The bifunctional leukotriene B₄ 12-hydroxydehydrogenase/15-oxo-prostaglandin 13-reductase (LTB₄ 12-HD/PGR) is an essential enzyme for eicosanoid inactivation. It is involved in the metabolism of the E and F series of 15-oxo-prostaglandins (15-oxo-PGs), leukotriene B₄ (LTB₄), and 15-oxo-lipoxin A₄ (15-oxo-LXA₄). Some nonsteroidal anti-inflammatory drugs (NSAIDs), which primarily acts as cyclooxygenase inhibitors also inhibit LTB₄ 12-HD/PGR activity. Here we report the crystal structure of the LTB₄ 12-HD/PGR, the binary complex structure with NADP⁺, and the ternary complex structure with NADP⁺ and 15-oxo-PGE₂. In the ternary complex, both in the crystalline form and in solution, the enolate anion intermediate accumulates as a brown chromophore. PGE₂ contains two chains, but only the α-chain of 15-oxo-PGE₂ was defined in the electron density map in the ternary complex structure. The α-chain was identified at the hydrophobic pore on the dimer interface. The structure showed that the 15-oxo group forms hydrogen bonds with the 2'-hydroxy group of nicotine amide ribose of NADP⁺ and a bound water molecule to stabilize the enolate intermediate during the reductase reaction. The electron-deficient C13 atom of the conjugated enolate may be directly attacked by a hydride from the NADPH nicotine amide in a stereospecific manner. The moderate recognition of 15-oxo-PGE₂ is consistent with a broad substrate specificity of LTB₄ 12-HD/PGR. The structure also implies that a Src homology domain 3 may interact with the left-handed proline-rich helix at the dimer interface and regulate LTB₄ 12-HD/PGR activity by disruption of the substrate binding pore to accommodate the α-chain.

Eicosanoids, such as prostaglandins, leukotrienes, and lipoxins, are endogenous lipid mediators and play key roles in a wide range of normal physiological and pathophysiological processes such as host defense responses and inflammation. The dominant eicosanoids, leukotriene B₄ (LTB₄), prostaglandin E₂ (PGE₂), and F (PGE₂ and PGF), and lipoxin A₄ (LXA₄) are rapidly inactivated by enzymatic degradation. A bifunctional LTB₄ 12-hydroxydehydrogenase/15-oxo-prostaglandin 13-reductase (LTB₄ 12-HD/PGR), a member of the zinc-independent medium chain dehydrogenase/reductase (MDR) family (1), is a key enzyme in the irreversible degradation of all three eicosanoids to remove these highly biologically active agents (2–4) (Fig. 1).

PGE₂ mediates a wide range of physiological processes in a variety of tissues (Fig. 1). It is involved in the relaxation of smooth muscle cells to protect against lung inflammation (5), regulating gastric acid and mucus secretion in the stomach (6), regulating water and mineral balance in the kidney (7), as well as having roles in immune responses, thermo-regulation, and vasopermeability. Overproduction of PGE₂ induces inflammation and can have oncogenic effects (8). PGE₂ production can be inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs), which act as cyclooxygenase inhibitors. NSAIDs are important drugs in the treatment of inflammatory disease and may have roles in cancer or Alzheimer disease therapy (9, 10).

LTB₄ and LXA₄ play important roles in inflammation and immune response (11–14) (Fig. 1). LTB₄ binds to its cognate receptors BLT₁ and BLT2, expressed on peripheral blood leukocytes, leading to the activation and chemotaxis of leukocytes (15, 16). In contrast LXA₄ inhibits LTB₄, regulates excessive leukocyte traffic, down-regulates leukocyte function, and promotes resolution of inflammation (17, 18).

PGE₂, LTB₄, and LXA₄ are rapidly degraded by separate enzymatic pathways, but the bifunctional LTB₄ 12-HD/PGR performs the first irreversible step of each degradation pathway (Fig. 1). LTB₄ is oxidized by LTB₄ 12-HD/PGR to 12-oxo-LTB₄, which is at least 100 times less potent than LTB₄ (2). In contrast, PGE₂ and LXA₄ are oxidized to 15-oxo-PGE₂ and 15-oxo-LXA₄, respectively, by NAD⁺-dependent 15-hydroxyprostaglandin dehydrogenase prior to LTB₄ 12-HD/PGR.

