INTRODUCTION

There is increasing evidence that hepoxilins are novel inflammatory mediators. In vitro studies have shown that hepoxilins cause the mobilization of intracellular calcium in human neutrophils, induce plasma leakage, and potently stimulate the chemotaxis of human neutrophils. In vivo, the hepoxilin pathway is activated in conditions with inflammation, for example, pathogen infection, psoriasis, and arthritis, and hepoxilins promote inflammatory hyperalgesia and allodynia. The "hepox" comes from hydroxy-epoxy, and the "ilin" comes from hepoxilins' activity as an insulin secretagogue (albeit an activity whose physiological significance remains unconfirmed).
Psoriasis is a common skin disorder that is characterized by hyperkeratosis, epidermal hyperplasia, T-cell and neutrophil recruitment, and changes in the vascular endothelial system. 

Pathogenic mechanisms of ichthyosis arising from environmental, infectious, and lifestyle factors. The etiology of psoriasis is thought to originate from an interplay of genetic, environmental, infectious, and lifestyle factors. The manner in which genetic and environmental factors interact to contribute to the molecular disease mechanisms has remained elusive. Upregulation of several variable lipid mediators, including the eicosanoids, in psoriatic keratinocytes was described previously, although some results were contradictory. Since hepxolin is less stable than other eicosanoids such as hydroxyeicosatetraenoic acid (HETE), the measurement of hepxolin is difficult. In this study, to clarify the relationship between hepxolin/hepxolin-related fatty acid derivatives and the development of psoriatic skin, we determined the amount of production of lipid mediators including hepxilins in plaque lesions of patients with psoriasis vulgaris (PV) and psoriatic arthritis (PsA) compared to normal controls.

## Methods

### Human skin tissues

Patients with PV and PsA were enrolled at the outpatient clinic of the Department of Dermatology, Nagoya University Hospital. Psoriatic skin was obtained from psoriatic plaque lesions in eight patients with PV or PsA (the psoriasis patient group (PPG); median age of 65.5 years; range of 57-78). Three PsA patients were included in the PPG (37.5%). The diagnoses were based on the clinical and histological findings of PV and PsA. Skin lesion severity was evaluated by using the Psoriasis Area and Severity Index (PASI), whose scores cover the range from 0 to 72. Skin samples from ten healthy individuals were used as controls (median age of 66.5 years; range of 53-86). A group of healthy control subjects was selected from individuals who had no history of psoriasis or other chronic inflammatory systemic diseases. The detailed clinical features are described in Table 1. All skin tissue samples were taken after written informed consents had been obtained. This study was approved by the Ethics Committee of the Nagoya University Graduate School of Medicine and was conducted according to the Declaration of Helsinki Principles.

### Materials for lipid analysis

Hepoxilin B_{12(10R,11S,12S)}, trioxilin B_{12}, and (10S,11S,12S)-trioxilin B_{12}, were supplied by Ono Pharmaceutical Co., Ltd., Osaka, Japan. 12-oxoETE, 12(S)-HETE, and 12(S)-HETE-d_{15} prostaglandin D_{2} (PGD_{2})-d_{4}, arachidonic acid (AA)-d_{6}, and leukotriene B_{4} (LTB_{4})-d_{4} were purchased from Cayman Chemical. Ethanol of high-performance

### Results

| Variable               | Normal | Psoriasis | P-value* |
|------------------------|--------|-----------|----------|
| Age (y)                | 10     | 8         | 0.929    |
| Male, n (%)            | 10     | 8         | 1        |
| Duration (mo)          | -      | 7         | -        |
| PASI                   | -      | 8         | -        |
| Smoking, n (%)         | 8      | 7         | 0.608    |
| Drinking, n (%)        | 8      | 7         | 0.608    |
| Hyperlipidemia, n (%)  | 10     | 8         | 0.631    |
| History of psoriatic arthritis, n (%) | - | 8 | - |

Abbreviations: PASI, Psoriasis Area and Severity Index.

Continuous variables are displayed as medians (minimum-maximum).

*P values were calculated using Wilcoxon rank-sum test for continuous variables and Fisher’s exact test for categorical variables.

