Biochemical and Biophysical Research Communications 454 (2014) 245–250

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Disruption of TGF-β signaling in smooth muscle cell prevents flow-induced vascular remodeling

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ARTICLE INFO

Article history:
Received 16 October 2014
Available online 24 October 2014

Keywords:
Vascular remodeling
TGF-β
Smooth muscle cell
Carotid

ABSTRACT

Transforming growth factor-β (TGF-β) signaling has been prominently implicated in the pathogenesis of vascular remodeling, especially the initiation and progression of flow-induced vascular remodeling. Smooth muscle cells (SMCs) are the principal resident cells in arterial wall and are critical for arterial remodeling. However, the role of TGF-β signaling in SMC for flow-induced vascular remodeling remains unknown. Therefore, the goal of our study was to determine the effect of TGF-β pathway in SMC for vascular remodeling, by using a genetical smooth muscle-specific (SM-specific) TGF-β type II receptor (Tgfbr2) deletion mice model. Mice deficient in the expression of Tgfbr2 (MyhCre.Tgfbr2$^{f/f}$) and their corresponding wild-type background mice (MyhCre.Tgfbr2$^{WT/WT}$) underwent partial ligation of left common carotid artery for 1, 2, or 4 weeks. Then the carotid arteries were harvested and indicated that the disruption of Tgfbr2 in SMC provided prominent inhibition of vascular remodeling. And the thickening of carotid media, proliferation of SMC, infiltration of macrophage, and expression of matrix metalloproteinase (MMP) were all significantly attenuated in Tgfbr2 disruption mice. Our study demonstrated, for the first time, that the TGF-β signaling in SMC plays an essential role in flow-induced vascular remodeling and disruption can prevent this process.

1. Introduction

Vascular remodeling is a complicated pathophysiological process that prominently implicated in many clinical manifestations of cardiovascular diseases [1,2]. Media thickening and macrophage infiltration are the major structural events that may lead to lumen narrowing in many clinical cardiovascular diseases [3,4]. The changes of wall mass and geometry both require macrophage infiltration, SMC proliferation, and extracellular matrix (ECM) deposition [5,6]. Understanding the pathogenesis of vascular remodeling is therefore likely to have significant therapeutic implications.

TGF-β signaling has been prominently implicated in many aspects of cellular activities with respect to vascular remodeling [7–9]. Under defined circumstances, TGF-β signaling regulates SMC proliferation and apoptosis [10–12], cellular differentiation and activation [13,14], vascular inflammation [15–18], and MMP-dependent proteolysis [19], all of these are significantly implicated in the pathogenesis of vascular remodeling [20–22].

SMCs are the major resident cells in artery, and are essential in maintaining the normal vascular structure, via controlled proliferation and by secreting a dynamic ECM [5,6,23,24]. Furthermore, SMC-derived cytokines are critical for activating and recruiting macrophages in the initiation and progression of vascular remodeling [20,25,26].

However, as a critical factor for vascular remodeling, the role of TGF-β signaling in SMC remains unknown. Therefore, the goal of our study was to determine the effect of TGF-β signaling in SMC for the pathogenesis of vascular remodeling.

Abbreviations: TGF-β, transforming growth factor-β; MMP, matrix metalloproteinase; SMC, smooth muscle cell; Tgfbr2, TGF-β type II receptor; MCP1, monocyte chemoattractant protein 1; MIP1α, macrophage inflammatory protein 1α; SM, smooth muscle; ECM, extracellular matrix; LCA, left carotid artery.

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http://dx.doi.org/10.1016/j.bbrc.2014.10.092
0006-291X/

2. Methods

2.1. Mice

The conditional SM-specific Tgfbr2-disruption mice with a C57BL/6 background were generously provided by George Tellides (Yale University School of Medicine, New Haven, CT). All male mice (MyhCre.Tgfbr2$^{f/f}$ and MyhCre.Tgfbr2$^{WT/WT}$) were treated by tamoxifen (Sigma–Aldrich, USA) at 1 mg/d i.p. for 5 consecutive days starting at 5 weeks of age. These mice have been used in our previous study to demonstrate SM-specific disruption of Tgfbr2 after tamoxifen treatment [27]. All procedures in this study were approved by the Institutional Animal Care and Use Committee of Peking University.

