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STIMULATION OF EPH-B4 PREVENTS ADULT VENOUS REMOLDING IN ARTERIAL ENVIRONMENT

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ABSTRACTS

Introduction: One third of the vein graft failure is due to unsuccessful adaptation characterized by excessive vein wall thickening and loss of venous identity. There is no proper solution till date. Recent studies suggest that Eph-B4, which is determinant of veins during embryonic period and thought to be passive in adulthood, might be responsible for retaining venous identity in adult. As such, we developed rat model vein graft implantation to discover whether stimulation of Eph-B4 prevents vein wall thickening and preserves venous identity in arterial environment. **Materials and Method:** Suprahepatic inferior vena cava was transplanted from a donor rat into the infrarenal abdominal aorta of a recipient rat. 24 rats were divided into two groups, 12 in Control group and 12 in Intervention group. Half of the vein grafts from each group were harvested after 1 week and the remaining half of the vein grafts were harvested after 4 weeks. Eph-B4 was stimulated by Ephrin-B2/Fc. H&E, immunohistochemical and immunofluorescence staining were performed to study the changes at cellular and molecular level. All the data were analyzed and statistically compared with the help of SPSS 12.0 software. $P<0.05$ was considered statistically significant. **Results:** After Ephrin-B2/Fc treatment, vein grafts showed reduced wall thickness and reduced α-actin expression compared with control group vein grafts in 4 weeks. However, no significant difference in wall thickness and α-actin expression was noted in 1 week. Moreover, control group vein grafts showed diminished Eph-B4 expression and loss of venous identity in the arterial environment whereas vein grafts derived from Ephrin-B2/Fc–injected rat showed retention of Eph-B4 expression. **Conclusion:** Eph-B4 is not only active in adult veins, but it also plays a key role in retention of venous identity by limiting vein wall thickening. Therefore, it is possible to prevent vein graft failure due to unsuccessful adaptation by stimulating Eph-B4. The ability of Ephrin-B2/Fc to stimulate Eph-B4 confined to the vein wall provides new therapeutic strategy.

KEYWORDS: Eph-B4; neointimal hyperplasia; vein graft adaptation; vein graft stenosis.

INTRODUCTION

Veins and arteries are structurally and molecularly distinct. In embryonic development, different genetic determinant represents veins and arteries.[1] Eph-B4 is a genetic marker of veins, while Ephrin-B2 is a genetic marker of arteries. Both of the markers are part of the Eph receptor tyrosine kinase (RTK) family. Although Eph-B4 is active during embryonic venous development[2-5], little is known about the role of Eph-B4 in the plasticity of adult veins.[6-11] Previous studies have shown that Eph-B4 in adulthood is associated with angiogesesis and tumorogenesia.[12- 14] However, the Function of Eph-B4 in normal adult veins is still unclear.

Bypass surgery with autologous vein is still gold standard for the treatment of advanced peripheral vascular disease and coronary artery disease.[6, 15] Increase pressure, flow and oxygen in new arterial environment leads to venous adaptation which determines long-term clinical performance of vein graft. Successful adaptation is characterized by wall thickening and venous dilation whereas unsuccessful adaptation may involve thorombosis and stenosis.[16, 17] However, the critical aspects of remodeling responsible for successful adaptation of vein graft in arterial environment is not well understood. In addition, failure of the PREVENT-III and PREVENT-IV trials suggests that inhibition of smooth muscle cell is not effective in preventing vein graft failure.[18, 19]

Preliminary studies have shown decreased Eph-B4 expression in jugular vein which was successfully transplanted into the carotid artery of rat. They also noted the association between intimal thickening and decrease Eph-B4 expression.[6] These findings suggest that Eph-B4, directly or indirectly plays a crucial role in

vein wall thickening. If Eph-B4 is active in adult veins and its loss can result in loss of venous identity, then stimulating Eph-B4 in vein graft might prevent venous remolding in arterial environment. In order to find the relation between Eph-B4 and venous remolding, we developed a surgical model of vein graft adaptation in rat and analyzed the effects of Eph-B4 stimulation on vein graft wall.

