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Short Communication

Frontier Progress on the Role and Mechanism of Ion Channels on Vascular Wall Cells in Vascular Fibrosis Remodeling

Xin Liao, Xiaolin Zhang, Hai Tian, Jun Cheng*

Key Lab of Medical Electrophysiology of Ministry of Education, Institute of Cardiovascular Research, Public Center of Experimental Technology, Southwest Medical University, Luzhou, China

ABSTRACT

Fibrosis is often an end-stage manifestation of chronic inflammatory diseases, affecting any tissue or organ in the body due to uncontrolled deposition of extracellular matrix molecules. Vascular fibrosis, characterized by the accumulation of extracellular matrix components, leads to vessel stiffness and is associated with various cardiovascular diseases. Ion channels in the cardiovascular system are important for maintaining normal physiological functions and play significant roles in processes such as ion transport and cell differentiation. Ion channels on fibroblasts, smooth muscle cells, and endothelial cells may be involved in vascular fibrotic remodeling. Understanding the mechanisms of vascular fibrosis and reversing this pathology could enhance our knowledge and treatment of fibrosis. This letter discusses ion channels known to contribute to vascular fibrotic remodeling and potential therapeutic targets for treating vascular fibrosis and promoting post-injury vascular repair.

Keywords: Ion channels, Vascular wall, Fibrosis, Vascular remodeling

INTRODUCTION

Vascular fibrosis is often caused by the excessive deposition of extracellular matrix components such as collagen and fibronectin, leading to reduced vascular compliance, luminal constriction and wall thickening, which can result in various cardiovascular diseases like aneurysms and atherosclerosis [1,2]. Ion channels on the vascular wall are involved in the pathogenesis of vascular fibrosis and may serve as potential therapeutic targets [3]. Early intervention could potentially halt or delay this pathology, making the elucidation of vascular fibrosis mechanisms beneficial for research on reversing vascular remodeling. Next, this letter briefly introduces the ion channels associated with vascular fibrosis remodeling.

Transient Receptor Potential (TRP) channels and vascular fibrotic remodeling

The TRP superfamily in humans comprises 28 types and 6 subgroups [4]. TRP channels play a significant role in calcium ion entry into cells [5]. Studies indicate that many TRP channels are pivotal in fibrotic diseases across various organs [4].

This section will introduce three TRP channels related to fibrosis:

TRPM7: Transient Receptor Potential Melastatin 7 (TRPM7) is widely expressed in the human body and is permeable to divalent cations such as Zn^{2+}, Ca^{2+} and Mg^{2+} [6-8]. Many divalent cations, like magnesium, play a vital role in regulating physiological activities and their depletion can lead to endothelial dysfunction, arterial remodeling and hypertension [7]. Since TRPM7 channels allow the passage of these divalent cations, damage to this channel can alter the levels of these ions in the body, potentially leading to inflammation or fibrosis [9]. Targeting this channel for treatment may, provide vascular protection, although the efficacy may vary across different animal models.

TRPC6: Transient Receptor Potential Cation Channel 6 (TRPC6) is a nonselective channel permeable to Na^{+} and Ca^{2+}, regulated by second messengers and phosphorylation. It plays a key role in Store-Operated Calcium Entry (SOCE), which is vital for cellular calcium homeostasis [10]. In pulmonary hypertension, TRPC6 upregulation in Pulmonary Artery Smooth Muscle Cells (PASMCs) increases SOCE, contributing

Correspondence to: Jun Cheng, Institute of Cardiovascular Research, Southwest Medical University, Luzhou, China, E-mail: lzcj1221@swmu.edu.cn

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to pulmonary vascular remodeling and fibrosis [11]. TRPC6 is also involved in fibroblast transformation and Endothelial Mesenchymal Transformation (EndMT) processes, suggesting it could be a therapeutic target to inhibit vascular remodeling and fibrosis in pulmonary hypertension [12].

TRPV4: Transient Receptor Potential Vanilloid 4 (TRPV4) channels is associated with skin fibrosis in scleroderma and increased TRPV4 channel activity is observed in lung fibroblasts of patients with idiopathic pulmonary fibrosis [13,14]. Knockout of TRPV4 in mice reduces fibrosis in organs such as the lungs and heart [15]. In summary, TRPV4 plays an important role in fibroblast activation and extracellular matrix remodeling, and its inhibition alleviates fibrosis in organs like the heart and lungs.

Calcium activation of potassium channels (K_{Ca}) and vascular fibrosis remodeling

The K_{Ca} family plays an essential role in cellular excitability and is categorized into three types based on their conductance: Small conductance (SK, ~4-14 pS), medium conductance (IK, ~32-39 pS) and large conductance (BK, ~200-300 pS) channels [16]. In pathological conditions, calcium-activated potassium channels are widely involved in the remodeling process of vascular fibrosis. BK, IK and SK calcium-activated potassium channels on vascular wall cells promote vascular inflammation by activating PI3K/Akt pathway. Activation of the classic fibrotic pathways such as Smad2/3, P38 and Ras ultimately leads to vascular remodeling and adverse progression of fibrosis.

