (oxLDL), has been identified as an apoptosis-promoting agent to a variety of cell types, including vascular smooth muscle cells,8,9 endothelial cells,10–12 and macrophages.13,14 Other modified LDLs, such as enzymatically degraded LDLs (E-LDL), can selectively induce the expression of monocyte chemotactic protein-1 and exert cytotoxic effects on human macrophages.15,16 In vitro treatment with oxLDL may activate the caspase-3,9 which acts as an effector in the downstream caspase death cascade. However, despite the well-defined

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ligand-receptor relationship between oxLDL and MSR, it remains largely unclear as to whether MSR-A mediates or modulates apoptotic effects of oxLDL and associated lipids. Our recent work has shown that differentiated MSR-A–expressing human THP-1 macrophages become resistant to apoptosis triggered by fluoride anions, a global activator of G protein. Chinese hamster ovary (CHO) cells with stable expression of MSR-A also exhibit increased resistance to the fluoride apoptotic stimulation. Moreover, recent studies have shown that expression of a scavenger receptor–like gene, the cellular stress response gene, prevents cellular damage by UV irradiation and oxidative stress and that thymocytes lacking the apoptosis inhibitor of macrophages, a member of the scavenger receptor cysteine-rich family, are more susceptible to apoptosis. Thus, these data seem argue against the notion that oxLDL triggers apoptosis in an MSR-A–dependent manner.

The present study was aimed to determine (1) whether the expression of MSR-A prevents oxLDL-induced apoptosis in differentiated human THP-1 monocytic macrophages, (2) whether overexpression of MSR-A in CHO cells reduces apoptosis triggered by oxLDL and oxysterol, and (3) whether resident peritoneal macrophages from the MSR-A–null (MSR/−/−) mice are more sensitive to oxLDL and oxysterol.

**Methods**

**Reagents**

Free cholesterol and 7-ketcholesterol (7-KC) were purchased from Sigma Chemical Co and dissolved in dimethyl sulfoxide at a stock solution of 10 mg/mL. Native LDL and oxLDL were obtained from Perlipure Inc. Acridine orange and ethidium bromide (nucleic acid–binding dyes) were obtained from Sigma. RPMI-1640 and F-12 medium were purchased from GIBCO. Phorbol 12-myristate 13-acetate (PMA) was obtained from Sigma and dissolved in dimethyl sulfoxide at a stock concentration of 10 mmol/L.

**Cell Culture and Treatment**

THP-1 and CHO cells were obtained from American Type Culture Collection. THP-1 cells were maintained in RPMI-1640 supplemented with 10% heat-inactivated FBS, 100-U/mL penicillin, and 100 μg/mL streptomycin. CHO cells were maintained in F-12 medium supplemented with 10% heat-inactivated FBS, 100 U/mL penicillin, and 100 μg/mL streptomycin. THP-1 cells were pretreated with or without 100 nmol/L of PMA, washed with PBS, and then treated with various concentrations of oxLDL and 7-KC, respectively. Control experiments were performed by using the same concentration of the vehicle, dimethyl sulfoxide.

**Resident Peritoneal Macrophage Isolation and Treatment**

Resident peritoneal macrophages were isolated from wild-type (MSR+/+) and homozygous MSR-deficient (MSR−/−) mice by peritoneal lavage as described previously. Briefly, mice injected with 0.2 mL of ketamine (100 μg/mL) underwent lavage with 8 mL of serum-free RPMI-1640 media into the peritoneal cavity. Peritoneal macrophages were obtained by centrifugation of the lavage fluid collected from the peritoneal cavity. The collected macrophages were resuspended in RPMI-1640 with 10% heat-inactivated FBS and incubated at 1×10⁶ cells per milliliter in 8-well chamber slides for 48 hours. The cells were then stimulated with oxLDL or 7-KC. After stimulation, the cells were fixed for terminal deoxynucleotidyl transferase (TdT)-mediated dUTP nick end-labeling (TUNEL) staining as shown below.

