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Sphingosine kinase-1/sphingosine-1-phosphate receptor type 1 signalling axis is induced by transforming growth factor-β1 and stimulates cell migration in RAW264.7 macrophages

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ABSTRACT

Macrophage recruitment to sites of inflammation is an essential step in host defense. However, the signals regulating the mobilization of these cells are still not fully understood. Sphingosine-1-phosphate (S1P), a pleiotropic bioactive lipid mediator, is known to regulate an array of biological activities in various cell types. Here, we investigated the roles of S1P and S1P receptors (S1PRs) in macrophage migration *in vitro*. Furthermore, we explored the cross-talk between transforming growth factor-β1 (TGF-β1) and S1P signalling pathways in this process. We found that S1P exerted a powerful migratory action on RAW264.7 macrophages, as determined in Boyden chambers. Moreover, by employing RNA interference technology and pharmacological tools, we have demonstrated that S1PR1, but not S1PR2 and S1PR3, is required for S1P-induced macrophage migration. Importantly, we observed a pronounced increase in sphingosine kinase-1 (SphK1) mRNA expression and subsequently increase in S1P production, following transforming growth factor-β1 (TGF-β1) stimulation in RAW264.7 macrophages. The expression of S1PR1, but not S1PR2 and S1PR3, was also significantly up-regulated after TGF-β1 stimulation. Interestingly, exogenously added S1P-induced up-regulation of SphK1 and the synthesis of additional S1P, suggesting a self-amplifying loop of S1P to enhance macrophage migration. In conclusion, our results reveal that SphK1/S1PR1 signalling axis is induced by TGF-β1 and stimulates cell migration in RAW 264.7 macrophages. This study provides new clues for the molecular mechanisms of macrophage recruitment during inflammation.

1. Introduction

Macrophages are versatile hematopoietic cells that fulfill manifold tasks in the immune system, including the initiation of inflammatory responses, execution of phagocytosis and pathogen killing, and facilitation of adaptive immunity [1]. In response to inflammatory signals, macrophages migrate and accumulate at the sites of inflammation. A multifaceted signalling cascade initiated by the inflammatory stimuli leads to macrophage activation and production of a vast array of pro-inflammatory cytokines and chemokines. Macrophages are the main phagocyte subtype participating in innate immune system, and their recruitment from the blood to sites of inflammation is a crucial process for macrophages to recognize and eliminate the host harmful microorganisms. Macrophages mediate immune responses, performing pro-inflammatory and anti-inflammatory roles by secreting cytokines and lipid mediators. They play diverse roles in host defense and in maintenance of homeostasis, and excessive or prolonged influx of effector cells can lead to tissue destruction and dysfunction. It has been documented that deficient phagocyte recruitment gives rise to chronic mucosal inflammation, but once disease is established, chronic stimulation of the immune system including overactivation of monocytes/macrophages, perpetuates and maintains disease activity [2,3]. Therefore, the role of macrophages in inflammation is complex. The mobilization of macrophages is tightly regulated during inflammation.

Among the chemokines and inflammatory mediators known to exert potent cellular chemotactic effects, the bioactive sphingolipid metabolite sphingosine-1-phosphate (S1P) is a very good candidate for the induction of cell motility [4]. Our recent reports also provided further evidence for S1P-induced cell migration in bone

Abbreviations: SphK1, sphingosine kinase-1; SphK2, sphingosine kinase-2; S1P, sphingosine-1-phosphate; S1PR1–5, S1P receptor type 1–5; S1PRs, S1P receptors; TGF-β1, transforming growth factor-β1; siRNA, small interfering RNA.