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All fatty acid hydroperoxides readily give rise to epoxyalcohol derivatives, although strictly speaking, only derivatives of the arachidonic acid hydroperoxide 12S-hydroperoxycisatetraenoic acid (12S-HPETE) merit the designation of “hepxolin.” Nonetheless, all the others are regarded as hepxolin-related or hepxolin-type fatty acid derivatives. In addition, a genetic defect linked to a deficiency in hepxolin formation has been described and is believed to be responsible for the scaly skin observed in ichthyosis. Pathogenic mechanisms of ichthyosis arising from mutations in the coding regions of ALOX12, which encodes 12R-lipoxygenase (ALOX12), and ALOXE3, which encodes lipoxygenase-3 (ALOXE3), have been reported in patients with autosomal recessive congenital ichthyosis. Pathogenic mechanisms of ichthyosis arising from ALOX12B and ALOXE3 mutations are now thought to be the deficient oxidation of linoleic acids of EOS ceramides and the malformation of the corneocyte lipid envelope. In addition, both enzymes convert arachidonic acids to the corresponding hepoxilin-like epoxyalcohols, 8R-hydroxy-11R and 12R-epoxyicosatrienoic acid, via 12R-HPETE. This sequence has been hypothesized to be a part of a novel lipoxygenase (LOX) pathway in skin that plays an important role in terminal differentiation. Thus, the hepoxilins play an important role not only in inflammation but also in the regulation of proliferation and differentiation of epithelial cells, especially keratinocytes.

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*P values were calculated using Wilcoxon rank-sum test for continuous variables and Fisher’s exact test for categorical variables.
liquid chromatography (HPLC) grade was purchased from Wako Pure Chemical Industries (Osaka, Japan) or Kishida Chemical Co., Ltd. (Osaka, Japan) Acetonitrile of HPLC grade or LC/MS grade was from Wako Pure Chemical Industries. Methanol of HPLC grade or LC/MS grade was from Nacalai Tesque, Inc. (Kyoto, Japan) and Wako Pure Chemical Industries. Acetic acid of guaranteed grade or of liquid chromatography/mass spectrometry (LC/MS) grade was from Wako Pure Chemical Industries.

2.3 | Determination of epidermal concentrations of hepoxilin B₃, 12-oxoicosatetraenoic acid (oxoETE), 12(S)-HETE, (10R,11S,12S)-trioxilin B₃, and (10S,11S,12S)-trioxilin B₃

Cryogenically crushed human epidermal fragments were suspended in 500 μL of ethanol. The epidermal suspension was centrifuged at 13 800 g at 4°C for 5 minutes. The entire volume of the resultant supernatant (epidermal extract) was collected. The deuterated compound 12(S)-HETE-d₈ was used as the internal standard (IS) for the quantification of hepoxilin B₃, 12-oxoETE, 12(S)-HETE, (10R,11S,12S)-trioxilin B₃, and (10S,11S,12S)-trioxilin B₃. An appropriate amount of IS was spiked in ethanol to make solutions of 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 50, and 100 ng/mL. For the quantification of hepoxilin B₃, 100 μL of the epidermal extract was spiked with 20 μL of IS solution of a specified concentration and diluted with 100 μL of water. For the quantification of the other analytes, 50 μL of the epidermal extract was spiked with 5 μL of the IS solution of a specified concentration and diluted with 50 μL of water.

For the quantification of hepoxilin B₃, samples were analyzed using a HPLC system Nexera-X2 (Shimadzu Corp.) coupled to electrospray ionization on a triple-quadrupole mass spectrometer API 5000 (AB Sciex Pte. Ltd., Framingham, MA, USA). Chromatographic separation was achieved on a Poroshell 120 SB-C₁₈ column (2.7 μm, 2.1 × 100 mm, Agilent Technologies, Inc., Santa Clara, CA, USA) using a flow rate of 0.2 mL/min at 40°C. Two solvents were used for gradient elution: (A) 0.1% acetic acid aqueous solution and (B) acetonitrile/methanol/acetic acid (40/60/0.1, v/v/v). The gradient program was as follows: 0 minutes - 50% B; 10 minutes - 90% B.

