Misrepair mechanism in the development of atherosclerotic plaques

Jicun Wang-Michelitsch¹*, Thomas M Michelitsch²

¹Department of Medicine, Addenbrooke's Hospital, University of Cambridge, UK (Work address until 2007)

²Institut Jean le Rond d’Alembert (Paris 6), CNRS UMR 7190 Paris, France

Abstract

Atherosclerosis is a disease characterized by the development of atherosclerotic plaques in arterial endothelium. The atherosclerotic plaques in a part of arterial wall are inhomogeneous on size and on distribution. In order to understand this in-homogeneity, the pathology of atherosclerotic plaques is analyzed by Misrepair mechanism, a mechanism proposed in our Misrepair-accumulation aging theory. I. Development of an atherosclerotic plaque is a result of repair of injured endothelium. Because of infusion and deposition of lipids beneath endothelial cells, the repair has to be achieved by altered remodeling of local endothelium. Such a repair is a manifestation of Misrepair. During repair, smooth muscular cells (SMCs) are clustered and collagen fibers are produced to the lesion of endothelium for reconstructing an anchoring structure for endothelial cells and for forming a barrier to isolate the lipids. II. Altered remodeling (Misrepair) makes a local part of endothelium have increased damage-sensitivity and reduced repair-efficiency; thus this part of endothelium will have increased risk for injuries, for lipid-infusion and for Misrepairs. Focal accumulation of Misrepairs and focal deposition of lipids result in development of a plaque. III. By a viscous circle between lipid-infusion and endothelium-Misrepair, growing of a plaque is self-accelerating. Namely, once a plaque develops, it grows in an increasing rate with time and it does not stop growing. Within a part of arterial wall, older plaques grow faster than younger ones; thus old plaques are always bigger than new ones, resulting in an in-homogenous distribution of plaques. The oldest and the biggest plaque is the most threatening one in narrowing local vessel lumen; therefore the accelerated growing of plaques is a fatal factor in atherosclerosis.

Keywords

Atherosclerosis, atherosclerotic plaque, in-homogeneity, focalization, Misrepair, aging, Misrepair-accumulation theory, altered remodeling, endothelium, infusion of lipids, damage-sensitivity, repair-efficiency, smooth muscular cells, collagen fibers, accelerated, and viscous circle

*email : thomasjicun@gmail.com
Introduction

Atherosclerosis is a disease characterized by the development of atherosclerotic plaques in arterial walls. Growing of a plaque makes local arterial wall thick and stiff and makes arterial lumen narrow. An atherosclerotic plaque can block blood circulation when it is too big or when it drops off from the wall, becoming a blood clot. Atherosclerosis is the main cause for several fatal diseases, including coronary artery diseases, cerebral thrombosis, and aortic aneurysm. In a part of arterial wall, atherosclerotic plaques distribute in-homogenously, and they have different sizes and different shapes. Atherosclerosis is a typical aging-associated disease; however traditional aging theories cannot interpret the in-homogeneity of plaques. For example, gene-controlling theory suggests that aging is a process that is controlled completely and independently by certain genes theory (Fabrizio, 2010; McCormick, 2012). However, if such genes exist, they should work in the same way in all cells, and aging changes should develop homogenously. Damage-accumulation theory predicts that aging is a result of accumulation of faults (damage) (Kirkwood, 2005). However, if the random faults are the origins of aging, accumulation of faults should result in a homogenous distribution of aging changes. In the present paper, we will demonstrate that our novel aging theory, the Misrepair-accumulation theory, is able to explain the in-homogeneity in the development of atherosclerotic plaques and other aging changes (Wang, 2009). Our discussion will tackle the following issues:

I. Development of an atherosclerotic plaque: a result of Misrepairs of endothelium
   1.1 An generalized concept of Misrepair
   1.2 Development of an atherosclerotic plaque: a result of Misrepairs for sealing endothelium

II. Accelerated growing of atherosclerotic plaques
   2.1 Accumulation of Misrepairs: focalized and self-accelerating
   2.2 Growing of an atherosclerotic plaque: self-accelerating
   2.3 Effect of low-dose aspirin on the growing of atherosclerotic plaques

III. Conclusions

I. Development of an atherosclerotic plaque: a result of Misrepairs of endothelium

On the mechanism of development of atherosclerosis, some theories have been proposed, including cholesterol (lipid)-deposition theory, myoblast-mutation theory, platelet-accumulation theory, and endothelium injury-response theory (Ross, 1986). Among them, the endothelium injury-response theory is mostly accepted till today. This theory suggests that development of atherosclerosis is an inflammatory response to the injuries of endothelium. In
fact, this response is finally for repairing and healing the injured endothelium however with a result of “Misrepair”, namely, an altered remodeling of the local endothelium.