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marrow-derived cells [5,6], hepatic stellate cells [7] and hepatic myofibroblasts [8]. The S1P level is determined by the balance between its formation, mediated by two sphingosine kinase (SphK) isoenzymes, SphK1 and SphK2, and its degradation, catalyzed by S1P lyase and S1P phosphatase. SphK1 is slightly more efficient than SphK2 in phosphorylating their primary intracellular substrate, sphingosine, whereas SphK2 is significantly more efficient toward unnatural substrates such as the immunomodulatory drug FTY720 [9]. Activation of SphK by numerous external stimuli increases S1P levels, which in turn can act in an autocrine or paracrine manner. Most of the characterized actions of S1P are mediated by a family of five specific G protein-coupled receptors named S1P receptor (S1PR) type 1–5 (S1PR1–5) [10]. The functional response of each cell to S1P varies depending on its S1PR repertoire. S1PR1, S1PR2 and S1PR3 are specifically involved in S1P-induced cell motility [4]. Although S1P is known to regulate the egress of lymphocytes from the lymphoid organs [11,12], the roles of S1P and S1PRs in macrophage migration are not fully understood.

In the present study, we characterized the role of SphK/S1P/S1PRs signalling axis in macrophage migration, and investigated the cross-talk between transforming growth factor-β1 (TGF-β1) and S1P signalling pathways in this process. Understanding the pathophysiological role of SphK/S1P/S1PRs will potentially provide new therapies to control a variety of inflammatory diseases.

2. Materials and methods

2.1. Materials

Dulbecco's modified eagle's medium (DMEM) was from Invitrogen (Grand Island, NY). Fetal bovine serum (FBS) was from Biochrom (Berlin, Germany). Polymerase chain reaction (PCR) reagents were from Applied Biosystems (Foster City, CA). S1P was from Biomol (Plymouth Meeting, PA). The specific S1PR1/3 antagonist VPC23019 and S1PR1 antagonist W146 were from Avanti Polar Lipids (Alabaster, AL). The specific S1PR2 antagonist (JTE-013) was from Cayman Chemical (Ann Arbor, MI). Recombinant human TGF-β1 was obtained from PeproTech (Rocky Hill, NJ). Bovine serum albumin (BSA) and other common reagents were from Sigma (St. Louis, MO).

2.2. Cell culture

RAW264.7 macrophages were obtained from the American Type Culture Collection (ATCC, Rockville, MD), and grown in DMEM supplemented with 10% FBS, 2 mM L-glutamine, 100 U/ml penicillin, and 100 μg/ml streptomycin at 37 °C in a humidified 5% CO_2 and 95% air.

2.3. Migration assay

Cell migration was determined in Boyden chambers as described previously [6] with minor modifications. In brief, RAW264.7 macrophages (2×10^5) suspended in 200 μl of serum-free DMEM were placed in the top well of the migration chamber and separated from chemoattractants in the bottom well by a filter with 5 μm pores. The chambers were incubated for 12 h at 37 °C in 5% CO_2. Migrated cells, which remained attached to the lower face of the porous membrane, were fixed with methanol for 1 h, and stained with Hematein for 30 min. Unmigrated cells on the upper membrane surface were removed with a cotton swab. The migration was quantified by analyzing at least 6 random fields per filter for each independent experiment.

2.4. RNA interference

The siRNA sequence targeting specifically mouse S1PR1–3 (L-051684-00, L-063765-00, L-040959-00) was synthesized by Dharmacon (Lafayette, CO). Forty to fifty percent confluent RAW264.7 cells were prepared. Transfection of siRNA was performed using Lipofectamine RNAiMAX (Invitrogen) according to the manufacturer's instructions. Control cells were treated with 40 nM RNAi Negative Control Duplexes (scramble siRNA). After 48 h cells were used to perform migration assay.

2.5. Measurement of S1P by high-performance liquid chromatography (HPLC) analysis

Serum-starved RAW264.7 cells were treated with TGF-β1 (5 ng/mL) or S1P (100 nM), and lipid was extracted from cells containing the culture medium. For S1P stimulation as control, we divided it into two parts: cells were incubated for 12 h in medium with vehicle; 100 nM S1P in medium without cells were incubated for 12 h in another culture plate, pooled them together, then lipid was extracted. Extraction and analysis of lipids were carried out as described previously [7].

