

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/357025934>

# Perivascular Adipocytes are Components of Adventitia: Vascular “Kuiper belt”

Preprint · December 2021

DOI: 10.13140/RG.2.2.34338.35520

---

CITATIONS

23

---

READS

210

1 author:



Xinggong Wang

Renji Hospital Affiliated to Shanghai Jiaotong University School of Medicine

51 PUBLICATIONS 776 CITATIONS

SEE PROFILE

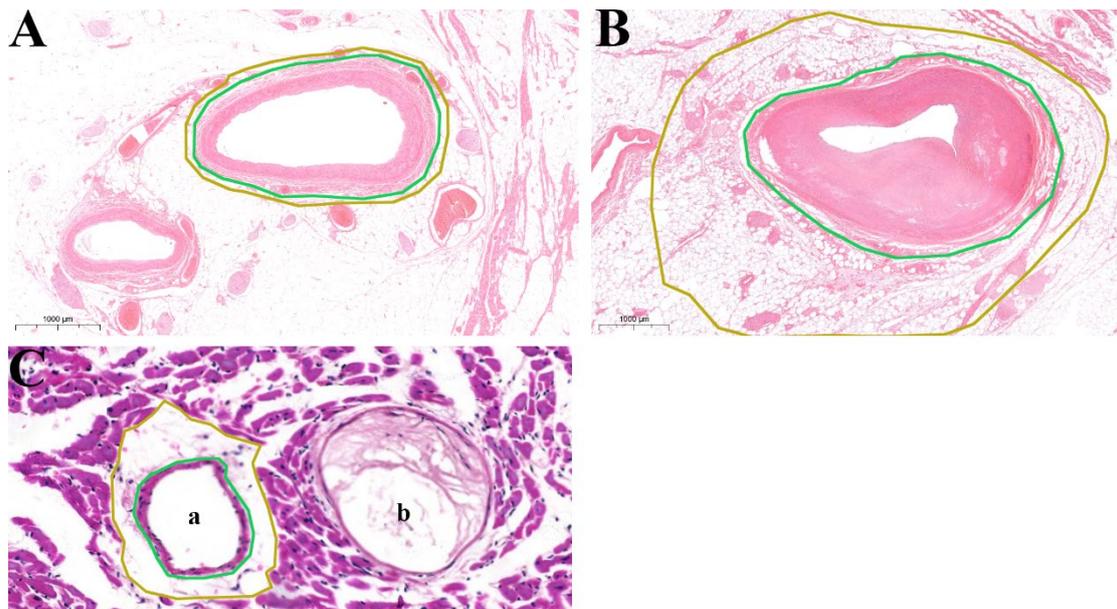
## Perivascular Adipose Tissue is Component of Adventitia: Vascular “Kuiper Belt”

Xinggong Wang, PhD

Department of Cardiology, Renji Hospital Affiliated to Shanghai Jiaotong University

School of Medicine, Shanghai, China

Email: [xinggangwang11@fudan.edu.cn](mailto:xinggongwang11@fudan.edu.cn)



**Figure 1. Perivascular Adipose Tissue is Component of Adventitia: Vascular “Kuiper Belt”**

The green mark is the inner boundary of the " Kuiper Belt " and the yellow mark is the outer boundary of the " Kuiper Belt ".

A: HE staining of normal human coronary artery showed that the vascular media is normal without obvious damage, and there is no obvious fibrous connective tissue

remodeling in both intima and adventitia. Like the intima, " Kuiper Belt " has no obvious fibrous connective tissue remodeling.

B: HE staining of human atherosclerotic coronary artery showed obvious destruction of the vascular media and obvious fibrous connective tissue remodeling of the intima and adventitia. Like the intimal fibrous connective tissue remodeling, "Kuiper Belt" has significantly fibrous connective tissue remodeling. It is suggested that there is obvious fibrous granulation tissue remodeling in intima / adventitia after vascular media dysfunction. "Kuiper Belt" is included in the scope of adventitia, which more objectively reflects the adventitia fibrous connective tissue remodeling.