### Table 2
Comparison of each hepoxilin and its related lipids between patients with psoriasis and normal controls

| Target         | Normal (N = 10) (10² ng/mg tissue) | Psoriasis (N = 8) (10² ng/mg tissue) | P-value* | FDR* |
|----------------|-----------------------------------|---------------------------------------|----------|------|
| Hepoxilin B₃   | 0.051 (0-2.85)                    | 1.25 (0.26-5.62)                      | 0.003    | 0.007|
| Hepoxilin A₃   | 0 (0-0)                           | 0 (0-0)                               | -        | -    |
| 12-HETE        | 0 (0-0)                           | 0 (0-0)                               | -        | -    |
| 12-HPETE       | 3.56 (0.69-39.77)                 | 19.20 (10.84-71.38)                  | 0.008    | 0.018|
| 12-KETE        | 0.031 (0-3.80)                    | 2.32 (0.31-10.03)                    | 0.002    | 0.006|
| Trioxilin B₃-1 | 0 (0-0.88)                        | 0.77 (0.6-6.52)                      | 0.017    | 0.026|
| Trioxilin B₃-2 | 0 (0-0)                           | 0.23 (0-9.40)                        | 0.015    | 0.025|
| 5R             | 0 (0-0)                           | 0 (0-2.28)                           | 0.264    | 0.281|
| 5S             | 0 (0-0)                           | 0 (0-6.00)                           | 0.104    | 0.134|
| 8R             | 0 (0-0)                           | 1.14 (0-4.36)                        | 0.015    | 0.025|
| 8S             | 0 (0-0)                           | 2.24 (0-8.70)                        | 0.015    | 0.025|
| 9R             | 0 (0-0)                           | 1.71 (0-6.48)                        | 0.015    | 0.025|
| 9S             | 0 (0-0)                           | 0 (0-0)                               | -        | -    |
| 11R            | 0 (0-4.43)                        | 1.21 (0-7.59)                        | 0.225    | 0.263|
| 11S            | 0 (0-0)                           | 0 (0-0)                               | -        | -    |
| 12R            | 0 (0-8.55)                        | 21.61 (9.53-125.78)                  | <0.001   | 0.002|
| 12S            | 8.18 (0-96.02)                    | 12.86 (6.23-34.94)                   | 0.155    | 0.185|
| 15R            | 0 (0-0)                           | 0 (0-6.00)                           | 0.104    | 0.134|
| 15S            | 5.42 (0-12.29)                    | 18.40 (6.01-116.97)                  | 0.001    | 0.005|
| HepoA₃R        | 0 (0-0)                           | 0 (0-0)                               | -        | -    |
| HepoA₃S        | 0 (0-0)                           | 0 (0-4.37)                           | 0.264    | 0.281|
| HepoB₃R        | 0 (0-0)                           | 0 (0-0)                               | -        | -    |
| HepoB₃S        | 0 (0-0)                           | 0 (0-3.81)                           | 0.104    | 0.134|

Abbreviations: HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; KETE, keto-eicosatetraenoic acid.
Data are displayed as medians (minimum-maximum).
Boldface indicates statistically significant results.
*FDR was calculated by Benjamini-Hochberg adjustment.
P values were calculated by Wilcoxon rank-sum test.
Electrospray ionization was performed in the negative ion mode with a temperature of 400°C. The ion spray voltage was set at −4500 V.

For the quantification of the other analytes, the same HPLC and mass spectrometry (MS) conditions as above were applied, except that Qtrap 5500 (AB Sciex Pte. Ltd.) was used as the mass spectrometer and the length of the Poroshell 120 SB-C18 column was 150 mm. Multi-reaction monitoring (MRM) was used for quantification of the analytes. The mass transitions (Q1/Q3, m/z), declustering potential (DP, V), and collision energy (CE, V) for hepoxilin B₃ were, respectively, 335/183, −70, and −20, those for 12-oxoETE were 317/179, −115, and −22, those for 12(S)-HETE were 319/179, −110, and −18, and those for (10R,11S,12S)-trioxilin B₃ and (10S,11S,12S)-trioxilin B₃ were 353/153, −85, and −22. For the IS, the mass transition was 327/184, and DP and CE were, 0 and −18, respectively.