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The atomic coordinates and structure factors (code 1V3T, 1V3U, and 1V3V) have been deposited in the Protein Data Bank, Research Collaboratory for Structural Bioinformatics, Rutgers University, New Brunswick, NJ (http://www.rcsb.org/).

1 The abbreviations used are: LTB₄, leukotriene B₄; PG, prostaglandin; LXA₄, lipoxin A₄; LTB₄ 12-HD/PGR, leukotriene B₄ 12-hydroxydehydrogenase/15-oxo-prostaglandin 13-reductase; PPII helix, a left-handed polyproline II helix; QOR, quinone oxidoreductase; SH3 domain, Src homology domain 3; MDR, medium chain dehydrogenase/reductase.

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reduction (13, 19). LTB₄ 12-HD/PGR then catalyzes the NAD(P)H-dependent reduction of both 15-oxo-PGE₂ to 13,14-dihydro-15-oxo-PGE₂ and 15-oxo-LXA₄ to 13,14-dihydro-15-oxo-LXA₄ (3, 4). The 15-oxo-PGE₂ reductase reaction is more active than the LTB₄ oxidase reaction for pig and guinea pig LTB₄ 12-HD/PGRs in vitro (4, 20). Although the \( K_m \) values for both substrates are almost identical, the \( k_{cat} \) value for 15-oxo-PGE₂ reduction is approximately 200 times higher than that for LTB₄ oxidation. Some NSAIDs, which primarily act as cyclooxygenase inhibitors, also inhibit LTB₄ 12-HD/PGR activity in vitro (21). The enzyme has been identified as dithiolethione-inducible gene-1 product, suggesting that increased metabolism of LTB₄ inhibits tumorigenesis (22). Antioxidative function of the enzyme in cells has been also reported (23).

Here we report the crystal structure of the LTB₄ 12-HD/PGR, the binary complex structures with NADP⁺, and the ternary complex structure of LTB₄ 12-HD/PGR with NADP⁺ and 15-oxo-PGE₂. Based on our findings, we propose a catalytic mechanism of the enzyme. Additionally the structure suggests SH3 domain (Src homology domain 3)-mediated regulation of LTB₄ 12-HD/PGR activity.

**FIG. 1. Pathway of eicosanoid metabolism.** Upper column, biosynthesis of specific prostaglandins is dependent on cell types; most cells (PGE₂), brain and mast cells (PGD₂), uterus (PGF₂α), endothelial cells (PGI₂, or prostacyclin), and platelets (TXA₂) (12). Leukotrienes are synthesized in inflammatory cells such as polymorphonuclear leukocytes, macrophages, and mast cells, and lipoxins are produced in airway epithelial cells or at inflammation sites (11–14). Lower column, eicosanoid action is mediated by specific cell surface receptors and is rapidly inactivated by enzymes (2–4). Two major pathways for LTB₄ inactivation are reported; the \( \omega \) oxidative pathway initially catalyzed by LTB₄ 20-hydroxylase is present in inflammatory cells (49), whereas in most other cells inactivation is catalyzed by LTB₄ 12-HD/PGR (2). LTB₄ 12-HD/PGR is emphasized in bold underlined text. The inactivation pathway of PGF₂α is identical to that of PGE₂.
were not included in the model because of poor or no electron density.
The apo structure, residues 12 and 250, were replaced with chloride, the water molecule was changed to a chloride ion. For refinement with DM (28), the overall figure of merit for the final experimental model was 0.75. The structural models were built using O (29) and Bobscript (34), and Raster3D (35).

EXPERIMENTAL PROCEDURES

Expression, Purification, and Crystallization—Guinea pig-LTB4 12-HD/PGR was purified with a glutathione-S-Sepharose 4B column (Amersham Biosciences, Uppsala, Sweden), and the N-terminal glutathione-S-transferase was cleaved with thrombin (Wako) for 20 h at room temperature, followed by further purification by cation exchange chromatography on a Mono S column (Amersham Biosciences) with 0–150 mM NaCl gradient. The sample (20 mg/ml) was crystallized by the batch method using the automated crystallization system TERA (24) by mixing equal volumes of protein concentration stepwise from 5% (w/v) up to 30% (w/v), whereas the ternary complex included 10 mM NADPH and 20.3 mM 15-oxo-PGE2. Crystals appeared within 1 week and were collected at 100 K at SPring-8 with an R-AXIS V detector (Rigaku). All data sets were processed using HKL2000 (26).