2.2. The mouse model for vascular remodeling

The mouse model of flow-induced vascular remodeling has been previously described [28]. After tamoxifen induction, 8-week-old male MyhCre.Tgfbr2$^{f/f}$ and MyhCre.Tgfbr2$^{WT/WT}$ mice were randomly separated into 2 groups: (1) partial carotid ligation; (2) sham-operated. After anesthesia, the three (internal carotid, occipital artery, and left external carotid) of four branches originating from left carotid artery (LCA) were ligated (8–0 silk) with the superior thyroid artery left intact, and the flow was reduced to flow via the intact superior thyroid artery as described previously [28]. Or the branches of the LCA were exposed, but not ligated (control). Carotid arteries were harvested at 1, 2, or 4 weeks after the surgery ($n = 30$ per treatment group per day) for analysis by histology, quantitative RT-PCR and immunohistochemistry.

2.3. Histology and immunohistochemistry

Mice were euthanized by an overdose of pentobarbital at 1, 2, or 4 weeks after the surgery, and the arteries were perfusion-fixed via the left ventricle at physiological pressure with 4% paraformaldehyde. Then fixed in 4% paraformaldehyde at 4 °C by overnight incubation followed by paraffin embedding and transversely sectioning at 4 μm. The sections were stained with hematoxylin-eosin (H&E), elastin-Van Gieson (EVG), and Masson's trichrome staining for histological analysis or with antibodies against PCNA (ZSGB-BIO, China), CD68 (Proteintech, USA), or MMP9 (Proteintech, USA) for immunohistochemical analysis. Quantitation of immunohistochemistry was determined by the ratio of the number of positive cells to total number of hematoxylin positive nuclei in a defined field (400X magnification) on multiple slides ($\geqslant$15 slides per mouse) [29]. H&E and EVG-stained sections of the mid-left carotid arteries were analyzed by microscopy. Medial thickness at four quadrants was measured and averaged over 15 separate sections using ImageJ software (http://rsbweb.nih.gov/ij/) [30]. Measurements were conducted by two trained, independent observers blinded to genotype and treatment conditions. The histological sections were analyzed by ImageJ software.

2.4. RT-PCR

mRNA was extracted from frozen carotid arteries with TRIzol reagent (Invitrogen, USA) as previously described [31,32]. The generation of cDNA was performed with iScript cDNA synthesis kit (Bio-Rad, USA). RT-PCR was carried out with Sensifast SYBR Supermix (Bioline, USA) with primers described previously [14,33]. Levels of mRNA were standardized with GAPDH. All experiments were performed in triplicate.

2.5. Statistical analysis

Statistical tests included Fisher's exact tests, ANOVA, and Bonferroni's multiple comparison tests. P values $\leqslant$0.05 were considered statistically significant. Data represent mean ± SEM when appropriate. Data were analyzed using Prism 6.0 software for Mac (GraphPad Software).