### Table 3: Comparison of each lipid mediator between patients with psoriasis and normal controls

| Target                      | Normal (N = 10) (ng/mg tissue) | Psoriasis (N = 8) (ng/mg tissue) | P-value* | FDRa |
|-----------------------------|-------------------------------|----------------------------------|---------|------|
| PGE3                        | 0 (0-1611)                    | 0 (0-8980)                       | 0.832   | 0.832|
| PGE1                        | 1199.5 (125-2600)             | 0 (0-5031)                       | 0.127   | 0.156|
| Tetranor-12-HETE            | 45 (0-779)                    | 860 (267-1829)                   | 0.007   | 0.017|
| 12,13-diHOME                | 861 (559-3126)                | 1884.5 (1308-7467)               | 0.016   | 0.025|
| 9-HEOTrE                    | 67 (0-461)                    | 2883 (983-5663)                  | <0.001  | 0.002|
| 13-HEOTrE                   | 0 (0-754)                     | 3258 (1237-13 099)               | <0.001  | 0.002|
| 13(s)-HEOTrE                | 0 (0-1168)                    | 0 (0-6879)                       | 0.127   | 0.156|
| 15-HEPE                     | 893 (0-2919)                  | 4560 (2440-58 842)               | 0.001   | 0.005|
| 11-HEPE                     | 0 (0-687)                     | 1223.5 (0-4810)                  | 0.010   | 0.022|
| 12-HEPE                     | 2093.5 (263-13 297)           | 7441.5 (4036-25 127)             | 0.021   | 0.030|
| 13-HDoHE                    | 12 240 (4812-53 576)          | 523 709 (83 956-1 164 152)       | <0.001  | 0.002|
| 17-HDoHE                    | 956.5 (0-3954)                | 274 305 (31 177-5 066 353)       | <0.001  | 0.002|
| 9-oxoODE                    | 610.5 (0-5029)                | 2439 (2412-52 905)               | 0.001   | 0.005|
| 14-HDoHE                    | 1284 (424-5126)               | 4586.5 (2920-13 613)             | 0.006   | 0.015|
| 10-HDoHE                    | 0 (0-1535)                    | 2860.5 (0-8246)                  | 0.001   | 0.004|
| 11-HDoHE                    | 0 (0-4563)                    | 9940.5 (4323-27 510)             | <0.001  | 0.002|
| 12-oxoETE                   | 0 (0-22 158)                  | 11 493 (0-65 199)                | 0.015   | 0.025|
| 8-HDoHE                     | 0 (0-0)                       | 570.5 (0-2972)                   | 0.005   | 0.013|
| 15-HETrE                    | 1273 (0-3664)                 | 8109 (3083-46 134)               | 0.001   | 0.002|
| 8-HETrE                     | 428.5 (0-12 908)              | 6361 (0-47 638)                  | 0.067   | 0.094|
| 11-HEDE                     | 1050 (45-4070)                | 4480 (1654-11 272)               | 0.010   | 0.022|
| 15-HEDE                     | 0 (0-557)                     | 21 147 (1349-34 022)             | <0.001  | 0.002|
| 15-oxoEDE                   | 75 (0-243)                    | 8114 (199-166 387)               | 0.001   | 0.004|
| EPA                         | 23 484.5 (7930-49 780)        | 61 649 (20 845-254 505)          | 0.013   | 0.025|
| DHA                         | 49 010 (30 751-104 059)       | 179 498 (40 853-361 440)         | 0.016   | 0.025|
| Arachidonic acid            | 119 911 (67 807-181 169)      | 318 063.5 (81 083-632 217)       | 0.016   | 0.025|
| PGD2                        | 2915 (0-38 340)               | 723 (0-11 356)                   | 0.247   | 0.275|
| 13,14-diH-15-oxo-PGE2       | 5693.5 (0-24 275)             | 3247 (0-7965)                    | 0.247   | 0.275|
| PGA2                        | 0 (0-10 823)                  | 2296 (0-21 055)                  | 0.306   | 0.319|
| PGE2                        | 14 462 (3087-60 663)          | 8688 (1954-148 420)              | 0.722   | 0.737|