1.1 A generalized concept of Misrepair

To have a unified understanding of aging changes, we proposed a generalized concept of Misrepair in the Misrepair-accumulation theory. The new concept of Misrepair is defined as *incorrect reconstruction of an injured living structure*. It is applicable to all living structures including molecules (DNAs), cells, tissues, and organs; and Misrepair of DNA is a special case. A Misrepair takes place when complete repair is impossible to achieve in the situation of a severe injury. The strategy of Misrepair is essential for maintaining the structural integrity and increasing the surviving chance of an organism. However, a Misrepair results in alteration of the structure and reduction of the functionality of a cell or a tissue. The changes of a structure caused by Misrepairs are irreversible and irremovable; thus they accumulate and deform gradually a living structure, appearing as aging of it. Aging of an organism is a process of accumulation of Misrepairs of its structure. Misrepairs enable an organism to survive till mature age to have children; therefore Misrepair mechanism is essential for the survival of a species. Aging of individuals is a sacrifice for species’ survival.

1.2 Development of an atherosclerotic plaque: a result of Misrepairs for healing endothelium

The pathological changing of an atherosclerotic plaque is complicated. The changing is corresponding to a series of responses of local tissue to the injuries of endothelium. A promoting affair of this process is an injury of endothelial lining and infusion of lipids through the lesion. Basement membrane is the anchoring matrix for endothelial cells; however lipid-deposition separates the endothelial cells from basement membrane. Without anchoring matrixes for endothelial cells, sealing of endothelium would be impossible. For rebuilding an anchoring structure, the smooth muscular cells (SMCs) in the media layer of the arterial wall proliferate, immigrate and cluster to the lesion of endothelium, and then produce collagen fibers. These collagen fibers are organized in a special structure and become the anchoring matrix for local endothelial cells. Infused lipids can possibly diffuse in the space between endothelial cells and basement membrane. For restricting the diffusion of lipids, local mononuclear cells cluster and swallow the lipids, functioning as the first barrier of lipids. However, too much lipids can overload the capacity of mononuclear cells; thus a fibrotic membrane made of SMCs and collagen fibers becomes the second barrier. This membrane and basement membrane compose into a fibrotic capsule, which can isolate the lipids and the foam cells in it. Isolating the lipids in this capsule is a part of sealing of endothelium. Without this capsule, lipid-diffusion could deprive more endothelial cells of their anchoring basement membrane. SMCs can deform reversibly, and they give the capsule a certain degree of deformity.

With increase of infusion of lipids, a capsule becomes bigger by including more lipids in more layers of membrane made of SMCs and collagen fibers, and a protruding fibrotic plaque...
develops. With death of foam cells and releasing of necrotic substance, a fibrotic plaque becomes an atherosclerotic plaque. Disruption of a protruding plaque can result in a big lesion in endothelium, which looks like an ulcer in the arterial wall. Healing of the endothelium of this ulcer needs to undergo along the edge of the lesion, resulting in a hole in the plaque. In summary, the changes of a plaque in different stages are results of repairs for healing the endothelium; however because of the deposition of lipids, the way of repair is changed and the structure of endothelium is altered. Development of a plaque is therefore a result of accumulation of Misrepairs.

II. Accelerated growing of atherosclerotic plaques

Atherosclerotic plaques develop focally, appearing as growing of plaques. Why do lipids infuse focally rather than homogenously in endothelium? In our view, the focal infusion of lipids and the focal development of plaques are results of focalized and self-accelerating accumulation of Misrepairs of endothelium. The self-accelerating on the growing of plaques is the mechanism for the in-homogeneity of plaques on distribution. Accelerated growing of a plaque is a fatal factor in atherosclerosis.

