

## Tunica Arterial Adventitia: A New Exploration in Intimal Hyperplasia

Wenjuan Tang<sup>1</sup>, Zhenjie Liu<sup>2</sup> and Yi Si<sup>2\*</sup>

<sup>1</sup>Department of Surgery, Affiliated Hospital of Nantong University, Nantong, China

<sup>2</sup>Department of Surgery, University of Wisconsin-Madison, Madison, WI, USA

### Abstract

Vascular interventions have become widely adopted for treatment of coronary and peripheral arterial atherosclerosis. Although there is increasing utilization of the new technology, restenosis still retarded the long-term outcome of the intervention. Histological studies have revealed that uninhibited neointimal cells play a vital role in the post-injury response. Among them, the majority of neointimal cell express smooth muscle cell (SMC) markers and thus, it was believed that the SMC in neighborhood migrate into the subintimal space, proliferate and secrete extracellular matrix, therefore contributing to the intimal hyperplasia. Many studies in this thematic review focus on the specifics of the injury, the cytokines and chemokines that drive SMC, and the nature of the migrated SMC. In addition, more studies documented that adventitia is an active participator instead of bystander through genetic-labeling and tracking adventitia in animal model. This brief review focuses on the recent findings of adventitia in vascular response after injury and highlights that multilineage cells in adventitia contribute to intimal hyperplasia synergistically with SMC.

**Keywords:** Intimal hyperplasia; Adventitia; Fibroblast; Progenitor cells

The adventitia of the arterial wall has been long recognized as a more collagen-rich supportive connective tissue compared to its adjacent structures, the intima and media. However, more data show that this definition is far too limiting. Experimental data have unambiguously shown that many kinds of arterial injury (i.e., arterial endothelial injury, vein bypass grafting) induce not only a variety of pathological changes in intima and media, but also adventitial remodeling [1-3]. It has also been reported that the adventitia's injury response is involved in intimal and medial restructuring [4]. The purpose of this brief review is to highlight the recent findings on the role of the adventitia in vascular injury responses.

### Normal Structure of Arterial Wall

Arterial walls have traditionally been divided into three distinct concentric layers surrounding the vessel lumen: intima, media, and adventitia. The tunica intima consists of a single layer of endothelial cells (ECs) in direct contact with blood flow. This tightly junctional monolayer of ECs rests on extracellular matrix components including collagen type IV, and heparin sulfate proteoglycans. The tunica media, consisting of layers of smooth muscle cells (SMCs), extracellular elastin fiber, and other matrix components, is responsible for the muscular construction of blood vessels. The tunica adventitia is mainly composed of collagens and other extracellular matrix proteins, but also contains fibroblasts, adipocytes, vasa vasorum, rare macrophages, and some perivascular nerves [1,5,6].

### Re-examing the Roles of Adventitia

For decades, vascular biology research has focused on the EC, SMC, and extracellular matrix (in tunica media) in vessel function and injury response [7]. However; other cellular components within the adventitia have also been implicated in these processes. Indeed, other than collagen and proteoglycans, the adventitial site of most arteries also has a substantial layer of adipocytes and fibroblasts adjacent to smooth muscle layer. The population of cells residing in the vascular adventitia was initially thought to be relatively static and passive, with only structurally supportive and anatomically protective roles [8]. Recent evidence, however, suggests dynamic roles: both vascular

fibroblasts and perivascular adipocytes are actively involved in the control of vascular SMC activation, phenotype switch, and perhaps vascular growth [7]. In addition, further evidence implies that the adult adventitia harbors progenitor cell populations that display multilineage differentiation potential and play various roles in arterial injury response [9-12]. However, despite these exciting discoveries reported in recent years by several laboratories, how these components interact to achieve a complex and integrated control of vascular tone remains an underexplored area in vascular biology research. Various investigators at the cutting edge of the field demonstrated that these cells spontaneously differentiate into adventitial pericytes, and can be differentiated into various vascular cells (endothelial and smooth muscle cells). In addition, these progenitor cells possess a crucial paracrine capacity and, thus, can maintain arterial homeostasis and respond to injury [13].