RESULTS AND DISCUSSION

Overall Structure of LTB4 12-HD/PGR—LTB4 12-HD/PGR is a homodimer with 2-fold symmetry (Fig. 2). As a member of the MDR family, it exhibits a typical alcohol dehydrogenase fold (36). Each monomer comprises a catalytic domain (residues 1–122 and 293–329) and a nucleotide binding domain (residues 123–292) arranged around a Rossmann fold. The substrates, NADP+ and 15-oxo-PGE2, are bound at the active site clefts located between the catalytic and nucleotide binding domains (Fig. 2).

Crystal Structure of LTB4 12-HD/PGR

Data collection and structure refinement statistics

Data collection

| Data set | Se-Met derivative | Apo | Binary | Ternary |
|----------|------------------|-----|--------|---------|
| Beam line | BL26B2          | BL45XU | BL45XU | BL45XU |
| Space group |               |            |         |         |
| Cell a, b, c (Å) | 59.5, 76.4, 80.5 | 76.6, 80.4, 79.9 | 93.5, 80.4, 81.1 | 93.5, 80.4, 81.1 |
| β (°) | 109.3 | 109.3 | 109.3 | 109.3 |
| Resolution (Å) | 46.2–23 | 46.2–23 | 46.2–23 | 46.2–23 |
| Wavelength (Å) | 0.99000 | 0.97324 | 0.97894 | 0.98600 |
| Observed ref. | 142,979 | 145,106 | 146,458 | 144,138 |
| Unique ref. | 29,342 | 29,800 | 29,997 | 29,678 |
| Completeness (%) | 96.9 (98.1) | 98.0 (98.0) | 98.5 (97.9) | 97.2 (98.2) |
| I/σ | 17.4 (4.11) | 16.7 (3.7) | 16.8 (3.5) | 15.8 (3.2) |
| Rmerge (%) | 5.6 (26.2) | 6.1 (28.4) | 7.0 (29.6) | 7.4 (37.6) |
| Structural refinement |           |       |       |       |
| Resolution (Å) | 32.2–2.0 | 24.5–2.3 | 32.1–2.0 |
| R (%)/Rfree (%) | 21.4/25.7 | 19.4/25.4 | 19.4/25.4 |
| r.m.s.d. of bond angles (°) | 0.009/1.39 | 0.006/1.28 | 0.006/1.28 |
| No. of waters/chlorides | 748/7 | 814/0 | 945/6 |

Structural Determination and Refinement—x-ray diffraction data were collected at 100 K at SRing-8 with an R-Axis V detector (Rigaku) for the Se-Met derivative and a Jupiter CCD (Rigaku) for the remaining data sets (Table I). For co-crystallization, the Se-Met derivative crystal was soaked in the precipitating solution including trehalose, increasing the concentration stepwise from 5% (w/v) to 30% (w/v), whereas the other crystals were treated with a 1:1 paraffin/Paratone-N mixture solution using a Shimadzu MultiSpec-1500. The reaction mixture solution was then mixed into the ternary complex solution. A half-volume of 2 N NaOH was further added into both solutions to allow measurement of the residual 15-oxo-PGE2 (32). The incubated ternary complex solution was ultrafiltered by Millipore Ultrafree®-MC centrifugal filter units (5,000 nominal molecular weight limit) to examine whether the colored material(s) is bound to LTB4 12-HD/PGR. Absorption spectra were measured for each reaction mixture solution using a Shimadzu MultiSpec-1500. The reaction mixture without the enzyme was used as a reference. For the ternary complex solutions without NADPH addition, a 10× diluted sample was measured after NaOH addition.

Molecular Graphics—The figures were prepared with Molscript (33), Bobscript (34), and Raster3D (35).
NADP$^+$ Binding to LTB$_4$ 12-HD/PGR in the NADP$^+$ Complex Structure—In the binary complex structures, the bound NADP$^+$ is in the anti configuration of the ribose-nicotinamide glycosidic bond, as commonly observed in alcohol dehydrogenases (36) (Fig. 3A). NADP$^+$ forms a number of hydrogen bonds with LTB$_4$ 12-HD/PGR, some of which are mediated by ordered water molecules. The amino acid residues lining the NADP$^+$ binding sites are well conserved in the LTB$_4$ 12-HD/PGRs of all species but not among the MDR family (Fig. 4). This may explain why the substrates directly interact with the bound NADP$^+$(H).