Abbreviations: DHA, docosahexaenoic acid; diHOME, dihydrometabolites; EPA, eicosapentaenoic acid; HDoHE, hydroxydocosahexaenoic acid; HETE, hydroxyeicosatetraenoic acid; HETrE, hydroxyeicosatrienoic acid; HODE, hydroxyoctadecadienoic acid; ND, not detected; PG, prostaglandin.

Data are displayed as medians (minimum-maximum).

Boldface indicates statistically significant results.

*FDR was calculated by Benjamini-Hochberg adjustment.

*P values were calculated by Wilcoxon rank-sum test.
TAKEICHI ET AL.

respectively, set at −80 and −20 for the quantification of hepxilin B₃ and at −110 and −18 for the quantification of the other analytes. The gradient program was as follows: 0 minutes - 27% B; 5 minutes - 27% B; 15 minutes - 70% B; 25 minutes - 85% B; 30 minutes - 100% B. The applied MRM parameters are described elsewhere.¹⁰

2.5 | Statistical analysis

Variables are expressed as medians (range) or n (%), and they were compared between patients and normal controls using the Wilcoxon rank-sum test and Fisher’s exact test. All P-values were two-tailed. A P-value of <0.05 was considered statistically significant. When the production of a lipid mediator was not detected, its amount was set as 0. Lipid mediators that were detected in at least one sample were subjected to further analysis. The amount of production of each lipid mediator was compared between patients and normal controls using the Wilcoxon rank-sum test. P-values for lipid mediators that were detected in at least one sample were adjusted for false discovery rate (FDR) based on the Benjamini and Hochberg method to correct for multiple testing. An FDR value of <0.05 was considered to be statistically significant. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA).

| Target | PsA (N = 3) (10² ng/mg tissue) | PsV (N = 5) (10² ng/mg tissue) | P-value* | FDR* |
|--------|------------------------------|------------------------------|----------|------|
| Hepoxilin B3 | 0.76 (0.43-1.25) | 1.34 (0.26-5.62) | 0.297 | 0.661 |
| Hepoxilin A3 | 0 (0-0) | 0 (0-0) | - | - |
| 12-HETE | 18.42 (11.91-19.99) | 32.77 (10.84-71.38) | 0.456 | 0.698 |
| 12-KETE | 0.73 (0.69-1.67) | 4.63 (0.31-10.03) | 0.180 | 0.661 |
| Trioxilin B3-1 | 0 (0-1.08) | 1.05 (0-6.52) | 0.285 | 0.661 |
| Trioxilin B3-2 | 0 (0-0.75) | 0.45 (0-9.40) | 0.427 | 0.698 |
| 5R | 0 (0-0) | 0 (0-2.28) | 0.439 | 0.698 |
| 5S | 0 (0-0) | 0 (0-6.00) | 0.242 | 0.661 |
| 8R | 0 (0-2.28) | 2.57 (0-4.36) | 0.266 | 0.661 |
| 8S | 0 (0-4.47) | 4.84 (0-8.70) | 0.266 | 0.661 |
| 9R | 0 (0-3.42) | 3.84 (0-6.48) | 0.266 | 0.661 |
| 9S | 0 (0-0) | 0 (0-0) | - | - |
| 11R | 0 (0-3.92) | 2.41 (0-7.59) | 0.427 | 0.698 |
| 11S | 0 (0-0) | 0 (0-0) | - | - |
| 12R | 13.46 (9.53-24.53) | 50.99 (13.82-125.78) | 0.101 | 0.661 |
| 12S | 11.51 (6.23-34.94) | 14.20 (6.36-18.47) | 0.882 | 0.882 |
| 15R | 0 (0-0) | 0 (0-0) | 0.242 | 0.661 |
| 15S | 15.20 (12.36-19.44) | 26.33 (6.01-116.97) | 0.297 | 0.661 |
| HepoA3R | 0 (0-0) | 0 (0-0) | - | - |
| HepoA3S | 0 (0-0) | 0 (0-4.37) | 0.439 | 0.698 |
| HepoB3R | 0 (0-0) | 0 (0-0) | - | - |
| HepoB3S | 0 (0-0) | 0 (0-3.81) | 0.242 | 0.661 |

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*P values were calculated by Wilcoxon rank-sum test.