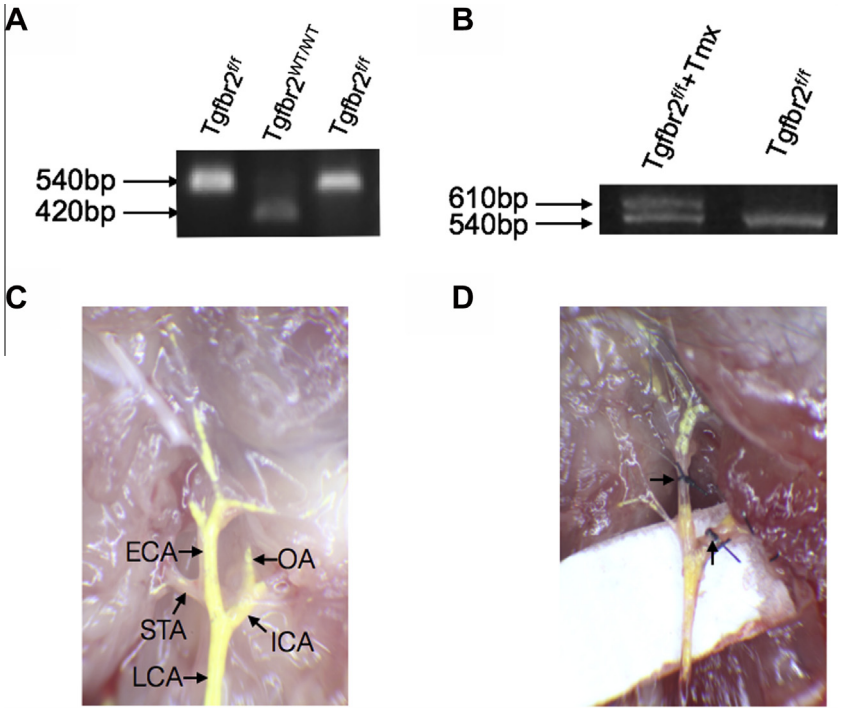

Fig. 1. The mouse model for vascular remodeling. (A) Genotyping for Tgfbr2-loxP allele, the 540 bp band indicates the loxP allele, the 420 bp band indicates the wild-type allele. (B) After tamoxifen treatment, successful deletion of Tgfbr2 is confirmed by the presence of a 610 bp band. (C) Gross appearance of left carotid artery (LCA) and its branches (ECA: external carotid artery, OA: occipital artery, STA: superior thyroid artery, ICA: internal carotid artery). (D) All branches, except for the STA, were ligated.