2.1 Accumulation of Misrepairs: focalized and self-accelerating

In general, a Misrepair can increase the surviving chance of an organism from a severe injury; however it results in alteration of the structure and reduction of the functionality of a tissue/organ. The part of tissue that contains a Misrepair will have reduced efficiency on making adaptive responses to environment changes; thus it becomes more sensitive to damage. In the same time, a Misrepair disturbs local substance-transportation and cell-communication, by which it reduces the repair-efficiency of local tissue. With increased damage-sensitivity and reduced repair-efficiency, this part of tissue will have increased risk to be injured and to be repaired with Misrepairs. In another word, Misrepairs have a tendency to accumulate to the part of tissue and its local area where an old Misrepair has taken place. The frequency of Misrepairs to this part of tissue will be increased and the affected area of tissue will be enlarged after each time of Misrepair in a viscous circle. Accumulation of Misrepairs is thus self-accelerating and focalized, resulting in the development of a spot or a plaque. The growing of a spot is also self-accelerating. Misrepair is the origin for the development of a spot, and it is also the force to drive and accelerate the growing of the spot. Multiple Misrepairs that occur to different parts of a tissue will result in development of multiple spots. Older spots grow faster than younger ones; thus older ones are always bigger than younger ones, resulting in the inhomogeneous distribution of spots.

2.2 Growing of an atherosclerotic plaque: self-accelerating

In atherosclerosis, lipid-infusion results in altered remodeling of endothelium; and this change on structure leads to increased damage-sensitivity and reduced repair-efficacy of local endothelium. On one hand, loss of anchoring to basement membrane makes the local endothelial cells fragile. These cells might not be able to deform efficiently for adapting to the
repeated deformations of the arterial wall. On the other hand, local substance-transportation and cell-communication can be disturbed by lipid-deposition and alteration of endothelium structure, and the repair-efficiency of local endothelium is reduced. Because of increased damage-sensitivity and reduced repair-efficiency, this part of endothelium has increased risk for injuries and for lipid-infusion. Each time of lipid-infusion will promote the clustering of SMCs and the production of collagen fibers for rebuilding anchoring structure for endothelial cells and for isolating the lipids. The fibrotic capsule made of SMCs, collagen fibers and basement membrane becomes bigger by including more lipids in more layers of SMCs and collagen fibers. Infusion of lipids and Misrepair of endothelium enhance each other by a viscous circle; and the enlargement of a fibrotic capsule is accelerated (Figure 1). Growing of a plaque is therefore self-accelerating. Namely, once a plaque develops, it cannot stop growing and it grows in an accelerated rate with time. Older plaques grow faster than younger ones, and older ones are always bigger than younger ones, resulting in an inhomogeneous distribution of plaques (Figure 2).

**Figure 1. A vicious circle between lipid-infusion and altered remodeling (Misrepair) of endothelium**

In atherosclerosis, lipid-infusion results in altered remodeling (Misrepair) of endothelium and formation of a plaque. This change on structure leads to increased damage-sensitivity and reduced repair-efficacy of local endothelium. As a result, injuries and lipid-infusion have increased opportunity to occur to this part of endothelium. Infusion of lipids and altered remodeling of endothelium compose a viscous circle, by which they enhance each other and accelerate the accumulation of Misrepairs of endothelium and the growing of a plaque.
Figure 2. Accelerated growing of atherosclerotic plaques

Focal deposition of lipids and focal accumulation of Misreparis of endothelium result in development of atherosclerotic plaques. Growing of a plaque is self-accelerating. Thus, older plaques grow faster than younger ones (1° > 2° > 3°), and older ones are always bigger than new ones (1° > 2° > 3°), resulting in an inhomogeneous distribution of plaques (A - B).

