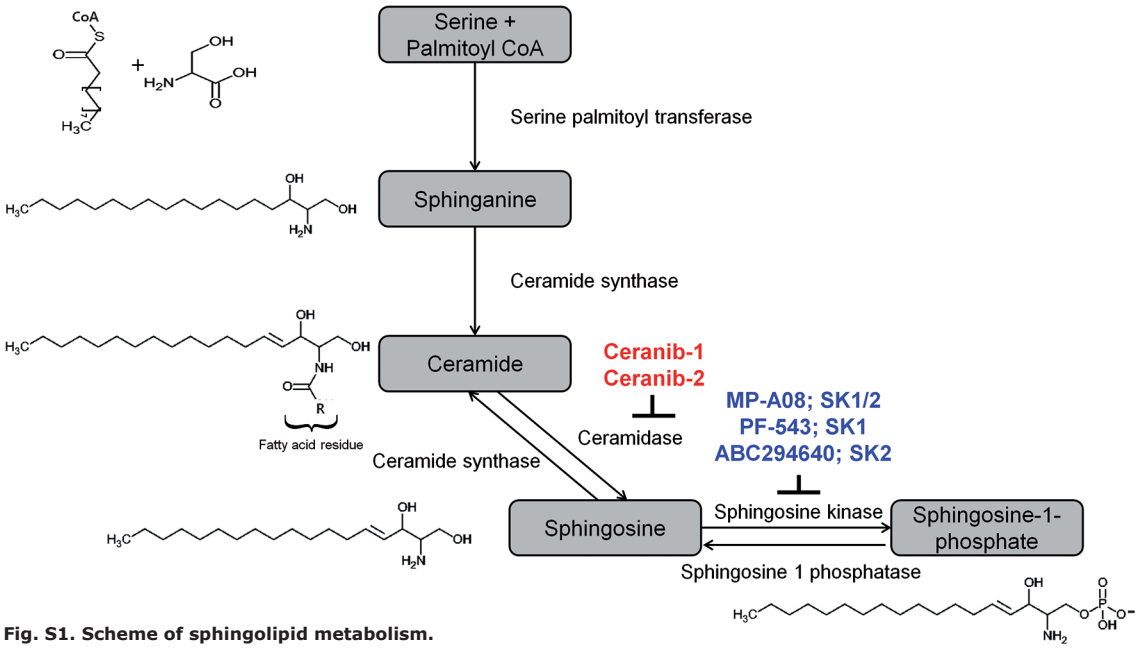

Fig. S1. Scheme of sphingolipid metabolism.