2.6. Real-time RT-PCR

Total RNA was extracted from RAW264.7 cells using RNeasy kit (Qiagen, Hilden, Germany). Real-time RT-PCR was performed as described previously [5]. Primers were as follows: Mouse S1PR1: sense, 5′-ACT TTG CGA GTG AGC TG-3′; antisense, 5′-AGT GAG CAT GTT ACA GC-3′. S1PR2: sense, 5′-TTC TGG AGG GTA ACA CAG TGG T-3′; antisense, 5′-ACA CCC TTT GTA TCA AGT GGC A-3′. S1PR3: sense, 5′-TGG TGT GCG GCT GTC TAG TCA A-3′; antisense, 5′-CAC AGC AAG CAG ACC TCC AGA-3′. SphK1: sense, 5′-TGT CAC CCA TGA ACC TGC TGT CCC TGC ACA-3′; anti-sense, 5′-AGA AGG CAC TGG CTC CAG AGG AAC AAG-3′. SphK2: sense, 5′-ACA GAA CCA TGC CCG TGA G-3′; anti-sense, 5′-AGG TCA ACA CCG ACA ACC TG-3′.18S rRNA: sense, 5′-GTA ACC CGT TGA ACC CCA TT-3′; antisense, 5′-CCA TCC AAT CGG TAG TAG CG-3′. Probes (Applied Biosystems) used for real-time RT-PCR were as follows: S1P phosphatase: MA00473016, and S1P lyase: MA00486079.

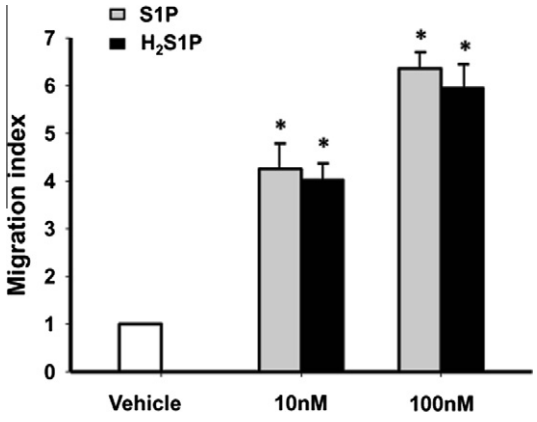

Fig. 1. S1P-induced cell migration in RAW264.7 macrophages via its specific receptors. Serum-starved RAW264.7 macrophages were allowed to migration for 12 h in the presence of varying concentrations of S1P and H_2S1P as indicated. Stock solutions of S1P and H_2S1P were dissolved in methanol at −80 °C. Dilutions of S1P and H_2S1P were freshly prepared after evaporation of methanol by resuspension in 0.4% fatty acid-free BSA and sonication. Data are presented as the mean ± SEM. $^*P < 0.05$, compared with control. BSA, bovine serum albumin; S1P, sphingosine-1-phosphate.