A well ordered hydrogen bond network around the 2'-hydroxyl group of the nicotine amide ribose contains two water molecules (W1 and W2) that are proposed to facilitate catalysis by stabilizing an enolate of the 15-carbonyl group of 15-oxo-PGE$_2$ through hydrogen bond formation (Fig. 3A). Tyr-245, whose hydroxyl group may be a proton donor to the 2'-hydroxyl group, is conserved among known LTB$_4$ 12-HD/PGRs of all species but not among the MDR family (Fig. 4). This may explain why the substrates directly interact with the bound NADP$^+$(H).

The LTB$_4$ 12-HD/PGR ternary complex crystal has a faint brown color (Fig. 3B), as observed in the enzyme solution with 20 mM NADP$^+$ and 0.5 mM 15-oxo-PGE$_2$ at neutral pH. The ternary complex solution mixture turned a faint brown color over time with a maximum absorption peak of 475 nm, characteristic of an enolate intermediate (Fig. 3C). The solution became colorless upon addition of 10 mM NADPH, whereas the addition of 0.4 M NaOH to the ternary complex mixture resulted in a much denser brown color with an absorption peak at 500 nm (Fig. 3C). These color changes have been utilized as an enzyme assay to quantify the remaining 15-oxo-PGE$_2$ (32). The addition of NADPH propagates the reduction of the 15-oxo-PGE$_2$ complex (faint brown) to 13,14-dihydro-15-oxo-PGE$_2$ (colorless). Ultrafiltration analysis showed that the faint brown chromophore in the ternary complex mixture was retained in the LTB$_4$ 12-HD/PGR protein fraction, and the absorption density of 475 nm concentrated proportionally to the ternary complex. These results indicate that the conversion of the colored 15-oxo-PGE$_2$ intermediate to colorless 15-oxo-PGE$_2$ is reversible. In addition, the intermediate remains bound to the active site of the enzyme.
In the crystal structure of the ternary complex, only the 
\omega\text{-}chain (from C12 to C20) of 15-oxo-PGE₂ was defined in the 
electron density (Fig. 3D). The \alpha,\beta-unsaturated 15-oxo moiety 
of the bound 15-oxo-PGE₂ is in direct van der Waals contact 
with the nicotine amide ring of the bound NADP⁺ (Fig. 3E).
The \omega\text{-}chain tail is buried in the hydrophobic pore composed of 
loop E-F and helices 1 and F at the dimer interface (Figs. 
2 and 3D). The 15-carbonyl group of the \omega\text{-}chain forms hydro-
gen bonds with the 2'-hydroxyl group of the nicotine amide 
ribose and the bound water W1 (Fig. 3E). The carbon atoms 
C12 to C16 including the 15-carbonyl oxygen in the \omega\text{-}chain are 
co-planar with a geometry consistent with the configuration of 
the conjugated \alpha,\beta-unsaturated carbonyl. The plane lies parallel 
to the nicotine amide ring of NADP⁺ with a π-π orbital 
interaction, which may produce the faint brown chromophore 
as a charge transfer complex (Fig. 3E). The conjugated 15-
carbonyl of the \omega\text{-}chain is stabilized by a hydrogen bonding 
network allowing formation of the enolate intermediate (Fig. 
3D). An enolate formation should cause electron deficiency of 
the conjugated C13 atom as the putative hydride ion acceptor.
in the reductase reaction. The distance of 3.8 Å between the C13 atom and the C4 position of the nicotine amide ring, the proposed hydride donor, allows for hydride transfer (36) (Figs. 3E and 5).

Hydrophobic residues from both subunits comprise the C9275-chain binding pore at the dimer interface (Fig. 3D). The alkyl chain between C16 and C20 of the C9275-chain is surrounded by Tyr-49 and Ile-52 on helix C9251, and Ala-241, Tyr-245, and Met-248 on the C9252E-F loop and Ile-271 on the edge of strand C9252 of the NADP+ bound subunit, and by Pro-257(B), Glu-258(B), Ile-261(B), and Tyr-262(B) on the helix αF of the countersubunit (B). These residues are likely to recognize the C9275-chain and determine LTB4 12-HD/PGR specificity, as they are highly conserved among LTB4 12-HD/PGRs but not among MDR families (20, 22, 37, 38) (Fig. 4).