2.3 Effect of low-dose aspirin on the growing of atherosclerotic plaques

The size of a plaque is an important factor for determining the degree of narrowing of local vessel lumen by plaques. However, for blocking an artery, the thickness of a plaque, namely the protruding degree of the plaque into arterial lumen, is more critical. Thus reducing the rate of increase of the thickness of plaques could be possibly a way to delay the blockage of arteries. A strategy that can induce a plaque to grow more flatly would be a solution for that. Some studies have shown that long-term low-dose aspirin can reduce the risk of atherosclerosis-caused heart attack (Hung, 2003; Elwood, 2006; Brotons, 2014). Aspirin has an effect on inhibiting inflammation and repair, and high-dose aspirin is dangerous by causing failure of repair. Differently, low-dose aspirin cannot completely inhibit repair, but it could possibly make a repair process slower. Slower repair will result in delayed healing of endothelium, prolonged infusion of lipids, and prolonged diffusion of lipids in endothelium. Diffusion of lipids between endothelial cells and basement membrane will make a plaque grow more in the direction along endothelium and less in the direction to lumen. Namely, delayed repair can make a plaque grow more flatly, and in this way the rate of increase of thickness of the plaque is slowed down. Low-dose aspirin may have reduced the risk of the atherosclerosis-associated diseases by altering the way of growing of plaques (Figure 3).
Figure 3. Effect of low-dose aspirin on the growing of atherosclerotic plaques

Low-dose aspirin cannot completely inhibit repair, but it could possibly make a repair process slower. Slower repair can result in delayed healing of endothelium, prolonged infusion of lipids, and prolonged diffusion of lipids in endothelium. Diffusion of lipids between endothelial cells and basement membrane will make the growing of a plaque more in the direction along endothelium and less in the direction to lumen. Thus low-dose aspirin can make a plaque grow more flatly (A-C), compared with that without treatment of aspirin (A-B). In this way, aspirin slows down the rate of increase of the thickness of plaques and reduce the risk of the atherosclerosis-associated diseases.

III. Conclusions

Development of an atherosclerotic plaque is a result of repair of injured endothelium. However, because of infusion of lipids, the repair has to be achieved by altered remodeling of local endothelium. This is a manifestation of Misrepair. A Misrepair makes a local part of endothelium have increased damage-sensitivity and reduced repair-efficiency; thus this part of endothelium will have increased risk for injuries, for lipid-infusion and for Misrepairs. Local deposition of lipids and local accumulation of Misrepairs result in development of a plaque. By a viscous circle between lipid-infusion and Misrepair of endothelium, growing of a plaque is self-accelerating. Once a plaque develops, it grows in an increasing rate with time and does not stop growing. Within a part of arterial wall, older plaques grow faster than younger ones, thus old plaques are always bigger than new ones, resulting in an in-homogenous distribution of plaques. The oldest and the biggest plaque is the most threatening one in narrowing local
arterial lumen. Low-dose aspirin can reduce the risk of the atherosclerosis-associated diseases possibly by altering the way of growing of plaques.

References

1. Brotons C, Benamouzig R, Filipiak KJ, Limmroth V, Borghi C. (2014) A Systematic Review of Aspirin in Primary Prevention: Is It Time for a New Approach? Am J Cardiovasc Drugs.
2. Elwood P, Longley M, Morgan G. (2006) My health: whose responsibility? Low-dose aspirin and older people. Expert Rev Cardiovasc Ther., 4(5), 755
3. Fabrizio P, Hoon S, Shamalnasab M, Galbani A, Wei M, Giaever G, Nislow C, Longo VD. (2010). Genome-wide screen in Saccharomyces cerevisiae identifies vacuolar protein sorting, autophagy, biosynthetic, and tRNA methylation genes involved in life span regulation. PLoS genetics 6(7):e1001024.
4. Hung J. (2003) Aspirin for cardiovascular disease prevention. Medical Issues Committee of the National Heart Foundation of Australia. Med J Aust, 179(3), 147
5. Kirkwood TB. (2005). Understanding the odd science of aging. Cell 120(4): 437-47
6. McCormick M, Chen K, Ramaswamy P, and Kenyon C. (2012). New genes that extend Caenorhabditis elegans' lifespan in response to reproductive signals. Aging Cell 11(2):192-202
7. Ross R. The pathogenesis of atherosclerosis. (1986) N Engl J Med. 314:488–500.
8. Wang J, Michelitsch T, Wunderlin A, Mahadeva R. (2009) Aging as a Consequence of Misrepair – a Novel Theory of Aging. ArXiv: 0904.0575. arxiv.org