MATERIALS AND METHODS

Antibodies and reagents

EphB4 Rabbit mAb and Alpha smooth muscle actin Rabbit mAb were primary antibodies. Anti-rabbit IgG HRP-linked Ab and Alex Fluor 488 anti-rabbit Ab were secondary antibodies. We purchased these antibodies from Cell signaling technology, Boston, MA, USA. Rat Ephrin-B2/Fc (R&D Systems) was used to stimulate Eph-B4 in vein graft.

Rat vein graft transplantation

All procedures and protocols were authorized by Kunming Medical University Animal Laboratory, Chenggong, Kunming, Yunnan, China. To create a model of vein graft adaptation, we observed the time course of physiological and morphological changes in veins implanted into allogeneic SD (Sprague Dawley) rats. In order to minimize possible immunological reaction from transplantation across strains and to avoid differences in susceptibility to vein wall thickening among strains, all the experimental rats were obtained from the same background, as previous studies have explained [20, 21]. Twenty four month old 24 male SD rats were divided into 2 groups, 12 in control group and 12 in intervention group. Vein transplantation was done in both groups. However, only intervention group was treated with Ephrin-B2/Fc to stimulate Eph-B4.

Approximately 4.0 mm intrathoracic inferior venacava was extracted from donor rat to get vein graft. For implantation, infrarenal abdominal aorta was isolated in recipient rat. Then the isolated aorta was temporarily occluded with micro-clamps and divided. The vein graft was then sutured to the divided aorta in continues and interrupted fashion with 8-0 nylon suture. Homeostasis and patency of the vein graft was maintained before abdomen closer.

The rats were sacrificed after surgery at 1week and 1 month with accepted euthanasia technique. Half of the vein graft was harvested at postoperative 1 week and the other half at 1 month. The harvested vein graft was preserved in liquid nitrogen for further analysis.

Ephrin-B2/Fc treatment

The pre-implantation vein graft was submerged in Ehprin-B2/Fc solution for 20 min. Then it was immediately transplanted into the intervention group rat. The intervention group rat was infused intraperitoneally with 20 µg (2µg/ml) of Ephrin-B2/Fc (Sino Biological Inc.) starting 24 hour after surgery and additional dose was given every 48 hours until harvest, as in accordance with previous vein graft model (R&D Systems).[22]

Histological, Immunohistochemical and immunofluorescence staining

All the procedures were conducted in the pathological laboratory of the First Affiliated Hospital of Kunming Medical University. After all the specimens were embedded in paraffin wax, they were cut in 5-µm slices then Hematoxylin & eosin (H&E), α-actin imunohistochemical, and EphB4 immunofluorescence staining were performed. For immunohistochemical and immunofluorescense, the deparaffinized slices of specimen were treated with xylene and ethanol. In order to retrieve antigen, the specimen were treated with 0.01M sodium citrate buffer (PH6.0). The specimens were treated with primary and secondary antibody according to the instruction manual provided by the manufacturing company. Alpha smooth muscle actin Rabbit mAb and Anti-rabbit IgG HRP-linked Ab treatment for immunohistochemial staining. Whereas, EphB4 Rabbit mAb and Alex Fluor 488 anti-rabbit Ab treatment for immunofluorescense staining. NIH Image J image analysis system and Axioimager A1 imaging system were used to capture images after immunohistochemical and immunofluoresence staining respectively.

Statistical analysis

All the variables were statistically analyzed by SPSS 12.0 software. Results are presented as Mean ± standard deviation. The data were compared with the help of single factor analysis variance between groups (one way ANOVA). The value of $P < 0.05$ was considered statistically significant.