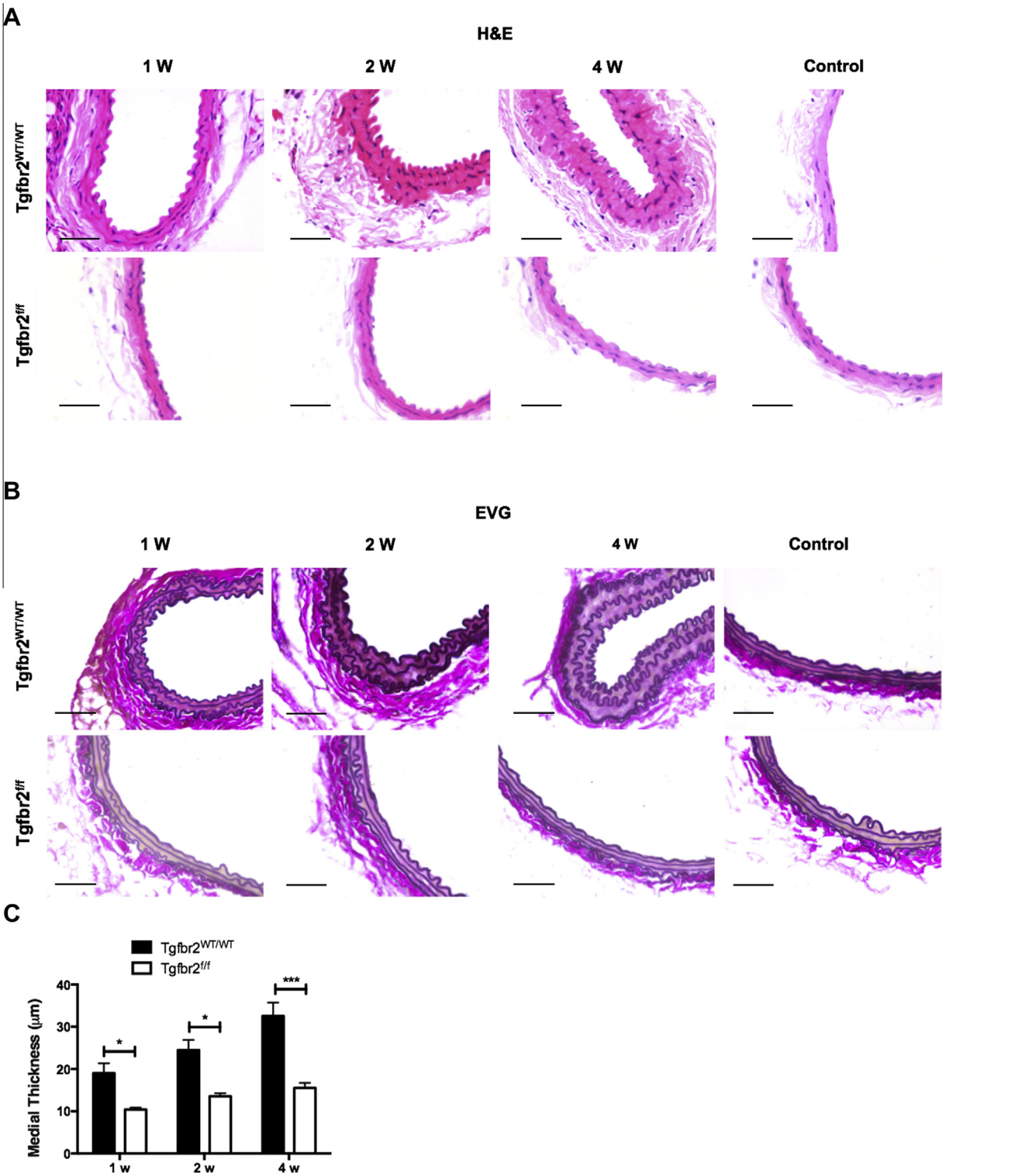

Fig. 2. Disruption of Tgfbr2 in SMC prevents flow-induced vascular remodeling. Representative photomicrographs of LCA from MyhCre.Tgfbr2$^{WT/WT}$ and MyhCre.Tgfbr2$^{f/f}$ mice at week 1, 2, and 4. (A) H&E staining (Scale bars: 25 μm). (B) EVG staining (Scale bars: 25 μm). Black staining indicates elastin. (C) Media thickness is shown for MyhCre.Tgfbr2$^{WT/WT}$ and MyhCre.Tgfbr2$^{f/f}$ mice at week 1, 2 and 4. $^{*}P < 0.05$, $^{***}P < 0.001$, $n \geqslant 10$ per group.

3. Results

3.1. SM-specific deletion of Tgfbr2 prevents flow-induced vascular remodeling

The goal of the present study was to determine the effect of TGF-β signaling in SMC for vascular remodeling, by using the conditional SM-specific Tgfbr2 deletion mice (Fig. 1A and B) [27] in the partial ligation model (Fig. 1C and D). These genetically modified mice have been used in our previous study to demonstrate SM-specific disruption of Tgfbr2 after tamoxifen treatment [27]. Deletion of SM-specific Tgfbr2 did not indicate any discernable differences in the vascular structure of carotid artery.

After partial ligation, the LCA of MyhCre.Tgfbr2$^{WT/WT}$ mice exhibited dramatic vascular remodeling during the time course (Figs. 2 and S1). And we observed a significant thickening of carotid media with an obvious increase in connective tissue and collagens (Figs. 2 and S1). Whereas the vascular remodeling of MyhCre.Tgfbr2$^{f/f}$ was significantly attenuated (Figs. 2 and S1). As expected, the sham-operated mice showed the minimal change in vascular structure (Figs. 2 and S1). The LCA of sham-operated MyhCre.Tgfbr2$^{WT/WT}$ mice was histologically indistinguishable from that of sham-operated MyhCre.Tgfbr2$^{f/f}$ mice (Figs. 2 and S1).

3.2. SM-specific deletion of Tgfbr2 diminishes proliferation of SMC

Proliferation of SMC together with macrophage infiltration, promotes extensive structural remodeling of the partially ligated carotid artery. As the major resident cells in the media of carotid artery, SMCs are critical for the pathogenesis of media thickening [5,34–36]. To determine the changes of SMC after deletion of Tgfbr2 that may prevent vascular remodeling, we evaluated the proliferation of SMC by PCNA expression.