15-Oxo-PGE2 and 15-Oxo-LXA4 Reductase, and LTB4 Oxidase Reaction Mechanisms of LTB4 12-HD/PGR—Based on the LTB4 12-HD/PGR crystal structures, a β-ketoreductase reaction mechanism is proposed (3, 20, 23) (Fig. 5). 15-Oxo-PGE2 reduction and NADP+ (H) recognition are shaded in black and gray, respectively. Residues that are conserved among LTB4 12-HD/PGRs in any species are in bold letters, and those conserved among the MDR families are emphasized by the boxed regions. Secondary structural elements are indicated by arrows (β-strand) and waved line (α-helix). The nucleotide binding domain and the PPII region are surrounded by a thin dotted line and a thick dashed line, respectively.
attacked by the A-side (pro-R) hydride anion (H_) of the C4 atom of the nicotine amide of NADPH (Fig. 5). The hydride anion should then transfer to the pro-S position of the enolate intermediate (39). Thus, the C14 atom of the enolate anion intermediate would be protonated at the final step of the reaction. The mechanism of the β-ketoreductase reaction is identical to that of an enoyl-acyl carrier protein reductase of Mycobacterium tuberculosis, whose enolate anion intermediate is stabilized by hydrogen bonds with the 2'-hydroxyl group of the nicotine amide ribose (40). This catalytic mechanism may be a common feature of β-ketoreductase reactions.

For the LTB4 oxidase reaction of LTB4 12-HD/PGR, some hydrophilic groups would be required as catalytic residues. In the LTB4 12-HD/PGR structure, Tyr-262 from the other subunit is the only candidate catalytic residue considering both the orientation of the side chain and conservation among species (20, 22, 37, 38) (Fig. 3D).

**Domain Movement**—Moderate domain movements are observed upon NADP+ binding compared with the apo form. The NADP+ binding site is wider in both the binary and ternary complexes than in the apo form. Superimposing the nucleotide binding domains of the apo and ternary complex structures of LTB4 12-HD/PGR revealed that the distances between the center of masses of each domain are 0.41 Å in the nucleotide binding domain and 1.14 Å in the catalytic domain, respectively. This corresponds to a domain rotation of ~1.6°. The most notable structural difference is in the binding site of the adenine moiety of NADP+. residues 316–323 on the helix α3 and the loop α3-β10. Although there are no direct interactions between these residues and NADP+ (Fig. 3A), the region is forced to open upon NADP+ binding as a result of steric hindrance with the adenine moiety of NADP+. This local conformational change may induce the entire domain movement. Such domain movement is also observed in Thermus thermophilus quinone oxide reductase (QOR) (41) and Candida tropicalis enoyl thioester reductase (42), although in these cases domain movement operates to close the NADP+ binding site upon NADP+ binding. A similar domain movement has also been reported for a zinc-dependent alcohol dehydrogenase (43). It is possible that this phenomenon is common to members of the alcohol dehydrogenase family.

The orientations of each subunit differ between LTB4 12-HD/PGR and QOR (Fig. 6). Superimposing the nucleotide binding domains of one subunit of LTB4 12-HD/PGR and E. coli QOR (44) revealed that the distance of the center of masses of each nucleotide binding domain is 1.1 Å in the superimposed and 9.3 Å in the countersubunit. Fifty-three residues (16.1%) are identical between guinea pig LTB4 12-HD/PGR (329 amino acid(s)) and E. coli QOR (328 amino acid(s)) (Fig. 4). In the dimer of LTB4 12-HD/PGR, both active sites are closer than those of QOR (Fig. 6). In addition, there is a cavity between subunits (Figs. 2 and 6). Interestingly, the ω-chain binding pore in LTB4 12-HD/PGR is in the dimer interface neighboring the cavity (Fig. 2).