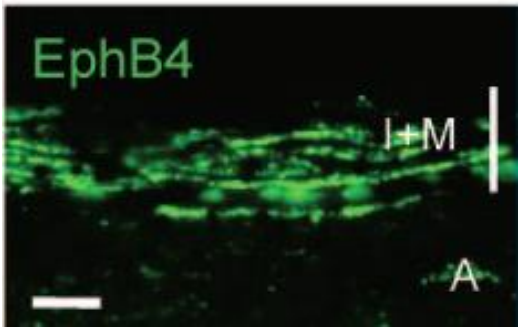
RESULTS

Activity of Eph-B4 decreases in arterial Environment

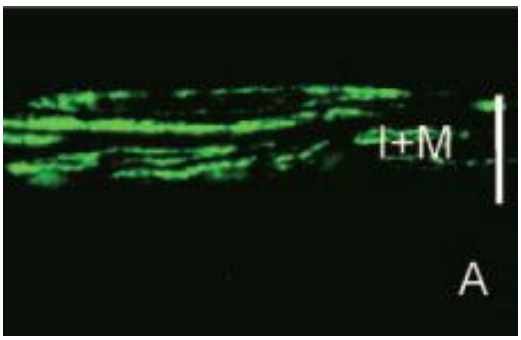
In arterial environment, Eph-B4 protein was diminished in all layers of rat vein grafts (Figure 1) which is consistent with previous model of rat vein graft adaptation.[6] Vein grafts obtained from Ephrin-B2/Fc–injected rat showed no change in Eph-B4 expression in 1 month with retention of venous identity (Figure 1 E), on the other hand, Eph-B4 expression in the control group was significantly lower in 1 month with thickening of vein wall (Table 1). This suggests that Eph-B4 is a critical determinate in preserving venous identity in arterial environment.

Table 1: Fluorescence intensity in normal inferior vena cava and different group at specific time period. * Compared to normal inferior vena cava, *P*<0.05, ※ Compared with the control group, *P*<0.05. Weak positive (+, refers to 25% of cells with EphB4 expression); moderately positive (++, indicates 25% -49% cell with Eph-B4 expression); strong positive (+++, means the total number of Eph-B4 positive cell above 50%).

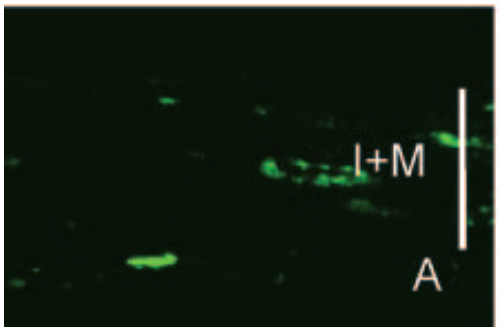
Group	Fluorescence intensity
Normal inferior vena cava	+++
Control group after 1 week	++*
Intervention group after 1 week	++*
Control group after 1 month	+*
Intervention group after 1 month	++*※



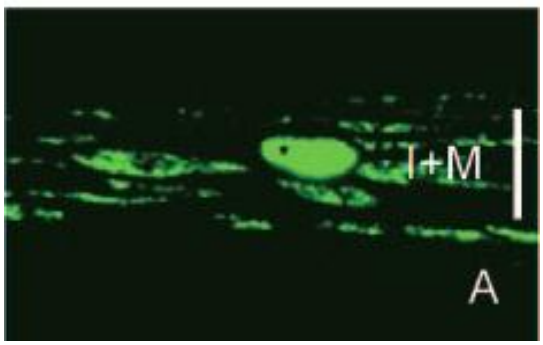
A. Normal supra-hepatic inferior venacava



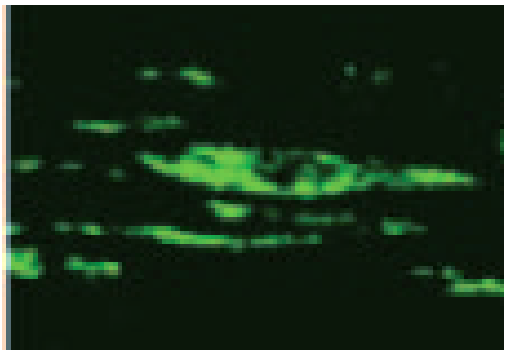
B. Control broup after 1 week



C. control group after 1 month.



D. Intervention group after 1 week



E. Intervention group afterr 1 month

Figure 1. Immunofluorescence staining of Eph-B4 in in normal inferior vena cava and different group at specific time period. Green color represents Eph-B4 expression. Intima (I), Media (M), Adventitia (A).