C: ApoE<sup>-/-</sup> mice, high-fat diet for 6 months, as shown by HE staining of mouse coronary artery and coronary vein. Fig. a show the mouse coronary artery, and there is no obvious intimal thickening of coronary artery. The area between green and yellow is the thick " Kuiper Belt " of the coronary artery. Fig. b is the mouse coronary vein, in which a very thin " Kuiper Belt " can also be observed. Due to the much higher hydrostatic pressure in the coronary artery, a thick vascular " Kuiper Belt " formed in the artery, while a very thin vascular " Kuiper Belt " formed in the vein for much lower hydrostatic pressure.

### **Main text**

Although we usually do not feel the loss and renewal of our skin epidermal cells, the cells have been in the process of death and renewal at all times. Blood vessels are similar to our skin. Vascular cells have been in the process of death and renewal at all

times. However, the gradual loss of smooth muscle cells in the media would cause irreversible damage to blood vessels, which may lead to pathological vascular remodeling<sup>1</sup>. Except for capillaries and venules, all vessels possess three layers: intima, media and adventitia<sup>2</sup>. Traditionally, under normal physiological conditions, the media is mainly composed of smooth muscle cells and a small number of fibroblasts; The intima is composed of endothelial cells and fibroblasts; The adventitia is mainly composed of fibroblasts and macrophages<sup>2</sup>. Among these cells, smooth muscle cells are stable cells with weak regeneration ability<sup>3</sup>. Endothelial cells, fibroblasts and macrophages are labile cells, which have strong ability of regeneration, transformation, repair, and remodeling<sup>4</sup>. Various risk factors can lead to the loss / dysfunction of smooth muscle cells, which can lead to vascular medial dysfunction<sup>5</sup>, thus leading to the significant increase of hydrostatic pressure on the single cell of the intima, media and adventitia<sup>4,6-8</sup>. Other cells, such as endothelial cells, fibroblasts, mesenchymal stem cells, pericytes, would be transformed into myofibroblasts<sup>8</sup> to remodel blood vessels, leading to pressure remodeling of myofibroblasts in the media, intima or adventitia<sup>4</sup>. This paper briefly introduces the remodeling of media and intima, and finally focuses on the remodeling of adventitia. I would explain in detail why the perivascular adipocytes are essentially the same as what the foam cells are in the intima. Therefore, perivascular adipocytes are the result of adventitia remodeling, just like the foam cells of intimal remodeling, so perivascular adipose tissue should be attributed to the adventitia. The role of perivascular adipose tissue in blood vessels is similar to that of the " Kuiper Belt " in the solar system. Therefore, the belt formed by vascular adventitia

remodeling composed of perivascular adipocytes and a small amount of fibrous connective tissue be named the **vascular " Kuiper Belt "**.

### **Media remodeling**

Because the media is located between the two elastic membranes, the media is a relatively stable layer of blood vessels<sup>4</sup>. This layer is mainly composed of a large number of smooth muscle cells and a small number of fibroblasts. Smooth muscle cells are stable cells, and their regeneration ability is very weak<sup>3</sup>. Various risk factors can lead to the loss / dysfunction of smooth muscle cells, which causes vascular media dysfunction<sup>1,5,9</sup>. Severe media dysfunction could lead to remodeling of myofibroblasts in media, intima or adventitia<sup>4,10</sup>. Vascular medial fibrosis can maintain the structural relative integrity and partial function of the media. With the gradual loss of smooth muscle cells in the vascular media, fibrous tissue will gradually degenerate, and the structure and function of the vascular media would gradually lose<sup>4</sup>.