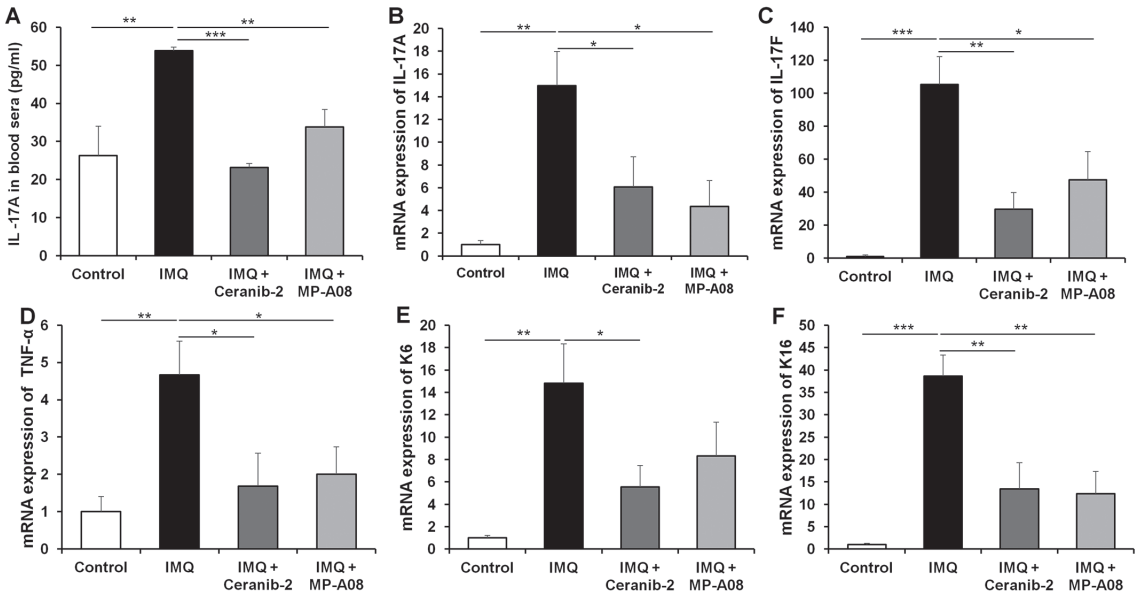

Fig. S2. Imiquimod (IMQ)-induced inflammation and keratinocyte hyperproliferation were partially normalized by Ceranib-2 or MP-A08 treatment. (A) Serum interleukin (IL)-17A levels were measured using a LEGEND MAX™ Mouse IL-17A ELISA Kit with Pre-coated Plates (BioLegend), according to the manufacturer's instructions. Real-time PCR was performed using cDNA from the skin to evaluate relative gene expression in each group, and the mRNA levels of (B) IL-17A, (C) IL-17F, (D) TNF-α, (E) keratin 6 (K6), and (F) keratin 16 (K16) were calculated and represented. Results are mean±SEM values ($n=5$). *$p<0.05$, **$p<0.01$, ***$p<0.001$.