Eph-B4 is active in adulthood and prevents vein wall thickening

After the surgical implantation, the vein graft wall thickness gradually increased with time. Remolding was positive even at one week (Figure 2, 3).The vein wall thickness continued to increase up to 4 week in control group (Table 2). However, in the intervention group, the vein graft wall did not increase at the same rate as in control group (Table 2). This finding is analogues to the results of previous study with functional human vein graft.[23, 24] Hence, the rat vein graft model is similar to human vein graft adaptation.[25] In addition, it supports our understanding that Eph-B4 remains active throughout life and it is a key factor which prevents vein wall thickening in arterial environment.

Table 2: Vein graft thickness in normal inferior vena cava and different group at specific time period. * Compared to normal inferior vena cava, *P*<0.05, ※ Compared with the control group, *P*<0.05.

Group	intima + media (μm)	Adventitia(μm)	(intima + media) /管壁
Normal inferior vena cava	6.64±0.48	40.64±2.22	0.16±0.01
Control group, 1 week	10.56±1.13*	40.88±6.52	0.27±0.04*
Intervention group, 1 week	11.26±0.70*	41.08±3.25	1.39±0.01*
Control group, 1 month	28.14±2.59*	40.12±2.95	0.70±0.04*
Intervention group, 1 month	19.25±1.77*※	40.10±2.52	0.48±0.03*※

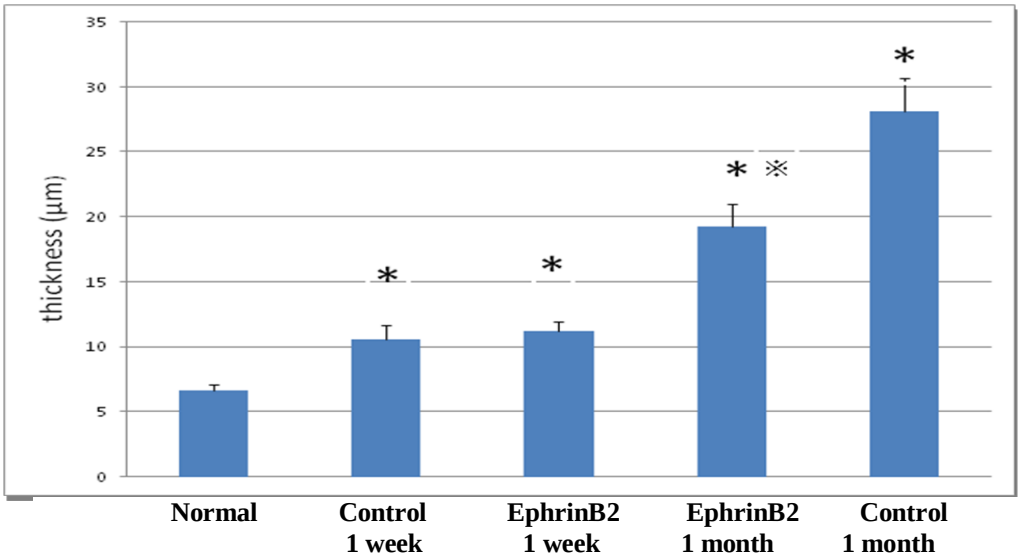
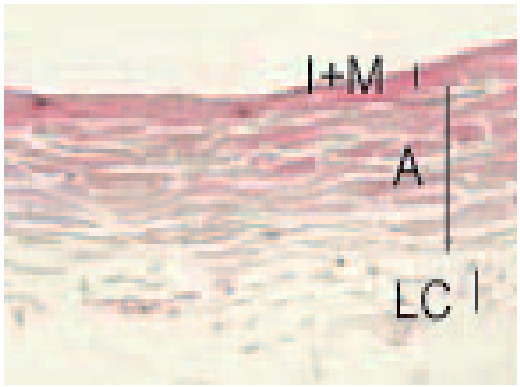
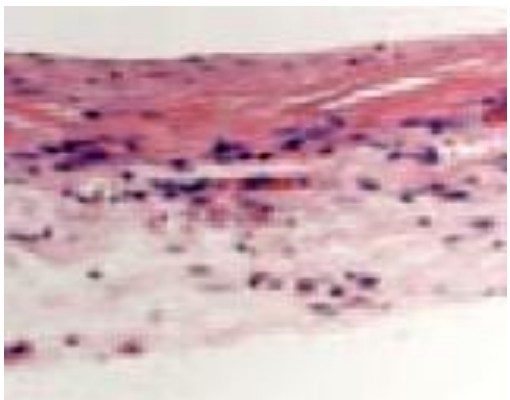