**Cell Viability Assay**

Cell viability was determined by staining with a combination of the nucleic acid–binding dyes acridine orange (10 μg/mL) and ethidium bromide (10 μg/mL) for 5 minutes on ice. After staining, viable and nonviable cells were counted on the basis of color and appearance under a fluorescence microscope. Acridine orange and ethidium bromide dyes can intercalate into DNA. Viable cells are stained with green nuclei by acridine orange, whereas nonviable cells are stained with ethidium bromide, producing a red or orange color in nuclei. At least 200 cells were counted. The percentage of dead cells was calculated by dividing the number of dead cells by total cell number.

**Analysis of DNA Fragmentation**

DNA was extracted from the cells stimulated by oxLDL and 7-KC in various concentrations for 24 hours in 6-well plates. After treatment, 5×10⁶ cells were lysed in 1 mL of DNA extract solution containing 100 mmol/L NaCl, 20 mmol/L Tris-HCl (pH 8.0), and 10 mmol/L EDTA at room temperature for 15 minutes. The cell lysates were incubated overnight with proteinase K (200 μg/mL) at 37°C, extracted for DNA with phenol/chloroform isomyl alcohol, and precipitated with the same volume of isopropanol. Remaining RNA was removed by digestion with RNase A (25 μg/mL) at 37°C for 30 minutes. After reextraction and precipitation, DNA concentration was determined by spectrophotometer at a wavelength of 260 nm. DNA at 20 μg per lane was loaded into 2% agarose gels with 0.5 μg/mL ethidium bromide and separated by electrophoresis at a constant voltage of 100 V for 1 to 2 hours at room temperature. The DNA ladder was visualized under UV light.

**Total RNA Isolation and RT-PCR**

Total RNA was extracted from THP-1 cells treated with or without PMA (100 nmol/L) for 48 hours by using the phenol/guaniadium thiocyanate method. cDNA was generated by reverse transcription (RT) from 1 μg of total RNA and a 30-cycle polymerase chain reaction (PCR) with specific primers for MSR-A types I and II (MSR-AI and MSR-AII, respectively), as described previously. RT-PCR for β-actin mRNA was used as an internal control. The PCR products were analyzed by electrophoresis on 2% agarose gels containing 0.5 μg/mL ethidium bromide.

**In Situ 3′ End Labeling of DNA Fragments (TUNEL)**

Mouse peritoneal macrophages treated with and without oxLDL or 7-KC in 8-well chamber slides for 24 hours were fixed with 3% paraformaldehyde in PBS. After they were washed in PBS, the cells were incubated with 2% H₂O₂ in methanol to inactivate endogenous peroxidase. Digoxigenin-conjugated dUTP was incorporated into 3′ ends of DNA with TdT by using an ApoTag in situ apoptosis detection kit (Oncor, Inc). The presence of digoxigenin-labeled DNA fragments was determined by using a peroxidase-conjugated antibody against digoxigenin. The chromogenic substance diaminobenzidine was used as a substrate for visualization of the immunostaining. The percentage of TUNEL-positive cells was calculated by dividing the number of positive cells by the total cell number.

**CHO Cell Line With Stable Overexpression of MSR-A**

CHO cells were transfected with MSR-A type I cDNA by a standard calcium phosphate precipitate method. After transfection, CHO cells were selected with G-418 medium for 4 weeks. The establishment of the CHO cell line with stable expression of MSR-A was confirmed by Northern and Western blotting.

**Flow Cytometry**

THP-1 cells were analyzed by flow cytometry for the expression of different isoforms of MSR, such as MSR-A, CD36, and CD68. The cells were pretreated with PMA and then exposed to 25 μg/ml oxLDL at 37°C for 24 hours. After they were washed in PBS, the cells were stained with monoclonal antibodies against MSR-A, CD36, and CD68, followed by incubating with FITC-conjugated anti-mouse IgG. The immunostains were detected by using a...
We observed that treatment with oxLDL significantly reduced the viability of MSR− and MSR+ THP-1 cells in a concentration-dependent manner, as determined by staining with acridine orange and ethidium bromide (Table). In contrast, under the same concentration, native LDL did not alter cell viability. Interestingly, the number of nonviable MSR+ THP-1 cells appeared significantly lower than the number of nonviable MSR− THP-1 cells (Table). Because internucleosomal DNA fragmentation biochemically characterizes apoptosis, we analyzed the sizes of DNA isolated from oxLDL-treated and untreated THP-1 cells by agarose gel electrophoresis. As shown in Figure 1b, PMA-treated THP-1 cells showed decreased fragmentation of DNA at the internucleosomal sizes compared with the untreated MSR− THP-1 cells. Morphological changes, including cell shrinkage, blebbing, chromatin condensation, and nucleus fragmentation, also occurred, suggesting that the cells underwent apoptosis.