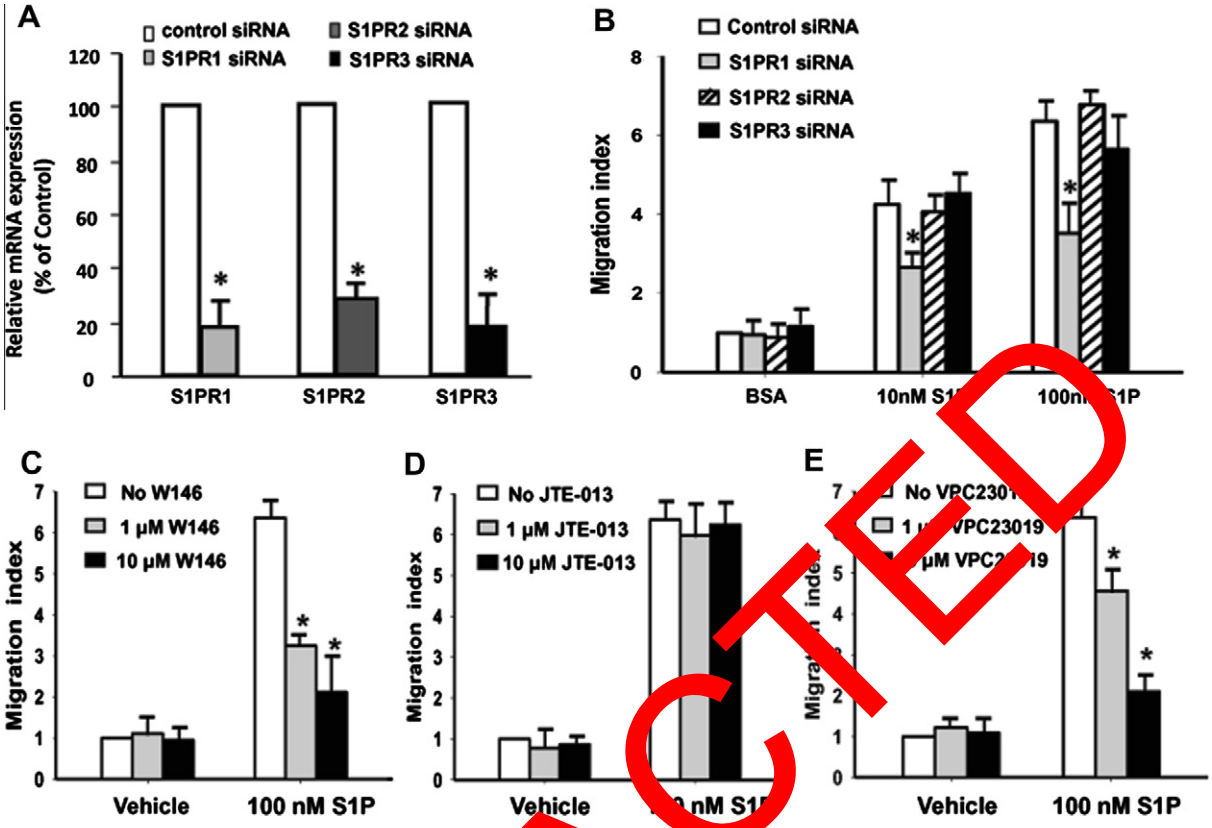

Fig. 2. Effect of S1PR1, S1PR2 and S1PR3 on S1P-induced migration of RAW264.7 macrophages. (A) Cells were transfected with control siRNA or with S1PR1-siRNA, S1PR2-siRNA or S1PR3-siRNA for 48 h. Then S1PR1, S1PR2 or S1PR3 mRNA was evaluated by real-time RT-PCR. (B) Effect of silencing S1PR1, S1PR2 or S1PR3 expression on RAW264.7 macrophage migration in response to S1P. (C-E) Effect of S1PRs antagonists on S1P-induced macrophage migration. Serum-starved cells were pretreated for 1 h with or without S1PR1 antagonist W146 (C), S1PR2 antagonist JTE-013 (D), S1PR1/3 antagonist VPC23019 (E). Pretreated cells were then allowed to migration in the presence of S1P. Data are presented as the mean ± SEM. $^*P < 0.05$, compared with control. S1PR1, 2 and 3, S1P receptor type 1–3; siRNA, small interfering RNA.

2.7. Statistical analysis

The results are expressed as mean ± SEM. Statistical significance was determined by Student's *t*-test. A *P* value of less than 0.05 was considered significant.

3. Results

3.1. S1P induces RAW264.7 macrophage migration via its specific receptors

To test the effect of S1P on macrophage migration, a transwell migration assay was performed in the murine monocyte/macrophage cell line RAW264.7. As shown in Fig. 1, S1P (1–100 nM) exerted a powerful dose-dependent migratory action. To determine whether S1P triggers cell migration in RAW264.7 macrophages via the cell surface receptors, we performed the same experiments using H_2S1P, a structural analog of S1P. H_2S1P is only able to mediate its effects through a surface bound S1PRs [13]. As shown in Fig. 1, the effect of S1P on RAW264.7 macrophage migration was completely mimicked by H_2S1P, suggesting that S1P induced cell migration via activation of plasma membrane S1PRs.