### **Intima remodeling**

Under normal physiological conditions, the intima is mainly composed of endothelial cells and fibroblasts. These cells have strong ability of proliferation, transformation and repair. Therefore, if a small number of endothelial cells injury, endothelial cells or fibroblasts could renew these damaged cells to remain the intact of the endothelium<sup>1</sup>. Human pathological studies found that the endothelium is intact seen by microscopy or electron microscopy in initial lesion of atherosclerosis<sup>11</sup>. Therefore, compared with the media, the slow injury of only a small number of intimal cells is unlikely to lead to serious intimal dysfunction.

Medical devices, vascular bending / bifurcation with rapidly varied flow, serious infection, inflammation, etc. could cause rapid and severe damage to the intima<sup>1,4,6</sup>. If the intima remodeling is insufficient, it would lead to dissection<sup>1</sup>. Only with intimal injury, if it can be repaired, it would be completely repaired and would not cause dissection<sup>1</sup>. Because the morphology of myofibroblasts is similar to that of smooth muscle cells and has common cell markers, such as  $\alpha$ -SMA, many previous studies mistook myofibroblasts in the intima as smooth muscle cells<sup>12</sup>.

My previous papers have described intimal remodeling in detail<sup>1,4-7,9,10,12-18</sup>. Therefore, it would not be described in detail here.

### **Adventitia remodeling**

The adventitia is mainly composed of fibroblasts, macrophages, fibrous connective tissue, etc<sup>2</sup>. Like intimal remodeling, adventitia remodeling also plays an important role in vascular remodeling<sup>4,16</sup>. Like our skin, vascular adventitia is being renewed all the times. Because the adventitia is closely connected with perivascular adipocytes, fibrous connective tissue is widely distributed in the surrounding adipocytes, and the scope of the adventitia is difficult to determine<sup>16</sup>. The traditional concept that the vascular adventitia is thin is actually inaccurate. In fact, the adventitia should be much wider than that of the traditional concept. In my paper, I have explained that intimal foam cells and perivascular adipocytes are essentially the same cells (intimal foam cells= perivascular adipocytes)<sup>16</sup>. The difference between adventitia and intima is mainly in the following aspects (Table 1).

	Source of Foam cells /Adipocytes	Cell size of Foam cells /Adipocytes	Looseness of Fibrous connective tissue
<b>Intima</b>	Myofibroblast, Macrophage, etc.	Smaller	Dense
<b>Adventitia</b>	Myofibroblast, Macrophage, etc.	Larger	Loose

**Table 1**

Therefore, the adventitia is actually much thicker and should include a large number of perivascular adipocytes<sup>16</sup> and some loose fibrous connective tissue (Figure 1). Therefore, adventitia should be composed of fibrous connective tissue, fibroblasts, macrophages and perivascular adipocytes (foam cells) outside the external elastic membrane (Figure 1). When vascular media dysfunction occurs, just like the intima fibrous connective tissue remodeling, it could also lead to adventitia “Kuiper Belt” fibrous connective tissue remodeling<sup>16,19</sup>(Figure 1). Perivascular adipocytes are the result of adventitia remodeling, just as the foam cells in the intima are the result of intimal remodeling (intimal foam cells= perivascular adipocytes)<sup>16</sup>. Because foam cells are part of the intima, perivascular adipocytes should also be part of the adventitia. Like the "Kuiper Belt" in the solar system, although the "Kuiper Belt" is close to the outer edge of the solar system and is so far from the sun, it still belongs to the scope of the solar system. Similarly, the perivascular adipocytes should also be included in the scope of vascular adventitia, which is more objective and reasonable (Figure 1).

All layers of blood vessels have certain plasticity. The plasticity of vascular media is poor, while the plasticity of intima / adventitia is strong. If vascular media dysfunction occurs, the intima / adventitia could fibrous connective tissue remodeling

to compensate for medial dysfunction, which leads to atherosclerosis, stiffening, aneurysms, etc<sup>4,6,17</sup> (Figure 1). This is not just a conceptual innovation, it would make us re understand the formation, remodeling and degradation of blood vessels. In the future, we would treat vascular diseases by regulating the vascular "Kuiiper belt"<sup>19,20</sup>.