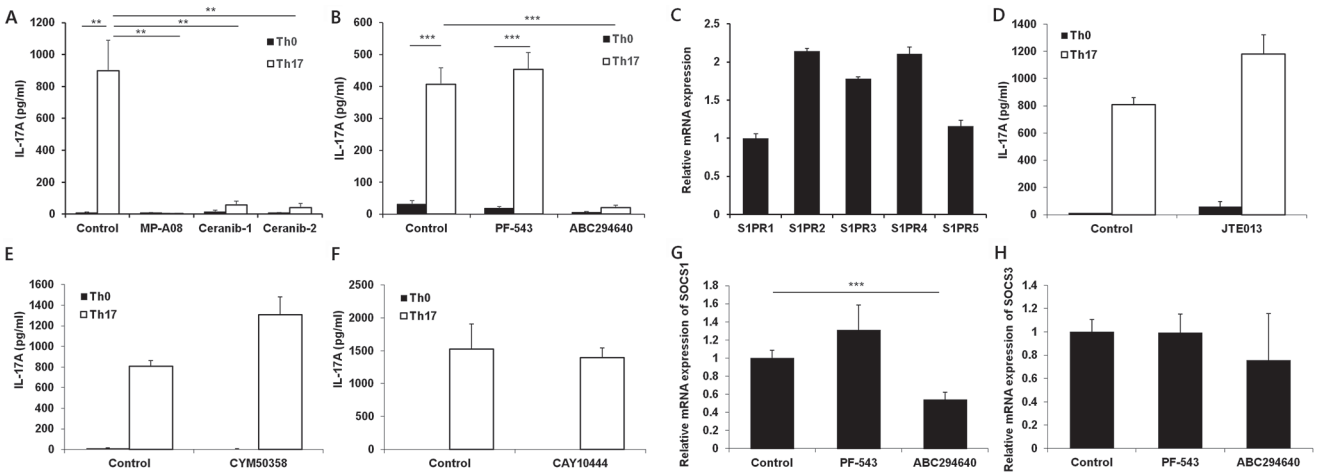

Fig. S3. T-helper 17 (Th17) differentiation of naïve CD4+ T cells was blocked by sphingosine kinase 2 inhibition. For Th17 differentiation, naïve CD4+ T cells isolated from the mouse spleen were cultured in the presence of soluble anti-CD28 (1 μg/ml), rmIL-2 (20 ng/ml), rmTGF-β (5ng/ml), rmIL-6 (25 ng/ml), and anti-IL-4 and anti-IFN-γ neutralizing antibodies (10 μg/ml) for 5 days. The cells were transferred to a new plate to incubate for 2 days and then were re-stimulated with Dynabeads Mouse T-Activator CD3/CD2 for 40 h. IL-17A levels in the supernatant were measured using an ELISA Kit (BioLegend), according to the manufacturer's instructions. IL-17A levels secreted from differentiated CD4+ T cells with chemical treatment of (A) Ceranib-1 (30 μM), Ceranib-2 (30 μM), or MP-A08 (15 μM); (B) PF-543 (30 nM) or ABC294690 (26 μM). (C) mRNA expression levels of sphingosine-1-phosphate receptors in murine naïve CD4+ T cells were examined using real-time PCR. IL-17A levels secreted from differentiated CD4+ T cells with chemical treatment of (D) JTE013 (5 μM), (E) CAY10444 (5 μM), and (F) CYM50358 (5 μM). mRNA expression levels of (G) SOCS1 and (H) SOCS3 in differentiated Th17 murine CD4+ T cells. Results are mean±SEM values ($n=6$). $^{**}p<0.01$, $^{***}p<0.001$.

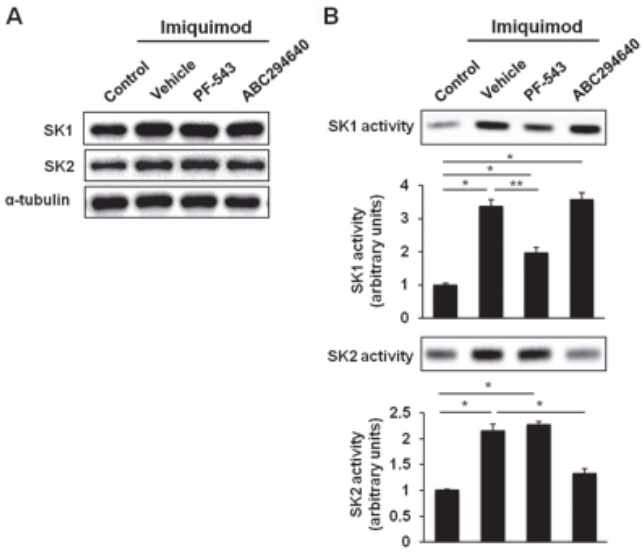

Fig. S4. PF-543 and ABC294640 selectively inhibit SK1 and SK2 activity, respectively. C57BL/6 mice were treated once daily with imiquimod (IMQ) cream or control vehicle cream applied to the shaved back for 6 consecutive days. Once daily MP-543 (a SK1 inhibitor) and ABC294640 (a SK2 inhibitor) application began at 3 days before application of IMQ cream and maintained during IMQ treatment. (A) Representative western blot analysis of SK1 and SK2 levels were examined using skin samples. (B) Skin SK1 and SK2 enzyme activities were measured ($n = 5$). Results are mean ± SEM ($n = 5$). *$p < 0.05$, **$p < 0.01$. The images are representative of 3 independent experiments.