As determined by immunohistochemistry, PCNA staining was significantly increased in the partially ligated carotid arteries of MyhCre.Tgfbr2$^{WT/WT}$ mice, and the PCNA expression peaked at week 1 (Fig. 3), then decreased through the 4-week process. (Fig. S2). In contrast, the expression of PCNA in the carotid arteries of MyhCre.Tgfbr2$^{f/f}$ was markedly reduced at all time points (Figs. 3 and S2).

3.3. SM-specific deletion of Tgfbr2 decreases macrophage infiltration

Macrophage infiltration is an important event for vascular remodeling [3,4,37,38]. Therefore, we examined the role of TGF-β in SMC for macrophage infiltration during vascular remodeling. Immunohistochemical staining for macrophage marker CD68 in the partially ligated LCA from MyhCre.Tgfbr2$^{WT/WT}$ mice showed a significant infiltration of macrophages in the media and adventitia that peaked at week 1 (Fig. 4A and B), then decreased through the 4-week process (Fig. S3). However, CD68 staining was markedly reduced in the LCA of MyhCre.Tgfbr2$^{f/f}$ at all time points (Figs. 4A and B, and S3).

In addition, we observed a remarkable increase in the mRNA expression for monocyte chemoattractant protein-1 (MCP1) and macrophage inflammatory protein 1α (MIP1α), that are known to be critical for macrophage infiltration [29,33,39], in the LCA of MyhCre.Tgfbr2$^{WT/WT}$ mice after partial ligation (Fig. 4C and D). In contrast, partial ligation in MyhCre.Tgfbr2$^{f/f}$ mice did not significantly increase MCP1 and MIP1α expressions (Fig. 4C and D).

3.4. SM-specific deletion of Tgfbr2 decreases MMP upregulation during vascular remodeling

MMPs have been prominently involved in the process of vascular remodeling [4,34]. Furthermore, the importance of MMP in the carotid remodeling is illustrated by the findings that inhibition of MMP can prevent the remodeling process [40].

As shown in Fig. 4E, MMP9 expression in the LCA of MyhCre.Tgfbr2$^{WT/WT}$ markedly enhanced at week 1 (Fig. 4E and F), and then decreased (Fig. S4). In contrast, the disruption of Tgfbr2 in SMC significantly attenuated the increase of MMP9 at all time points (Figs. 4E and F, and S4).

4. Discussion

In our study, we explored the effect of TGF-β signaling in SMC for vascular remodeling and found that it is essential for the pathogenesis of flow-induced vascular remodeling. Furthermore, disruption of Tgfbr2 can prevent the process.

At present, a widely used model for vascular remodeling involves partial ligation of left common carotid artery [5], and this model recapitulates three of the key pathological features of human vascular remodeling: intense local inflammatory infiltration, elevated expression of MMP, and the transition of SMC [3,5,40,41].

Previous studies have implicated TGF-β in a wide variety of vascular physiological activities, including cell proliferation, apoptosis, differentiation, and migration [42,43]. In addition, TGF-β pathway regulates the expression of molecules involved in the initiation and resolution of inflammation [16,17,23,44], which is very important for the structural reorganization of a vessel. Furthermore, blockage or neutralization of TGF-β signaling can attenuate vascular remodeling [23,45].

TGF-β signaling can regulate multiple downstream pathways, including both canonical (Smad-dependent) and noncanonical (Smad-independent) pathways. As the main signaling of canonical TGF-β pathway, Smad2 pathway has been demonstrated to be involved in the process of vascular remodeling [46,47]. And as a major noncanonical signaling, ERK pathway regulates cell proliferation, apoptosis, migration and MMP expression, all of these are significantly implicated in the pathogenesis of vascular remodeling [4,34]. Furthermore, complete inhibition of ERK pathway alone is able to totally downregulate MMP9 expression [34].