## References

- 1 Wang, X. Atherosclerosis. *Researchgate:354706286*, doi:10.13140/RG.2.2.28605.18402/1.
- 2 Standring, S. *GRAY'S Anatomy*. 41 edn, 134 (elsevier, 2016).
- 3 Holifield, B. *et al.* Differentiated vascular myocytes: Are they involved in neointimal formation? *Journal of Clinical Investigation* **97**, 814-825, doi:10.1172/jci118481 (1996).
- 4 Wang, X., Sun, A. & Ge, J. Medial Injury/Dysfunction Induced Granulation Tissue Repair is the Pathogenesis of Atherosclerosis. *arXiv:2010.06683*.
- 5 Wang, X. Types of Vascular Media Dysfunction and Possible Risk Factors. *Researchgate:355486212*, doi:10.13140/RG.2.2.16052.99202.
- 6 Wang, X. & Ge, J. Haemodynamics of atherosclerosis: a matter of higher hydrostatic pressure or lower shear stress? *Cardiovasc Res* **117**, e57-e59, doi:10.1093/cvr/cvab001 (2021).
- 7 Wang, X. & Ge, J. Hypertension Aggravates Atherosclerosis: A Matter of Pressure Remodeling of Myofibroblasts or LDL Accumulation? *J Am Coll Cardiol* **77**, 2619-2620, doi:10.1016/j.jacc.2021.03.305 (2021).
- 8 Tomasek, J. J., Gabbiani, G., Hinz, B., Chaponnier, C. & Brown, R. A. Myofibroblasts and mechano-regulation of connective tissue remodelling. *Nature Reviews Molecular Cell Biology* **3**, 349-363, doi:10.1038/nrm809 (2002).
- 9 Wang, X. In Situ Venous Atherosclerosis. *Researchgate:355339577*, doi:10.13140/RG.2.2.11589.99040.
- 10 Wang, X. Muscle Dysfunction and Myofibroblasts Remodeling in Cardiovascular Diseases. *Researchgate:355910950*, doi:10.13140/RG.2.2.29958.09284.
- 11 Shor, A. *Chlamydia Atherosclerosis Lesion: Discovery, Diagnosis and Treatment*. 71 (Springer, 2007).
- 12 Wang, X. & Ge, J. Atherosclerotic Plaque Healing. *New England Journal of Medicine* **384**, 293-293, doi:10.1056/NEJMc2033613 (2021).
- 13 Wang, X. Macrophages Transform into Foam Cells by Phagocytosing Tissues Formed by Myofibroblasts. *Researchgate:354508855*, doi:10.13140/RG.2.2.26707.91680/2.
- 14 Wang, X. Promising Etiological Treatments of Artery Diseases. *Researchgate:354507399*, doi:10.13140/RG.2.2.15802.72641/1.
- 15 Wang, X. Steroid Hormones Affect Vascular Diseases through Myofibroblasts. *Researchgate:354534894*, doi:10.13140/RG.2.2.17257.62565.
- 16 Wang, X. Intimal Foam cells and Perivascular Adipocytes are Essentially Similar.

- Researchgate:356972652*, doi:10.13140/RG.2.2.29364.17284.
- 17 Wang, X. & Ge, J. Myofibroblast Forms Atherosclerotic Plaques. *bioRxiv:2020.07.20.212027*, doi:10.1101/2020.07.20.212027.
- 18 Wang, X. & Ge, J. Spontaneous Coronary-Artery Dissection. *New England Journal of Medicine* **384**, 1077-1077, doi:10.1056/NEJMc2100339 (2021).
- 19 Wang, X. Physical Principles of Vascular Developing and Remodeling. *Researchgate:357220855*, doi:10.13140/RG.2.2.20693.76003.
- 20 Wang, X. & Tian, S. Principle of Transformation between Fibrous Connective Tissue and Adipose Tissue. *Researchgate:357657830*, doi:10.13140/RG.2.2.17756.10883.