3.2. S1PR1 is required for RAW264.7 macrophage migration toward S1P

Next, we examined the S1PR subtype implicated in the stimulation on migration exerted by S1P in RAW264.7 macrophages. For this purpose, small interfering RNA (siRNA) was used to knock-down S1PR1, S1PR2 or S1PR3 expression. As it can be observed in Fig. 2A, transfection of RAW264.7 macrophages with S1PR1-, S1PR2- or S1PR3-siRNA decreased its expression by 83%, 76% and 84%, respectively. S1PR1-, S1PR2- or S1PR3-targeted siRNA did not alter expression of other S1PRs, which confirmed the specificity of these siRNA (data not shown). Furthermore, silencing of S1PR1 expression by siRNA markedly lessened the migratory effect exerted by S1P, but there was no change in migratory action with S1PR2- or S1PR3-siRNA treatment (Fig. 2B). These results indicated that S1PR1, but not S1PR2 and S1PR3, contributed positively to S1P-induced migration of RAW264.7 macrophages.

To further confirm the involvement of S1PR1 in the stimulation of cell migration, the selective S1PR antagonists were employed. As shown in Fig. 2C–E, S1P-induced migration of RAW264.7 macrophages was completely blocked by W146 (an S1PR1 antagonist) or VPC23019 (an S1PR1/3 antagonist), in a concentration-dependent manner. However, pretreatment with JTE-013 (S1PR2 antagonist) did not alter S1P-induced macrophage migration. In addition, treatment with W146, JTE-013, or VPC23019 alone had no effect on RAW264.7 macrophage migration.

Taken together, these results demonstrate that S1PR1, but not S1PR2 and S1PR3, is responsible for S1P-induced cell migration in RAW264.7 macrophages.

3.3. SphK1/S1P is up-regulated by TGF-β1 in RAW264.7 macrophages

TGF-β1, a multifunctional cytokine, is shown to interact with the S1P system in many cell types [14], however, cross-talk between TGF-β1 and S1P in macrophages remains unknown. Real-time RT-PCR analysis revealed a pronounced increase in SphK1