**TABLE 4** Comparison of each hepxilin and its related lipids between patients with psoriasis and psoriatic arthritis
3 RESULTS

3.1 Hepoxilin and its related lipids in psoriatic skin

First, we measured the content of hepoxilin B3, hepoxilin A3, 12-HPTE, 12-HETE, 12-keto-eicosatetraenoic acid (KETE), and trioxilin B3 in the skin specimens collected from the PPG and 10 normal controls. In the PPG, all hepoxilins and their related lipids were more abundant than in the normal controls (Table 2). Among these lipids, we could not detect (below the limit of quantification) hepoxilin A3 or 12-HPETE in the PPG or the control group, and trioxilin B3-2(S) was only detected in the PPG (Table 2).

3.2 Each isomer of hepoxilin and HETE in psoriatic skin

Next, all of the hepoxilin and HETE contained in the skin samples were separated for each isomer, and the amount of each isomer was measured. The results are presented in Table 5. The isomers of hepoxilin and HETE were compared between psoriasis and psoriatic arthritis (PsA) using the Wilcoxon rank-sum test and the Benjamini-Hochberg adjustment for multiple comparisons. The data are displayed as medians (minimum-maximum), and the P-values were calculated by Wilcoxon rank-sum test.
3.2 | Each lipid mediator in psoriatic skin

To ascertain which pathway is important in the development of psoriatic skin, the amount of each metabolic product in arachidonic acid and eicosapentaenoic acid (EPA) systems contained in the skin samples from the PPG and the controls was measured. Median values for each lipid in skin tissues from the PPG and the controls are described in Table 3. Lipids produced in the LOX pathway were more abundant in the skin tissue from PPG than in the skin from controls, whereas the lipids produced by COX pathway tended to be less abundant in the psoriatic skin.

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3.4 | Comparison of lipid production between psoriatic arthritis and psoriasis vulgaris (psoriasis without arthritis)

Furthermore, we compared the amounts of each lipid between PsA patients and PV patients (Tables 4 and 5). Within this analysis, prostaglandins (PGs) E1, E2, and E3 extracted from lesional skin samples were more abundant for the PsA patients than for the PV patients, although statistical significance was not obtained. No significant difference was present between the two study groups in any hepoxilin derivatives or lipid mediators.

4 | DISCUSSION

To the best of our knowledge, no reports have given a comprehensive analysis of lipid mediators in psoriatic skin lesions. Most of the hepoxilins and their related lipids that were evaluated in this study tended to be more abundant in the lesional skin of the PPG than in skin from the controls (Tables 2 and 3). Hepoxilins are classified into type A and type B.2 Because of the differences in chemical stability,
hepoxilin B3 is commonly detected in tissue extracts, whereas the hepoxilin A3 may appear as the corresponding hydrolysis product, trioxilin A3. In the literature, the level of hepoxilin B3 was greatly increased in the lesional scales in psoriasis, along with the corresponding trioxilin B3. Our results are consistent with these findings. However, the previous report used extracts from scales (not skin samples from biopsy) and used the different methods (gas chromatography-mass spectrometry). These studies were performed at least two decades earlier, and the clinical features of psoriasis and the number of patients were not included in the previous report.