**A Left-handed Polyproline II Helix (PPII Helix) Recognition and Activity Regulation by SH3 Domain Binding**—The PPII helix of the loop βE-αF may be recognized by the SH3 domain. The enzyme activity could be modulated by the change in the interface interaction of the ω-chain binding pore architecture, which includes Ala-241, Tyr-245, Met-248, Pro-257(B), Glu-258(B), Ile-261(B), and Tyr-262(B) in the vicinity of the loop (Fig. 6A). The sequence of the PPII helix, Leu-251-Pro-Pro-Gly-Pro-Ser-256, is conserved among LTB4 12-HD/PGRs in all known species (20, 23, 37, 38) (Fig. 7A). Parallels can be drawn to that of the p85 subunit of phosphatidylinositol 3-kinase, which is bound by the SH3 domain of Fyn (45) (Fig. 7B). In the case of LTB4 12-HD/PGR, Pro-252, Pro-253, and Pro-255 occupy the P–1, P0, and P2 positions, respectively, and may be recognized by a proline-rich binding groove of an SH3 domain. SH3 recognition sequences often include a basic residue at either the N- or C-terminal side of the P-X-P motif (46). In LTB4 12-HD/PGR Arg-247 is at the N-terminal side of the PPII helix and forms part of a β-turn structure. The guanidino group of Arg-247 occupies a similar position to that of the p85 subunit phosphatidylinositol 3-kinase structure (45) (Fig. 7B). These similar structures suggest that the PPII helix in LTB4 12-HD/PGR binds to a specific SH3 domain to regulate enzymatic activity, as described for 5-lipoxygenase. The activity of 5-lipoxygenase is regulated by a tyrosine kinase (47), which modulates binding of the SH3 domain of the growth factor-bound receptor protein 2 (Grb2) to the proline-rich region of 5-lipoxygenase (48).

We propose that binding of an SH3 domain to LTB4 12-HD/PGR modulates enzyme activity by causing domain re-orientation. The open conformation of the dimer may allow adequate changes of the dihedral angles of the loop βE-αF residues on both sides of the PPII helix, such that an SH3 domain can be bound to each subunit (Fig. 7C). The SH3 domain binding followed by domain re-orientation should disturb the hydrophobic pore, which accommodates the ω-chain of 15-oxo-PGE2. This would result in an LTB4 12-HD/PGR-QOR complex, which is no longer able to bind substrate (Fig. 7C). Therefore, we propose...
that there is a currently unknown protein with an SH3 domain that recognizes the PPII helix and thus regulates LTB4 12-HD/PGR activity. The eicosanoid degradation pathway may thus be regulated by a protein with an SH3 domain, similar to that seen for the LTB4 synthesis pathway.

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REFERENCES
1. Nordling, E., Jornvall, H., and Persson, B. (2002) Eur. J. Biochem. 269, 267–276
2. Yokomizo, T., Izumi, T., Takahashi, T., Kasama, T., Kobayashi, Y., Sato, F., Taketani, Y., and Shimizu, T. (1993) J. Biol. Chem. 268, 18128–18135
3. Ensor, C. M., Zhang, H., and Tai, H. H. (1998) Biochem. J. 330, 103–108
4. Clish, C. B., Levy, B. D., Chiang, N., Tai, H. H., and Serhan, C. N. (2000) J. Biol. Chem. 275, 25372–25380
5. Pavord, I. D., and Tattersfield, A. E. (1995) Lancet 345, 436–438
6. Miller, T. A. (1983) Am. J. Physiol. 245, G601–G623
7. Parnova, R. G. (2000) Membr. Cell Biol. 13, 287–301
8. Harris, S. G., Padilla, J., Koumas, L., Ray, D., and Phipps, R. P. (2002) Trends Immunol. 23, 144–150
9. Ricchi, P., Zarrilli, R., Di Palma, A., and Acquaviva, A. M. (2003) Br. J. Cancer 88, 803–807
10. Hoozemans, J. J., Veerhuis, R., Rozemuller, A. J., and Eikelenboom, P. (2003) Curr. Drug Targets 4, 461–468
11. Samuelsson, B. (1988) Science 295, 568–575
12. Shimizu, T., and Wolfe, L. S. (1990) J. Neurochem. 55, 1–15
13. Maddox, J. F., and Serhan, C. N. (1996) J. Exp. Med. 183, 137–146
14. Yokomizo, T., Izumi, T., and Shimizu, T. (2001) Arch. Biochem. Biophys. 385, 231–241
15. Yokomizo, T., Izumi, T., Chang, K., Takuwa, Y., and Shimizu, T. (1997) Nature 387, 620–624
16. Yokomizo, T., Kato, K., Terawaki, K., Izumi, T., and Shimizu, T. (2000) J. Exp. Med. 192, 421–432
17. Lawrence, T., Willoughby, D. A., and Gilroy, D. W. (2002) Nat. Rev. Immunol. 2, 787–795
18. Levy, B. D., Clish, C. B., Schmidt, B., Gronert, K., and Serhan, C. N. (2001) Nat. Immunol. 2, 612–619
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