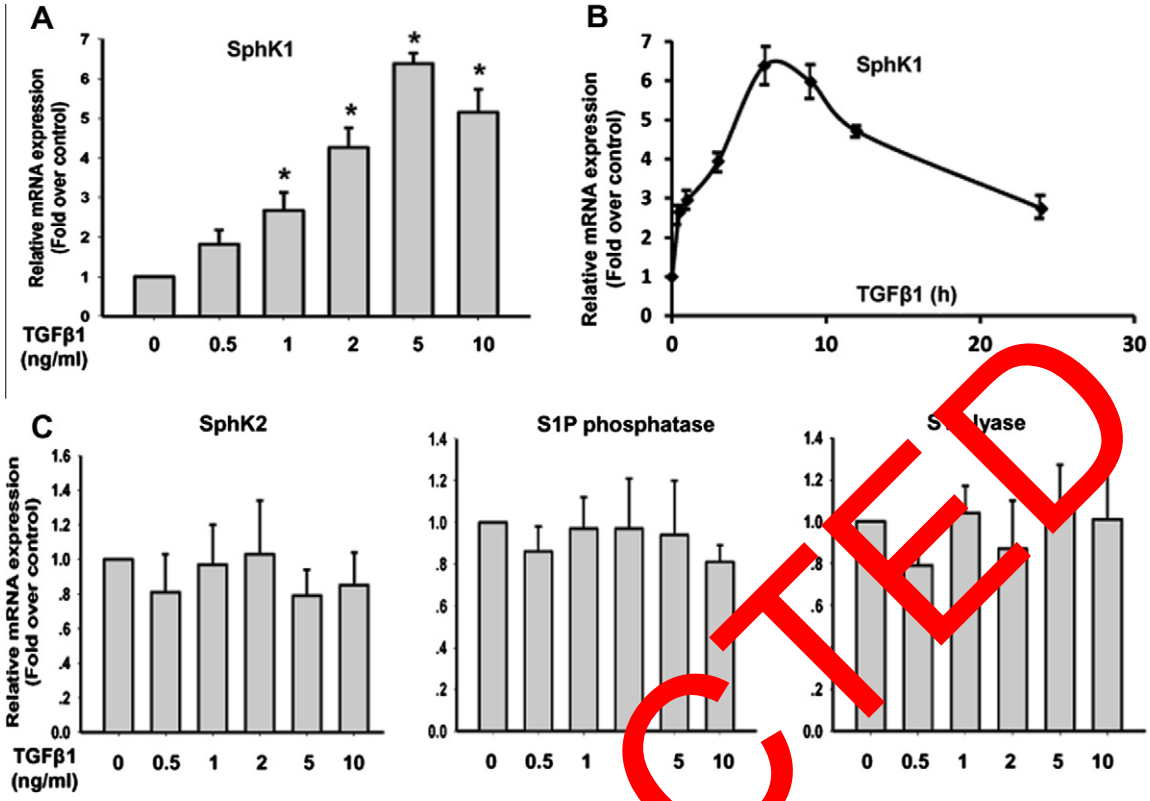

Fig. 3. Expression of enzymes involved in determining S1P abundance in RAW264.7 macrophages following TGF-β1 stimulation. (A) SphK1 mRNA expression in RAW264.7 macrophages was evaluated by real-time RT-PCR, following TGF-β1 stimulation at the indicated concentrations for 6 h. (B) SphK1 mRNA expression in RAW264.7 macrophages following 5 ng/mL TGF-β1 stimulation for different periods. (C) The mRNA levels of SphK2, S1P phosphatase, and S1P lyase in RAW264.7 macrophages following varying concentration of TGF-β1 stimulation as indicated. Data are presented as the mean ± SEM. $^{*}P < 0.05$, compared with control. SphK1, sphingosine kinase-1; SphK2, sphingosine kinase-2.

mRNA expression stimulated by TGF-β1 in a dose dependent manner, with a maximal increase at a concentration of 5 ng/mL at 6 h (Fig. 3A and B). In contrast, the expression levels of SphK2, S1P phosphatase, and S1P lyase were not affected by TGF-β1 treatment (Fig. 3C). Furthermore, we determined whether TGF-β1 stimulation resulted in corresponding increases of S1P in macrophages. S1P levels were tested by HPLC in confluent serum-starved cells treated with TGF-β1 for 6 or 12 h. As shown in Fig. 4A, S1P levels in RAW264.7 macrophages and their supernatants were significantly increased following treatment with 5 ng/mL TGF-β1. These results demonstrated that the increase of S1P levels in RAW264.7 macrophages results from up-regulation of SphK1 expression, but not inhibition of the S1P-degrading enzymes, S1P phosphatase and S1P lyase.

Intriguingly, exogenously added S1P-induced significant up-regulation of SphK1 mRNA expression (Fig. 4B) and the synthesis of additional S1P in RAW264.7 macrophages (Fig. 4C). These data suggested a self-amplifying loop of S1P with the potential capacity to enhance cell migration.

3.4. TGF-β1 strongly modulates S1PRs expression in RAW264.7 macrophages

To gain further insight into the involvement of S1PRs in the actions stated above, we assessed the change of S1PRs expression pattern in RAW264.7 macrophages with TGF-β1 stimulation. Quantitative analysis of S1PRs expression performed by real-time RT-PCR indicated that TGF-β1 strongly modified S1PRs expression. In particular, it significantly increased S1PR1, but unaltered S1PR2 and S1PR3 mRNA expression (Fig. 4D). These results revealed that TGF-β1 not only induced SphK1/S1P signalling as mentioned above, but also up-regulated S1PR1 expression in RAW264.7 macrophages.