### Adventitia and Intimal Hyperplasia

Under normal conditions, the mature arterial wall has a low to undetectable proliferation rate of ECs and SMCs. Once subjected to injury, however, all three layers demonstrate significantly increased proliferative ability. Many reported results have suggested that the proliferation and migration of medial SMCs promote the aggregation of neointimal cells that highly express SMC markers. Therefore, it has been believed that medial SMCs play a vital role in neointimal formation [14-16]. Nevertheless, in the past decade, this view was greatly challenged by studies that transplanted extrinsic cells into adventitia or labeled intrinsic adventitial cells to investigate their roles in response to vessel injury [17-20]. Those studies indicated that the resident adventitial

**\*Corresponding author:** Yi Si, Department of Surgery, University of Wisconsin-Madison, 1111 Highland Ave, Madison, WI, 53705, USA, Tel: 608-261-1864; Fax: 608-262-3330; E-mail: [si@surgery.wisc.edu](mailto:si@surgery.wisc.edu)

Received April 18, 2013; Accepted June 10, 2013; Published June 12, 2013

**Citation:** Tang W, Liu Z, Si Y (2013) Tunica Arterial Adventitia: A New Exploration in Intimal Hyperplasia. J Vasc Med Surg 1: 108. doi: [10.4172/2329-6925.1000108](https://doi.org/10.4172/2329-6925.1000108)

**Copyright:** © 2013 Tang W, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

cells are able to migrate into the neointima and contribute to intimal hyperplasia following injury. Based on the results of many studies which have shown phenotypic transformation of adventitial fibroblasts to SMC-like myofibroblasts, those cells are thought to play a pivotal role in the vessel injury response [20,21]. Additionally, some recent studies found that adventitial progenitor cells and adipocytes may participate in neointimal formation and vascular remodeling after injury [10,22]. Accumulating evidence has shown that the adventitia functioning as progenitor cell niche maintains arterial wall integrity [11,23-25].

Experimental evidence has elaborated a direct role of adventitial cells in mediating vascular tone. Fibroblasts and macrophages in adventitia can produce nitric oxide in response to injury, in turn affecting vessel contraction and vessel remodeling [26]. However, how adventitial cells sense injury and consequently initiate the remodeling in an “outside-in” manner remains unclear. Likewise, the crosstalk between adventitia and intima or media is not entirely understood. Although sympathetic nerve terminals in adventitia are found to diffuse into media and induce SMC contraction, cell or neuron signaling involved in this process requires more thorough investigation. Therefore, the study of the adventitia will further elucidate its role within vascular biology.

## Summary

We expect that more questions will be put forth with increased studies of the adventitial layer of arterial wall. Investigating these questions will provide a better understanding on how various vascular cellular components interact each other to maintain and restore vessel functions.