Vascular remodeling is a structural reorganization of a vessel involving multiple cell activities, including SMC proliferation, macrophage migration, and ECM restriction [24]. During carotid remodeling, resident SMCs undertake the transition to a dynamically proliferative and inflammatory state characterized by downregulation of smooth muscle contractile genes and upregulation of

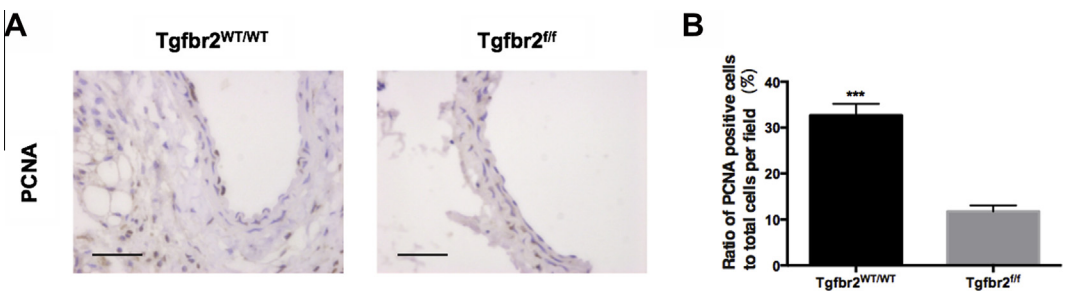

Fig. 3. SM-specific deletion of Tgfbr2 diminishes proliferation of SMC in the pathogenesis of vascular remodeling. Representative photomicrographs of LCA from MyhCre.Tgfbr2$^{WT/WT}$ and MyhCre.Tgfbr2$^{f/f}$ mice at week 1. (A) Proliferating cell shown by PCNA staining. (Scale bars: 25 μm). (B) Quantification of immunopositive cells at week 1. $^{***}P < 0.001$, $n \geqslant 10$ per group.