4. Discussion

S1P is a pleiotropic bioactive lipid mediator that exerts an array of biological activities, including cell migration, survival and differentiation in various cell types [15]. Moreover, S1P is now recognized as a critical regulator of many physiological and pathophysiological process, including cancer, inflammation, diabetes, atherosclerosis and osteoporosis [10]. More recently, data from other groups as well as our own have shown that S1P acted on several types of target cells and was engaged in pro-fibrotic process through multiple mechanisms [5,6,8,16]. In this study, we describe an additional function regulated by SphK1/S1P/S1PR1 signalling axis involving the initiation of immune response. By employing RNA interference technology and pharmacological tools, we have demonstrated that S1PR1 play an important role in S1P-induced cell migration in murine monocyte/macrophage cell line RAW264.7.

Most of the known actions of S1P are mediated by S1PRs. The coupling of these receptors to different G proteins explains their differential signal transduction properties and also the varied cellular effects of S1P. In particular, S1P receptor coupling to Gi leads to activation of Rac and cell migration, while coupling to G12/13 leads to inhibition of Rac and cell migration [17]. Indeed, S1PR1 and S1PR2 have opposing effects on cell migration. S1PR1 is a Gi-coupled receptor that stimulates migration in mouse embryonic fibroblasts [18] and lymphocytes [12]. In contrast, S1PR2, coupled more strongly to G12/13, is known to inhibit migration in other cell