### Results

**MSR+ THP-1 Cells Resist Apoptosis Triggered by OxLDL**

Human THP-1 monocytic cells expressed high levels of mRNA for MSR-Al and MSR-AII after stimulation with PMA (Figure 1). To determine the extent of apoptosis in the MSR− THP-1 cells, the cells were pretreated with PMA and then treated with various concentrations of oxLDL for 24 hours. We observed that treatment with oxLDL significantly reduced the viability of MSR− and MSR+ THP-1 cells in a concentration-dependent manner, as determined by staining with acridine orange and ethidium bromide (Table). In contrast, under the same concentration, native LDL did not alter cell viability. Interestingly, the number of nonviable MSR+ THP-1 cells appeared significantly lower than the number of nonviable MSR− THP-1 cells (Table). Because internucleosomal DNA fragmentation biochemically characterizes apoptosis, we analyzed the sizes of DNA isolated from oxLDL-treated and untreated THP-1 cells by agarose gel electrophoresis. As shown in Figure 1b, PMA-treated THP-1 cells showed decreased fragmentation of DNA at the internucleosomal sizes compared with the untreated MSR− THP-1 cells. Morphological changes, including cell shrinkage, blebbing, chromatin condensation, and nucleus fragmentation, also occurred, suggesting that the cells underwent apoptosis.

### Table: Difference in Viability of MSR+ and MSR− THP-1 Cells Treated With and Without OxLDL and 7-KC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MSR−</th>
<th>MSR+</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>OxLDL, µg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3.6±1.2</td>
<td>5.8±1.4</td>
<td>ND</td>
</tr>
<tr>
<td>50</td>
<td>18.3±5.1</td>
<td>11.9±1.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>100</td>
<td>29.3±5.6</td>
<td>16.3±2.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>200</td>
<td>36.3±4.5</td>
<td>23±4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>7-KC, µg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2.6±0.6</td>
<td>5.6±0.4</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>23±2</td>
<td>12.5±1.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>10</td>
<td>28±4</td>
<td>18±1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>20</td>
<td>48±4</td>
<td>29±6</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are mean±SD (n=3). ND indicates not determined. THP-1 cells pretreated with or without PMA (100 nmol/L) were exposed to oxLDL or 7-KC in various concentrations for 24 hours. Cell viability was determined by staining with acridine orange and ethidium bromide.
the internucleosomal DNA fragmentation were diminished in the MSR−/− cells compared with the MSR+/− THP-1 cells (Table and Figure 2). These results indicate that PMA-pretreated MSR-A–expressing THP-1 macrophages were resistant to apoptosis induced by 7-KC.

To determine whether other isoforms of MSR participate in the regulation of apoptosis induced by oxLDL and oxysterols, we analyzed the expression of CD36 and CD68, 2 isoforms of MSR, in the PMA-differentiated THP-1 cells by flow cytometry after stimulation with oxLDL. We observed that compared with untreated control cells, there were no significant increases in the numbers of CD36-positive cells (11% versus 12% in control cells) and CD68-positive cells (20% versus 19% in control cells) in the PMA-pretreated cultures 24 hours after stimulation with oxLDL (50 μg/mL). Similarly, we found that the 7-KC–treated cells exhibited no changes in the expression of the 2 proteins. This suggests that MSR-A other than CD36 and CD68 contributed to the resistance of the cells to apoptosis induced by oxLDL and 7-KC.

**Overexpression of MSR-A by cDNA Transfection Inhibits Apoptosis Induced by OxLDL in CHO Cells**

To further confirm that expression of MSR itself prevents apoptosis induced by oxLDL and 7-KC, we recently established a CHO cell line with stable overexpressed MSR-AI by transfection with the MSR-AI cDNA. Under baseline conditions, CHO cells expressed little MSR activities, but transfection with a cDNA coding for this receptor dramatically increased MSR expression in the cells, as shown previously.5,24 Figure 3a demonstrates that the CHO cells with stable expression of MSR showed significantly higher viability than untransfected wild-type CHO cells when treated with the same concentrations of oxLDL. Agarose gel electrophoresis of DNA revealed a decrease in internucleosomal fragmentation of DNA in the MSR−/− cells compared with wild-type control cells (Figure 3b). These results suggest that overexpression of MSR-AI might increase the resistance of CHO cells to apoptosis induced by oxLDL.