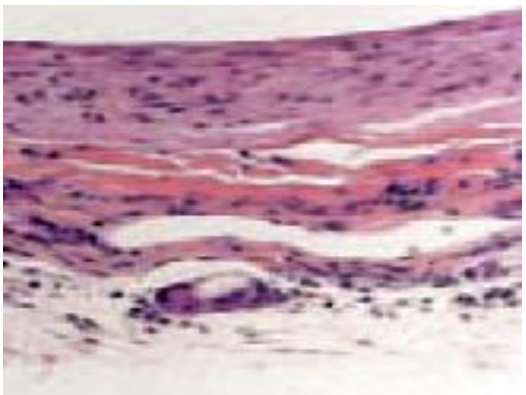
Figure 2. Vein graft thickness in normal inferior vena cava and different group at specific time period. * Compared to normal inferior vena cava, *P*<0.05, ※ Compared with the control group, *P*<0.05.



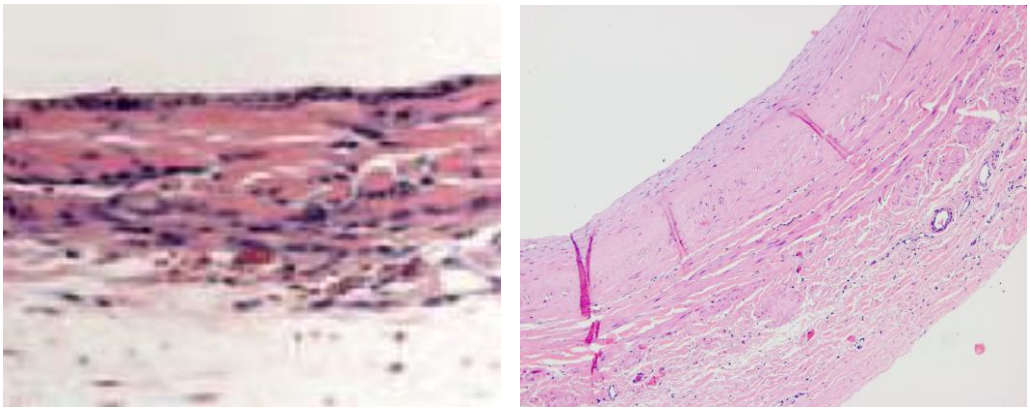
A. Normal inferior vena cava.



B. Control group after 1 week



C. Control group after 1 month



D. Intervention group after 1 week **E. Intervention group after 1 month**

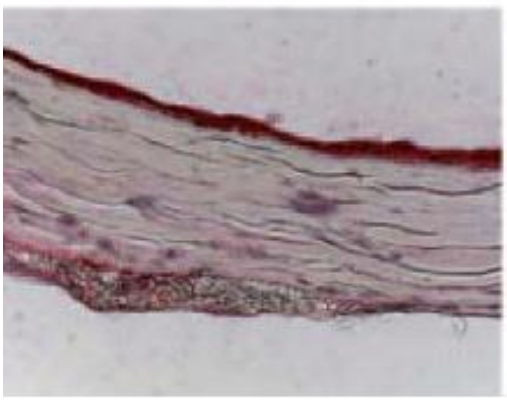
Figure 3. H&E staining of normal inferior vena cava and the vein graft in different group at specific time period. Intima (I), Media (M), Adventitia (A), Loose connective tissue (LC)