## References

1. Coen M, Gabbiani G, Bochaton-Piallat ML (2011) Myofibroblast-mediated adventitial remodeling: An underestimated player in arterial pathology. *Arterioscler Thromb Vasc Biol* 31: 2391-2396.
2. Goel SA, Guo LW, Liu B, Kent KC (2012) Mechanisms of post-intervention arterial remodelling. *Cardiovasc Res* 96: 363-371.
3. Yu P, Nguyen BT, Tao M, Campagna C, Ozaki CK. (2010) Rationale and practical techniques for mouse models of early vein graft adaptations. *J Vasc Surg* 52: 444-452.
4. Stenmark KR, Davie N, Frid M, Gerasimovskaya E, Das M (2006) Role of the adventitia in pulmonary vascular remodeling. *Physiology (Bethesda)* 21: 134-145.
5. Thyberg J (1998) Phenotypic modulation of smooth muscle cells during formation of neointimal thickenings following vascular injury. *Histol Histopathol* 13: 871-891.
6. Mitchell RN, Libby P (2007) Vascular remodeling in transplant vasculopathy. *Circ Res* 100: 967-978.
7. Kwan CY, Hsieh WT, To PN, Wang HD (2010) New perspectives on vascular wall signaling: Role of perivascular adipocytes and fibroblasts. *Acta Pharmacol Sin* 31: 1022-1025.
8. Sartore S, Chiavegato A, Faggini E, Franch R, Puato M, et al. (2001) Contribution of adventitial fibroblasts to neointima formation and vascular remodeling: From innocent bystander to active participant. *Circ Res* 89: 1111-1121.
9. Grudzinska MK, Kurzejamska E, Bojakowski K, Soin J, Lehmann MH, et al. (2013) Monocyte chemoattractant protein 1-mediated migration of mesenchymal stem cells is a source of intimal hyperplasia. *Arterioscler Thromb Vasc Biol* 33: 1271-1279.
10. Hu Y, Zhang Z, Torsney E, Afzal AR, Davison F, et al. (2004) Abundant progenitor cells in the adventitia contribute to atherosclerosis of vein grafts in apoE-deficient mice. *J Clin Invest* 113: 1258-1265.
11. Zengin E, Chalajour F, Gehling UM, Ito WD, Treede H, et al. (2006) Vascular wall resident progenitor cells: A source for postnatal vasculogenesis. *Development* 133: 1543-1551.
12. Campagnolo P, Cesselli D, Al Haj Zen A, Beltrami AP, Krankel N, et al. (2010) Human adult vena saphena contains perivascular progenitor cells endowed with clonogenic and proangiogenic potential. *Circulation* 121: 1735-1745.
13. Lin CS, Lue TF (2013) Defining vascular stem cells. *Stem Cells Dev* 22: 1018-1026.
14. Clowes AW, Reidy MA, Clowes MM (1983) Kinetics of cellular proliferation after arterial injury. I. Smooth muscle growth in the absence of endothelium. *Lab Invest* 49: 327-333.
15. Schwartz SM, Stemerman MB, Benditt EP (1975) The aortic intima. II. Repair of the aortic lining after mechanical denudation. *Am J Pathol* 81: 15-42.
16. Regan CP, Adam PJ, Madsen CS, Owens GK (2000) Molecular mechanisms of decreased smooth muscle differentiation marker expression after vascular injury. *J Clin Invest* 106: 1139-1147.
17. Mason DP, Kenagy RD, Hasenstab D, Bowen-Pope DF, Seifert RA, et al. (1999) Matrix metalloproteinase-9 overexpression enhances vascular smooth muscle cell migration and alters remodeling in the injured rat carotid artery. *Circ Res* 85: 1179-1185.
18. Li G, Chen SJ, Oparil S, Chen YF, Thompson JA (2000) Direct in vivo evidence demonstrating neointimal migration of adventitial fibroblasts after balloon injury of rat carotid arteries. *Circulation* 101: 1362-1365.
19. Rodriguez-Menocal L, St-Pierre M, Wei Y, Khan S, Mateu D, et al. (2009) The origin of post-injury neointimal cells in the rat balloon injury model. *Cardiovasc Res* 81: 46-53.
20. Si Y, Ren J, Wang P, Rateri DL, Daugherty A, et al. (2012) Protein kinase c-delta mediates adventitial cell migration through regulation of monocyte chemoattractant protein-1 expression in a rat angioplasty model. *Arterioscler Thromb Vasc Biol* 32: 943-954.
21. Mallawaarachchi CM, Weissberg PL, Siow RC (2005) Smad7 gene transfer attenuates adventitial cell migration and vascular remodeling after balloon injury. *Arterioscler Thromb Vasc Biol* 25: 1383-1387.
22. Takaoka M, Nagata D, Kihara S, Shimomura I, Kimura Y, et al. (2009) Periadventitial adipose tissue plays a critical role in vascular remodeling. *Circ Res* 105: 906-911.
23. Pasquinelli G, Tazzari PL, Vaselli C, Foroni L, Buzzi M, et al. (2007) Thoracic aortas from multiorgan donors are suitable for obtaining resident angiogenic mesenchymal stromal cells. *Stem Cells* 25: 1627-1634.
24. Hoshino A, Chiba H, Nagai K, Ishii G, Ochiai A (2008) Human vascular adventitial fibroblasts contain mesenchymal stem/progenitor cells. *Biochem Biophys Res Commun* 368: 305-310.
25. Passman JN, Dong XR, Wu SP, Maguire CT, Hogan KA, et al. (2008) A sonic hedgehog signaling domain in the arterial adventitia supports resident sca1+ smooth muscle progenitor cells. *Proc Natl Acad Sci U S A* 105: 9349-9354.
26. Kleschyov AL, Muller B, Keravis T, Stoeckel ME, Stoclet JC (2000) Adventitia-derived nitric oxide in rat aortas exposed to endotoxin: Cell origin and functional consequences. *Am J Physiol Heart Circ Physiol* 279: H2743-2751.