**Expression of MSR by cDNA Transfection Inhibits Apoptosis Induced by 7-KC in CHO Cells**

To determine whether MSR expression confers resistance of CHO cells to apoptosis induced by the oxysterol, 7-KC, we examined the viability of wild-type and MSR-AI-transfected CHO cells after treatment with 7-KC. We observed a concentration-dependent increase in the percentage of cell death in untransfected wild-type cells treated with 7-KC for 24 hours (Figure 4a). However, the percentage of cell death was much lower in the transfected cells than in the wild-type control cells. Agarose gel electrophoresis also showed a reduction in DNA cleavage in the CHO cells with overexpressed MSR (Figure 4b). Thus, the MSR-overexpressing CHO cells were also resistant to apoptotic stimulation by 7-KC.

**MSR-A–Null Macrophages Exhibit Increased Sensitivity to Apoptosis Induced by OxLDL and 7-KC**

To further verify the antiapoptotic effect of MSR-A on macrophages, we treated resident peritoneal macrophages isolated from wild-type (MSR+/+) and MSR-knockout (MSR−/−) mice with oxLDL and 7-KC. We observed that treatment with oxLDL led to increased numbers of cell death...
in MSR−/− macrophages compared with wild-type cells in a concentration-dependent manner (Figure 5), as determined by staining with acridine orange and ethidium bromide. The percentage of cell death was determined by dividing the number of dead cells by the total number of cells. Data represent mean±SD of at least 3 independent experiments. *P<0.05 (ANOVA).

Discussion
As part of the innate immune system, macrophages recognize and remove denatured macromolecules, pathogenic microor-
oxLDL compared with other forms of MSR, such as CD36 and CD68. The major ligand used for evaluating MSR activity is acetylated LDL, an artificially modified lipoprotein that may not exist in vivo. Hence, the physiological ligand for MSR-A has not been characterized at this time point. Nevertheless, the observation that oxLDL and 7-KC induce apoptosis of THP-1 and CHO cells confirms and extends previous findings by other groups that oxLDL treatment can trigger vascular cell apoptosis. Because we observed no major change in the expression of CD36 and CD68 in the PMA-differentiated THP-1 cells after stimulation with oxLDL and because oxLDL can trigger apoptosis in MSR-negative cells, it is unlikely that CD36 and CD68 are the principal contributors to the resistance of macrophages to apoptosis induced by oxLDL and oxysterols.

The mechanism underlying the inhibitory effect of MSR on oxLDL-mediated apoptosis remains to be determined. OxLDL is composed of various cytotoxic components, including oxysterols. 7-KC is the second most abundant oxysterol found in human atherosclerotic lesions after 27-hydroxycholesterol. Whether 7-KC is a major cytotoxic component in oxLDL remains to be investigated. The intracellular domains of MSR do not contain the sequences of any known signaling factor–binding sites. Although ligand transporting to lysosomes via the MSR pathway can help to remove and degrade oxLDL, the MSR-mediated endocytosis may not be the sole or major mechanism by which MSR prevents apoptosis. This notion is supported by the fact that there is a low affinity between oxLDL and MSR-A and no 7-KC binding to MSR-A. Our recent studies have provided an additional interpretation for the protective effect of MSR, showing that expression of MSR-A blocks apoptosis induced by oxLDL and oxysterols.

Figure 6. In situ detection of DNA fragments by TUNEL in MSR<sup>+/+</sup> and MSR<sup>−/−</sup> peritoneal macrophages treated with 7-KC. Wild-type (WT, a and b) and MSR<sup>−/−</sup> (c and d) peritoneal macrophages treated with 7-KC in an 8-well chamber slide were labeled with digoxigenin-conjugated dUTP and TdT by use of an ApoTag in situ apoptosis detection kit (Oncor, Inc). The presence of digoxigenin-labeled DNA fragments was determined with a peroxidase-conjugated antibody against digoxigenin, with diaminobenzidine as a substrate. a and c, Phase-contrast microscopy. b and d, Light microscopy. Note an increased number of MSR<sup>−/−</sup> macrophages with shrunken and TUNEL-positive nuclei stained brown.