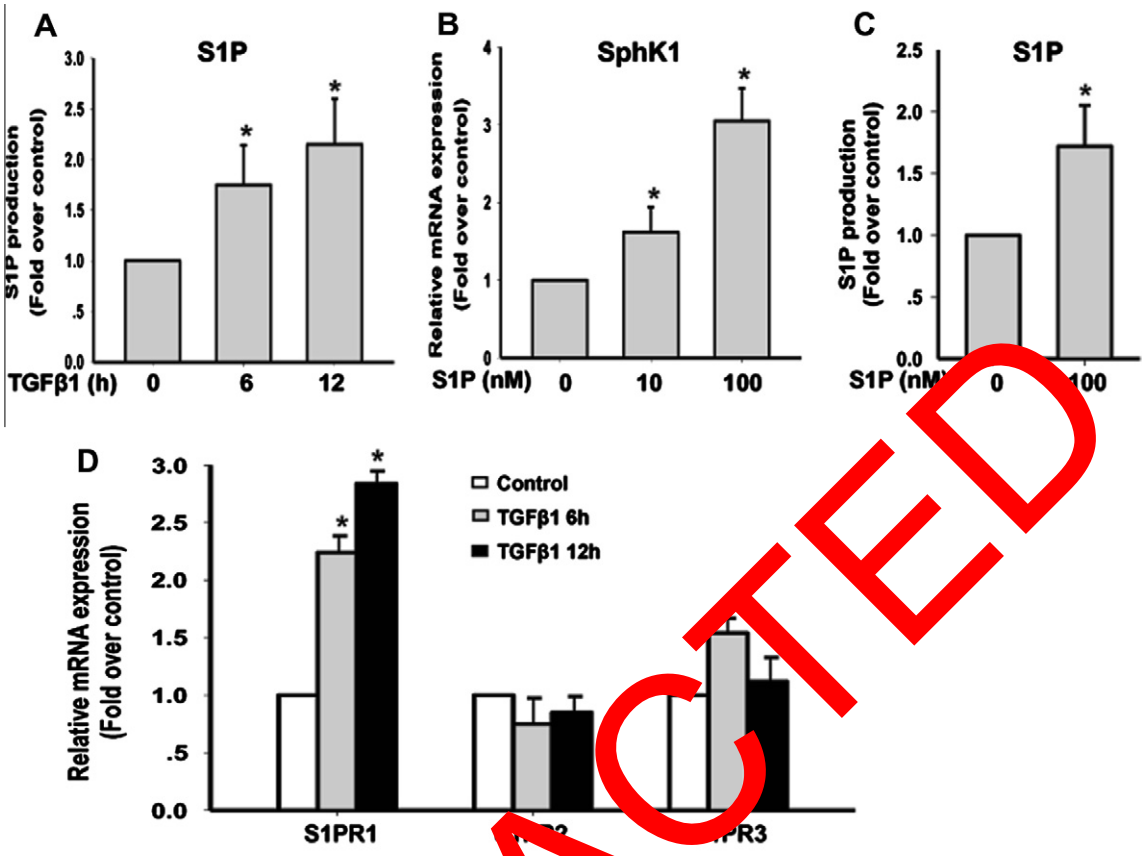

Fig. 4. S1P/S1PR1 was induced by TGF-β1 stimulation in RAW264.7 macrophages. (A) TGF-β1 (5 ng/mL)-induced S1P production, as measured by HPLC analysis. (B) S1P-induced up-regulation of SphK1 expression. (C) S1P-induced S1P production. (D) Modulation of S1PRs expression in RAW264.7 macrophages with TGF-β1 (5 ng/mL) stimulation. Data are presented as the mean ± SEM. $^{*}P < 0.05$, compared with control.

types, like vascular smooth muscle cells [1] and fibroblasts cells [20]. Our previous studies also demonstrated S1PR1/3-mediated stimulatory and S1PR2-mediated inhibitory signalling in S1P-induced migration of LX-2 cells [7] and human hepatic fibroblasts [8]. Here, we observed that S1PR1, but not S1PR2 and S1PR3, was required for S1P-indcued migration in RAW264.7 macrophages. Our finding is in agreement with the previous reports in other innate immune cells, like lymphocytes [19–21]. Their findings confirmed that S1P promoted T and B cell egress from lymphoid organs by acting on S1PR1 [12,21]. However, there are also reports of S1P lacking a chemotactic effect in mouse bone marrow-derived macrophages but inhibiting cell migration toward CXCL12 and C5a via S1PR2 [22]. In addition, Xu et al. recently reported that S1PR3 promoted recruitment of monocyte/macrophages in inflammation and atherosclerosis [23]. Such differences are probably due to the different tissue sources of the used macrophages as well as their different activation states and different S1PRs expression pattern. Therefore, a further insight into the mechanistic details of S1P/S1PRs signalling axis is necessary to understand macrophage migration *in vitro* and *in vivo*.

The S1P level in tissue is normally low, and it is significantly increased under pathologic conditions such as tissue injury and inflammation [10]. Importantly, recent several reports have demonstrated that S1P has multiple cross-talks with other cytokines, particularly TGF-β1 in a variety of cell types, including fibroblasts, myoblasts, and cancer cells [14,24–27]. Our recent findings indicated that SphK1/S1P/S1PR signalling axis was required for TGF-β1-induced differentiation of bone marrow-derived mesenchymal stem cells into myofibroblasts [28]. In this study, we also observed a pronounced increase in SphK1 mRNA level and subsequently increase in S1P production, following TGF-β1 stimulation in RAW264.7 macrophages. Another important finding of this study was that TGF-β1 modified S1PR expression pattern. The expression of S1PR1 was up-regulated by TGF-β1 stimulation, which coincided with the role of S1PR1 in macrophage migration. Further work is needed to elucidate the possible signals of S1P/S1PR-mediated transactivation of TGF-β1 signalling pathway. These cross-talks may give rise to a feed-forward, amplifying loop between S1P and TGF-β1 in stimulating cell migration.

Intriguingly, exogenous S1P treatment increased SphK1 expression and additional S1P production in RAW264.7 macrophages. Our findings are in agreement with the previous studies performed in other cell types, such as human hepatic stellate cell line, LX-2 cells [7] and HeLa cells or MEL-7 cells [29]. These studies suggest a self-amplifying loop of autocrine S1P with the potential capacity to enhance biological activities.

In summary, our results unravel an important role of SphK1/S1PR1 signalling axis in macrophage migration. Importantly, we have identified the unique ability of TGF-β1 to exploit S1P signalling to stimulate macrophage migration, by altering SphK1 and S1PR expression pattern. Moreover, our data suggest a self-amplifying loop of S1P to enhance cell migration. These findings may provide new clues for the molecular mechanisms of macrophage recruitment *in vivo*.

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