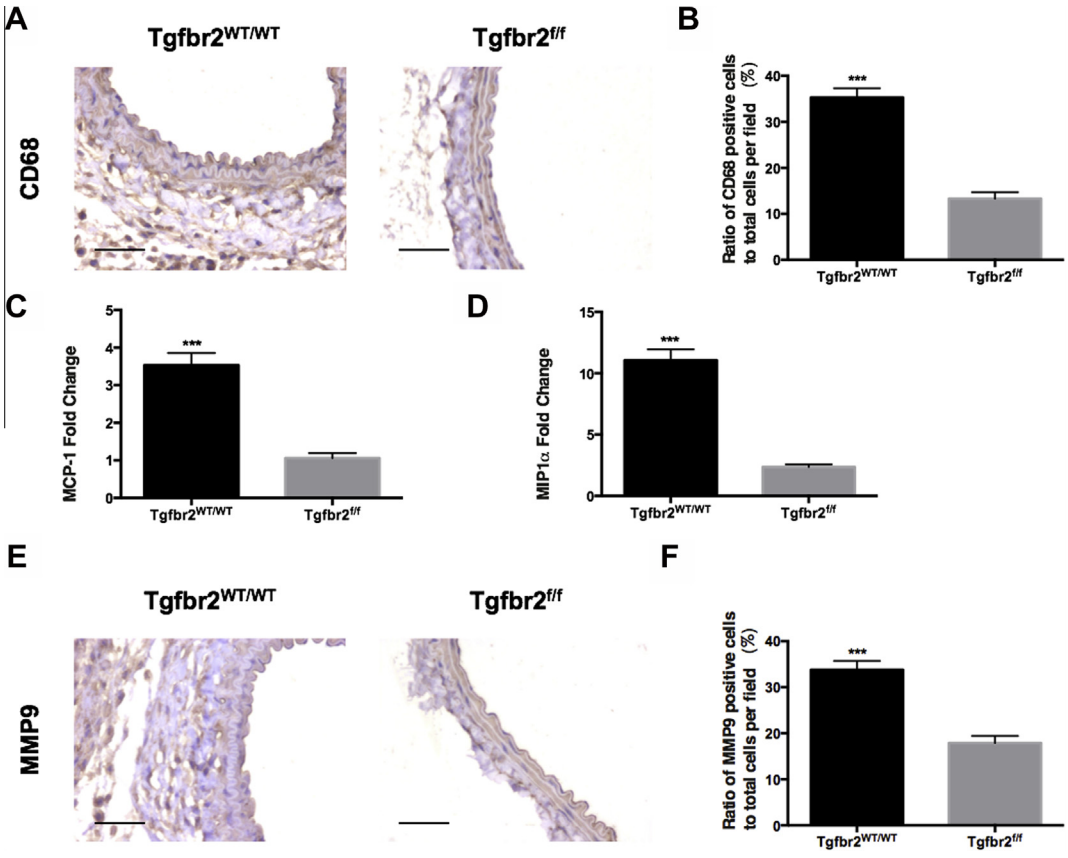

Fig. 4. SM-specific deletion of Tgfbr2 reduces macrophage infiltration and MMP9 upregulation. Representative photomicrographs of LCA from MyhCre.Tgfbr2$^{WT/WT}$ and MyhCre.Tgfbr2$^{f/f}$ mice at week 1. (A) Brown staining indicates CD68 expression at week 1, and sections are counterstained with hematoxylin (blue). (Scale bars: 25 μm). (B) Quantification of immunopositive cells at week 1. $^{***}P < 0.001$, $n \geqslant 10$ per group. (C) Quantitative PCR analysis of monocyte chemoattractant protein-1 (MCP-1) mRNA expression in the LCA of MyhCre.Tgfbr2$^{WT/WT}$ and MyhCre.Tgfbr2$^{f/f}$ mice at week 1. $^{***}P < 0.001$, $n \geqslant 10$ per group. (D) Quantitative PCR analysis of macrophage inflammatory protein1α (MIP1α) mRNA expression in the LCA of MyhCre.Tgfbr2$^{WT/WT}$ and MyhCre.Tgfbr2$^{f/f}$ mice at week 1. $^{***}P < 0.001$, $n \geqslant 10$ per group. (E) Brown staining indicates MMP9 expression at week 1, and sections are counterstained with hematoxylin (blue). (Scale bars: 25 μm). (F) Quantification of MMP9-immunopositive cells at week 1. $^{***}P < 0.001$, $n \geqslant 10$ per group. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

multiple growth factors, chemokines, and cytokines. And in our study proliferation of SMC was significantly attenuated in SM-specific Tgfbr2 deletion mice.

Inflammatory cells, such as macrophages, play a critical role in vascular remodeling of carotid artery in response to flow changes [3,4,37,38]. Inflammatory cells, known for their secretion of cytokines and proteinases, including MMP, are emerging as key modulators for various tissue remodeling [4,34]. And depletion of macrophage or MMP9 can reduce flow-induced remodeling of carotid artery [40,48]. Consistent with previous findings, our study showed significantly increased level of macrophages in the carotid arteries of MyhCre.Tgfbr2$^{WT/WT}$ mice after partial ligation. In contrast, SM-specific deletion of Tgfbr2 prominently reduced macrophage infiltration and attenuated MMP9 upregulation.

The pathogenesis of vascular remodeling involves progressive cycles of inflammation [36,49], proliferation [50,51], and ECM deposition [6,24], the products of this process driving subsequent cell migration and inflammation. We speculate that, SMCs are essential in initiating and promoting this pathogenesis, and SMC-derived factors play a critical role in the initial stage of vascular remodeling [24–26].

5. Conclusion

In summary, our work investigated previously unanswered questions in regard to the role of TGF-β pathway in SMC for vascular remodeling and demonstrated that TGF-β signaling in SMC contributes to the pathogenesis of flow-induced vascular remodeling and disruption can prevent this process. Furthermore, the results suggest that targeting TGF-β pathway in SMC could be a novel therapeutic strategy for preventing cardiovascular diseases related to vascular remodeling.

Acknowledgments

This work was supported by a Peking University People's Hospital Research and Development Funds grant 2118000537 (to W. Li), and the Specialized Research Fund for the Doctoral Program of Higher Education of China grant 2109000075 (to X.M. Zhang).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2014.10.092.

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