Eph-B4 prevents hyperplasia of smooth muscle cell

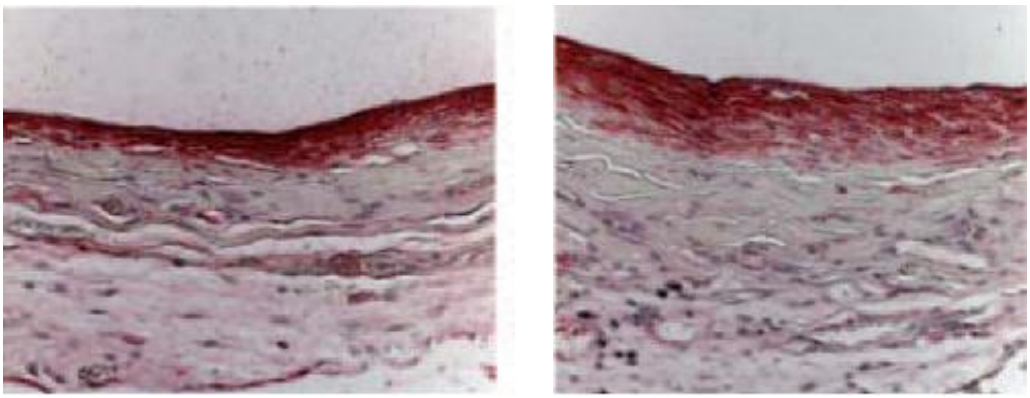
In our study, the expression of smooth muscle α-actin continuously increased in vein graft after transposition to arterial environment. This indicates neointimal hyperplasia associated with remolding (Table 3, Figure 4). Notably, after Ephrin-B2/Fc treatment, vein grafts showed reduced numbers of layers of α-actin – positive cells compared with control group vein grafts (Figure 4). This finding compliments our understanding that stimulation of EphB4 by direct interaction of Ephrin B2 ligand might prevent remodeling and ultimately preventing vein graft failure.

Table 3. Alpha-actin expression in normal vena cava and transplanted vein graft. The value of Optical Density (OD) represents the content of α-actin in normal vena cava and transplanted vein graft. * Compared with normal inferior vena cava, *P*<0.05, ※ Compared with the control group, *P*<0.05.

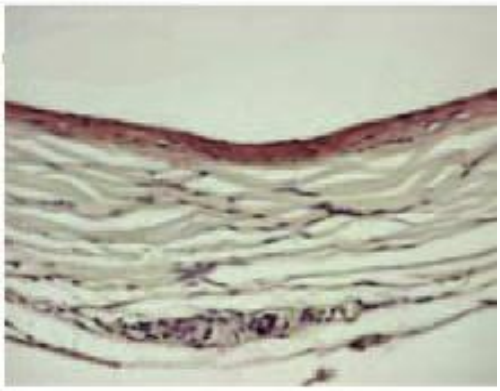
Group	OD value
Normal inferior vena cava	2.43±0.89
Control group after 1 week	5.54±0.04*
Intervention group after 1 week	4.98±1.21*
Control group after 1 month	9.21±0.09*
Intervention group after 1 month	7.99±1.30*※



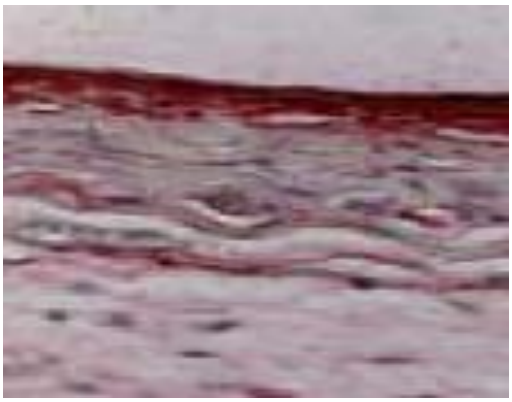
A. Normal inferior vena cava



B. Control group after 1 week **C. Control group after 1 month**



D. Intervention group after 1 month



E. Intervention group after 1 month

Figure 4. Immunohistochemical stain of smooth muscle α-actin in normal vena cava and the vein graft in different group at specific time period. α-actin positive cell is represented by reddish brown granular precipitation in the cytoplasm. Intima (I), Media (M), Adventitia (A), Loose connective tissue (LC).