Other ion channels on vascular cells and vascular fibrosis remodeling

In addition to TRP and K_{Ca} ion channels widely involved in vascular fibrosis, other types of ion channels include Piezo1, the mechanically sensitive ion channel on smooth muscle cells, the L-type calcium ion channel, the ORAI1/STIM1 channel, and the Volume-Regulated Anion Channel (VRAC) on fibroblasts. The current activity and downstream signals of these channels are involved in the regulation of vascular cell proliferation, migration and differentiation. Pathologically, they also activate TGF-β/Smad and p38-MAPK signaling pathways, which play a key role in the occurrence and progression of fibrosis.

CONCLUSION

Vascular fibrosis is present in many fibrotic diseases and contributes to disease progression and deterioration. It primarily results from the deposition and reorganization of excessive extracellular matrix components, a process mediated by vascular smooth muscle cells, endothelial cells, and fibroblasts. Numerous ion channels on these cells are involved in vascular fibrosis. Understanding the mechanisms and downstream signaling pathways of these ion channels in vascular fibrosis could provide strategies and insights for future anti-fibrotic therapies.

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CONFLICTS OF INTEREST

There is no conflict of interest

REFERENCES

1. Tsamis A, Krawiec JT, Vorp DA. Elastin and collagen fibre microstructure of the human aorta in ageing and disease: A review. J R Soc Interface. 2013 Jun 6;10(83):20121004.
2. Intengan HD, Schiffrin EL. Vascular remodeling in hypertension: Roles of apoptosis, inflammation, and fibrosis. Hypertension. 2001;38(3):581-587.
3. Park KS, Pang B, Park SJ, Lee YG, Bae JY, Park S, et al. Identification and functional characterization of ion channels in C^{D34+} hematopoietic stem cells from human peripheral blood. Mol Cell. 2011;32:181-188.
4. Inoue R, Kurahara LH, Hiraishi K. TRP channels in cardiac and intestinal fibrosis. Semin Cell Dev Biol. 2019;94:40-49.
5. Nilius B, Owsianik G, Voets T, Peters JA. Transient receptor potential cation channels in disease. Physiol Rev. 2007;87(1): 165-217.
6. Touyz RM. Transient receptor potential melastatin 6 and 7 channels, magnesium transport, and vascular biology: Implications in hypertension. Am J Physiol Heart Circ Physiol. 2008;294(3):H1103-1118.
7. Yogi A, Callera GE, Antunes TT, Tostes RC, Touyz RM. Transient Receptor Potential Melastatin 7 (TRPM7) cation channels, magnesium and the vascular system in hypertension. Circ J. 2011;75(2): 237-245.
8. Nadler MJ, Hermosura MC, Inabe K, Perraud AL, Zhu Q, Stokes AJ, et al. LTRPC7 is a Mg.ATP-regulated divalent cation channel required for cell viability. Nature. 2001;411(6837):590-595.
9. Antunes TT, Callera GE, He Y, Yogi A, Ryazanov AG, Ryazanova LV, et al. Transient Receptor Potential Melastatin 7 Cation Channel Kinase: New Player in Angiotensin II-Induced Hypertension. Hypertension. 2016;67(4):763-773.
10. Shin KC, Ali G, Ali Moussa HY, Gupta V, de la Fuente A, Kim HG, et al. Deletion of TRPC6, an Autism Risk Gene, Induces Hyperexcitability in Cortical Neurons Derived from Human Pluripotent Stem Cells. Mol Neurobiol. 2023;60(12):7297-7308.
11. Jain PP, Lai N, Xiong M, Chen J, Babicheva A, Zhao T, et al. TRPC6, a therapeutic target for pulmonary hypertension. Am J Physiol Lung Cell Mol Physiol. 2021;321(6):L1161-L1182.
12. Kong C, Zhang F, Hu R,Wang L. METTL3 Promotes Endothelium-Mesenchymal Transition of Pulmonary Artery Endothelial Cells by Regulating TRPC6/Calcineurin/NFAT Signaling Pathways. Evid Based Complement Alternat Med. 2023;2023(1):8269356.
13. Goswami R, Cohen J, Sharma S, Zhang DX, Lafyatis R, Bhawan J, et al. TRPV4 ION Channel Is Associated with Scleroderma. J Invest Dermatol. 2017;137(4):962.
14. Rahaman SO, Grove LM, Paruchuri S, Southern BD, Abraham S, Niese KA, et al. TRPV4 mediates myofibroblast differentiation

and pulmonary fibrosis in mice. J Clin Invest. 2014;124(12): 5225-5238.

15. Ji C, McCulloch CA. TRPV4 integrates matrix mechanosensing with Ca2+ signaling to regulate extracellular matrix remodeling. FEBS J. 2021;288(20):5867-5887.

16. Orfali R, Albanyan N. Ca^{2+}-Sensitive Potassium Channels. Molecules. 2023; 28(2):885