Figure 7. Quantification of the TUNEL positivity in MSR<sup>+/+</sup> and MSR<sup>−/−</sup> peritoneal macrophages treated with or without oxLDL and 7-KC. Peritoneal macrophages treated with or without oxLDL and 7-KC, respectively, were fixed with 3% formaldehyde in PBS. TUNEL staining was performed with an ApoTag in situ apoptosis detection kit (Oncor, Inc). The percentage of TUNEL-positive cells was calculated by dividing the number of positive cells by the total cell number. a, Macrophages treated with oxLDL. b, Macrophages treated with 7-KC. Data represent mean ± SD of at least 3 independent experiments. *P < 0.05 (ANOVA).

THP-1 cells, a human monocytic leukemia cell line, can differentiate into macrophage-like cells, after exposure to the transforming agent, phorbol esters. The differentiated THP-1 macrophages express high levels of MSR and behave in a manner highly similar to that of native monocyte-derived macrophages. PMA is a potent activator of protein kinase C. Regulation of apoptotic death by the protein kinase C pathway has been recently reported in the cells. However, in the present study, we observed no difference in cell death
between PMA-treated and untreated THP-1 cells. Very recently, we have shown increased expression of apoptosis-promoting genes, such as FasL, and CPP-32 (caspase-3) in PMA-differentiated THP-1 cells, but there is no increase in the number of cells bearing markers of apoptosis.17 It is reasonable to expect that the expression of MSR-A plays a role in the regulation of apoptosis of macrophages. Nishio and Watanabe9 reported that oxysterols induced apoptosis in cultured smooth muscle cells through CPP-32 activation and bcl-2 protein downregulation. However, it is unclear whether 7-KC exerts a similar effect on macrophages and whether MSR can block the regulatory effects of 7-KC on the cells. Munn and colleagues18 reported that macrophage colony-stimulating factor (CSF)–differentiated macrophages are resistant to apoptosis, whereas granulocyte-macrophage CSF–differenti- and interferon-γ–differeniated macrophages are sensitive to apoptosis. Interestingly, macrophage CSF increases but interferon-γ and granulocyte-macrophage CSF decrease the expression of MSR.17–19

Recently, several proteins with the MSR cysteine-rich domain (SRCR), such as cellular stress response elements18 and apoptosis inhibitors of macrophages,19 have been reported to exert protective effects on apoptosis of fibroblasts and macrophages, respectively. The mechanism underlying the protective effects of the SRCR-containing proteins is unknown. The mRNA and protein levels of MSR-AI with the SRCR domain are not appreciable in most peripheral blood monocytes, but MSR-AI expression elevates dramatically when monocytes differentiate into macrophages. The increased expression of MSR-AI concurs with the development of resistance to apoptosis in the monoocyte-derived macrophages. Further investigation is needed to delineate the relationship of MSR-AI expression with the macrophage resistance to apoptosis.

It has been shown that macrophages of atherosclerotic lesions express high levels of MSR-A,4 suggesting that the expression of MSR is associated with maturation of monocytes and resistance of certain macrophages to apoptosis in atherosclerosis. Most of the plaque macrophages contain substantial amounts of lipids, mainly cholesterol, that are derived from modified lipoproteins internalized via the scavenger pathway. The increased expression of MSR-A may not only promote the uptake of those lipid components but also contribute to the longevity of the lipid-rich foam cells by increasing the resistance of the cells to cytotoxic effects of oxLDL and oxysterols. Recently, Kocks and colleagues40,41 reported lower levels of apoptosis in certain atherosclerotic lesions than previously thought, suggesting that nonspecific staining for the cells undergoing apoptosis or attenuation of apoptosis might occur in the lesions. Our present data appear to support the notion that in atherosclerotic plaque, there is a mechanism that is responsible for the inhibition of apoptosis and that leads to long-term accumulation of lipid-laden macrophage-derived foam cells during atherogenesis.

Acknowledgments

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References


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