Interestingly, 12R-HETE was markedly increased in the skin samples of the PPG. This result is consistent with lipid analyses in previous reports. The first indication of a role for oxidized polyunsaturated fatty acids in skin biology came in the mid-1970s, when an accumulation of 12-HETE and free arachidonic acid was discovered in psoriatic epidermis. A decade later, 12-HETE in psoriatic skin lesions was shown to be mainly 12R-HETE. The synthesis of 12R-HETE in psoriasis had been thought to be induced by inflammation in the epidermis. Yet 12R-HETE itself showed only modest pro-inflammatory activity. From a current perspective, the abundance of 12R-HETE in psoriasis may merely reflect the production of free...
arachidonic acids in psoriatic lesions. Such acids are not present in normal skin but are present at the inflammation sites of psoriatic lesions. Sufficient amounts of arachidonic acid available as substrates together with the high expression of 12R-LOX may account for the excess of 12R-HETE in psoriatic epidermis. 12R-HETE is produced from arachidonic acid by the addition of a hydroxyperoxide group. This reaction is catalyzed by 12R-LOX. The amount of synthesized 12R-HETE is expected to depend on the amount of 12R-HPETE as a precursor of 12R-HETE. In this context, we speculate that the addition of a hydroxyperoxide group to arachidonic acid by 12R-LOX is abnormally upregulated in psoriatic skin lesions, resulting in the overproduction of 12R-HETE, which leads to the excessive 12R-HETE in psoriatic epidermis.

LTB₄ is a strong chemoattractant and chemoactivator of neutrophils. LTB₄ synthesis from arachidonic acid is mediated by the activity of 5-LOX together with a 5-LOX-activating protein. LTB₄ is produced from LTA₄ by LTA₄ hydrolase. 12R-HETE can also activate the LTB₄ receptor, but with less efficiency. Several LTB₄ antagonists are known, and their clinical evaluation is ongoing. In vivo, SC53228, an LTB₄ antagonist, inhibits LTB₄-induced skin inflammation in guinea pigs and counteracts inflammation induced by 12R-HETE. The compound has been selected for clinical trials for a number of diseases including psoriasis, although no clinical benefit has been reported.

In the present study, the lipids produced in the LOX pathway, including hepoxilin, were more abundant in the skin lesions for the PPG than in the skin of the normal controls. In contrast, the lipids produced by the COX pathway were decreased in the skin lesions of the PPG (Figure 1B and Table 3). From these results, the LOX pathway was more predominant than the COX pathway in the lesional skin of the PPG. Therefore, our results suggest that an imbalance between LOX and COX pathways may contribute to the pathomechanisms of psoriasis.

None of our results correlated with the PASI scores for the PPG in the present study (data not shown). The absence of correlation might be due to the fact that the severity of the psoriatic changes and the levels of inflammation at the skin biopsy sites were not directly associated with the PASI scores of the patients. In addition, various treatments which the patients had might have affected both the PASI and the levels of lipid mediators.

The clinical course of psoriasis may be complicated by the concomitant joint disease PsA in 7%-40% of patients. Although early diagnosis may lead to early treatment and benefits for PsA patients, the reliable prediction of PsA development in PV patients has not been established. Recently, a group for the research and assessment of psoriasis and psoriatic arthritis proposed serum biomarkers including interleukin-6, matrix metalloproteinase-3, and others as markers to distinguish PsA from PV. In the present study, interestingly, PGE₂ and PGE₃ were more highly expressed in the skin samples from PsA than in those from PV. Different from PGE₂, PGE₃ has anti-inflammatory effects on endothelial cells and certain subsets of leukocytes. In addition, PGE₃ may have antiproliferative and anti-inflammatory activities. In contrast,
in the case of rheumatoid arthritis, PGE$_2$ has been found in the synovial fluid and the roles of PGE$_2$ in inflammation was emphasized.$^{20}$ Perhaps the inflammation in the affected joints of patients with PsA might correlate with the production of PGE$_2$ and PGE$_3$ (Figures 2 and 3).

To ascertain whether there are any molecular differences between the psoriasis plaque lesions from PsA patients and those from PV patients, we analyzed the difference in amounts of each lipid in the two groups (Table 5). In the present study, no significant differences were found in the levels of hepoxilin derivatives and lipid mediators between the two groups, although the small sample size of our study for this analysis was a limitation of the present study. The further accumulation of samples from psoriasis cases with and without PsA is needed to confirm the molecular role of PGs in PsA.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Takuya Takeichi https://orcid.org/0000-0001-5958-2875

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