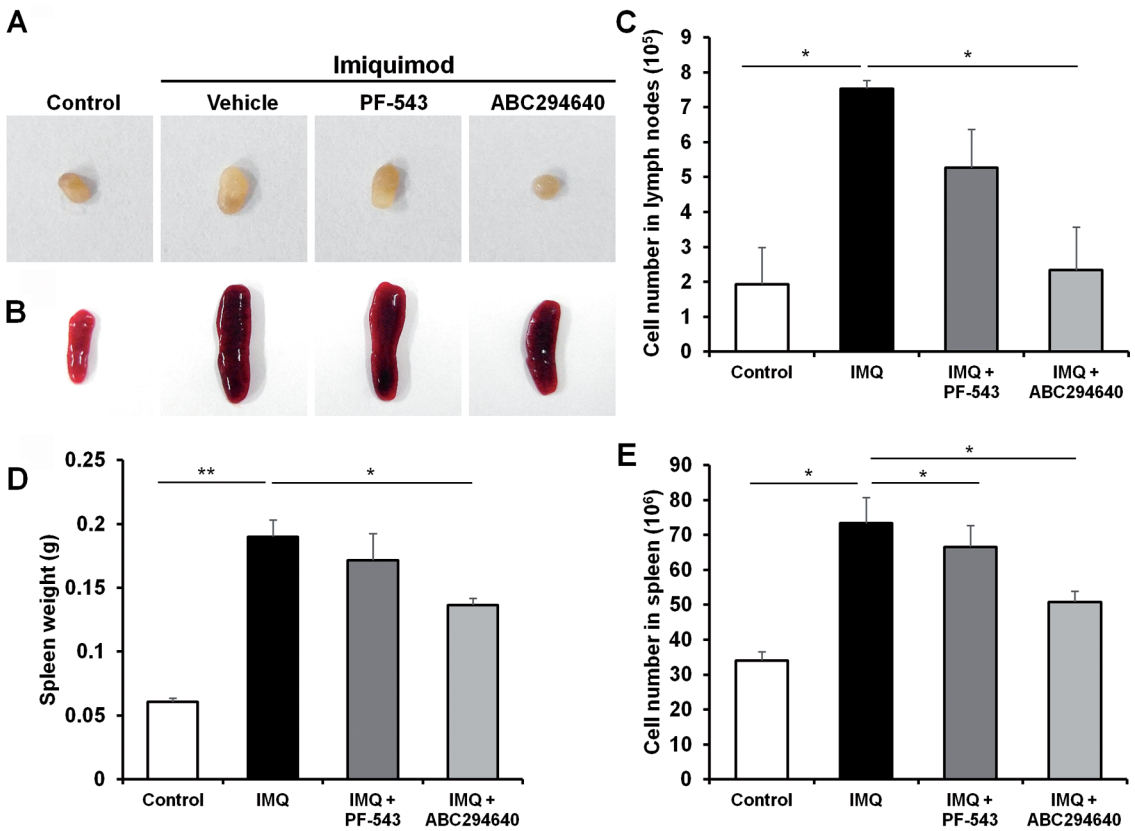

Fig. S5. SK2 inhibition reduces the enlargement of lymphoid organs upon imiquimod (IMQ) treatment. Gross morphological examination of (A) inguinal lymph nodes and (B) spleens. (C) Total cell numbers in the inguinal lymph nodes were counted for each group. (D) Spleen weights and (E) total spleen cell numbers were examined. Results are mean ± SEM values ($n = 5$). *$p < 0.05$, **$p < 0.01$.

Table SI. Primers used for real-time PCR

Gene	Primer sequence (5'-3')	Reference
IL-17A	F: ATCAGGACGCGCAAACATGA	39
	R: TTGGACACGCTGAGCTTTGA	
IL-17F	F: GTCGCCATTCAGCAAGAAAT	
	R: GGTGCAGCCAACTTTTAGGA	
TNF-α	F: GCAAGCTTCGCTCTTCTGTCTACTGAACTT	
	R: GCTCTAGAATGAGATAGCAAATCGGCTGAC	
K6	F: CTGGTAGTGGCTTTGGCTTC	
	R: AGGCTCTGGTTGATGGTGAC	
K16	F: GGTGGCCTCTAACAGTGATCT	40
	R: TGCATACAGTATCTGCCTTTGG	
Gapdh	F: CACTCTTCCACCTTCGATGC	41
	R: CCCTGTTGCTGTAGCCGTAT	
SOCS1	F: CCTCCTCGTCCTCGTCTTC	42
	R: AAGGTGCGGAAGTGAGTGTC	
SOCS3	F: AGCTCCAAAAGCGAGTACCA	43
	R: AGCTGTCGCGGATAAGAAAG	
S1PR1	F: CTGTTAGATGTGGGCTGCAA	44
	R: ATGATGGGGTTGGTACCTGA	
S1PR2	F: TCAGGGCATGTCACTCTGTC	
	R: ATGGCCAGGAGGCTAAAGAC	
S1PR3	F: TGCTGGCTAATTGCCTTCTC	
	R: TGGAGTAGAGGGGCAAGATG	
S1PR4	F: CTCCAAGGGCTATGTGCTCT	44
	R: ATTGGCTCGGACCACTCTAA	
S1PR5	F: ACAACTACACCGGCAAGCTC	45
	R: AGCACAATGAAGGCACACAC	