DISCUSSION

Unsuccessful adaptation with insufficient and excessive neointimal hyperplasia remains the major cause of vein graft failure worldwide. Although there has been significant advancement in vascular biology which has discovered many potential treatment strategies, so far none have successfully translated clinically. In the recent years, few researchers have suggested stimulation of Eph-B4 to prevent vein graft wall thickening.[6, 26] Using a rat model which mimics human vein graft adaptation, we proved this theory. We showed that Eph-B4 remains active in adulthood and stimulation of Eph-B4 prevents venous remolding and preserves venous identity in arterial environment. Moreover, Eph-B4 receptor tyrosine kinase can simply be stimulated by its ligand Ephrin-B2 which is a feed-forward type of positive regulation associated with Eph-B4. This new data provides new dimension in the treatment of vein graft failure due to unsuccessful adaptation, where conventional treatment have shown least success rate.

In our study, the thickness of the transposed vein graft increased with time. The remolding was positive even in first week and the wall thickness continued increasing till 4th week (Figure 3 B, D, Table 2), consistent with the results of late dilation and aneurysmal degeneration in long-standing functional human vein grafts.[23] Hence, the rat vein graft model closely replicates human vein graft adaptation and we can relate our findings with human vein graft. Consistent with previous studies and as expected, the expression of Eph-B4 was noticeably reduced in vein graft after transposition to the arterial circulation. However, the vein graft wall thickness and Eph-B4 expression remained unchanged in the Ephrin-B2/Fc injected rats (Table 2). Alpha-actin, which is a marker of Smooth Muscle, increased significantly in its expression after vein graft transposition (Figure 4, Table 3). This indicates smooth muscle cell proliferation in arterial environment. It is also worth noting that Alpha-actin expression was more in control group then in intervention group (Table 3). All of these data suggest that Eph-B4 signaling in vein graft might take part in the mechanism by which Eph-B4 limits venous adaptation to the arterial environment. Moreover, our finding suggests that the venous adaptation to the arterial environment, that is, Eph-B4 dependent venous remodeling, is different from the response of the arterial wall to injury. As such, the therapies that inhibit arterial smooth muscle cell proliferation, migration, and neointimal hyperplasia, are not effective in preventing vein graft failure, as has been reported in previous clinical trials.[18] However, further research might be needed to strengthen our findings on the role of Eph B4 in the adaption mechanism. For instance, comparing the morphological and physiological changes of transplanted vein graft under arterial environment in wild-type (Eph B4 +/+ type, control group), wild-type ephrinB2-Fc injection group and EphB4 +/- type (EphB4 knockout) rat; Using in-vitro cell culture technology, cultured mouse (phB 4 / + type and phB 4 / - type) vein endothelial cells to analyze the difference EphB4 expression from in vitro experiments which is visible on the vein graft adaptation (VGA) influencing processes and regulatory mechanisms.

To match the diameter of donor inferior vena cava with the recipient abdominal aorta, the donor and recipient rats were similar in size, weight and age. As suggested by previous studies, we selected donor and recipient rats from similar background to minimize immunological reaction from transplantation across strains. Surprisingly, there was no event of immunological rejection after transplantation.[20, 21] The transplanted inferior vena cava reacted to the arterial environment with changes in wall thickness, which resemble to the remodeling of human vein graft in arterial environment.[25] Different from other similar studies, we used 8-0 nylon suture for anastomosis of vein graft to the aorta. Interrupted stay suture was done for stabilization of vein graft followed by continuous suture to complete the anastomosis. This technique reduced surgery time and minimized post operative complications such as bleeding, thrombosis and occlusion.

CONCLUSION

In conclusion, not only Eph-B4 is active in adult veins, but it also plays a key role in the retention of venous identity by limiting vein wall thickening. Therefore, it is feasible to reduce incidents of vein graft failure due to unsuccessful adaptation by simply stimulating Eph-B4. The ability of Ephrin-B2/Fc to stimulate Eph-B4 confined to the vein wall leads us to innovative and more effective strategy to prevent vein graft failure in the future. However, further research might be needed to strengthen our findings on the role of Eph B4. Finally, our study provides basis for further in-vitro experiments.

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