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BIOLOGICAL CAUSES, TREATMENT AND PREVENTION OF THE ORIGIN OF ATHEROSCLEROSIS

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Annotation: Atherosclerosis is caused by plaque (fatty deposits) build up in the arteries. These deposits are made up of cholesterol, fatty substances, cellular waste products, calcium and fibrin.

Key words: vascular diseases, cardiovascular disease, Atherosclerosis,cerebrovascular diseases.

The core of the pathogenesis of atherosclerosis is a disease state of the arterial wall. In order to understand the pathogenesis of atherosclerosis, it is thus necessary to know about the function and normal morphology of non-pathological arteries.

Three layers of arterial vessel

The normal arterial vessel consists of 3 layers, namely intima, media and outer adventitia.

The intima is located closest to the arterial lumen and is therefore most 'intimate' with the blood. This layer is composed of a single layer of endothelial cells (endothelium), connective tissue, and several smooth muscle cells. The endothelium functions as an active metabolic barrier as well as a carrier between blood and the arterial wall. It plays a crucial role in atherosclerosis. Connective tissue consists of a matrix of collagen, proteoglycans and elastin. Lymphocytes, macrophages and other types of inflammatory cells may occasionally reside in the intima.

The media is the middle layer and its inner and outer boundaries are formed by the internal and external elastic laminae. The media consists of layers of smooth muscle cells with contractile and synthetic function. As for the contractile function, smooth muscle cells enable vasoconstriction and vasodilatation. As for the synthetic function, they are responsible for the growth of the vascular extracellular matrix.

The most external vessel wall layer is called the adventitia and contains fibroblasts, connective tissue, nerves, lymphatics and vasa vasorum. Inflammatory cells may also occasionally reside in the adventitia.

There is a constant dynamic interchange between the arterial wall and its cellular components and the surrounding extracellular matrix. By understanding the physiology of this dynamic interchange and the function of each cellular component, the dysfunction of these cellular components leading to atherogenesis can be better understood.

Cellular components involved in atherosclerosis

Endothelial cells

The normal artery wall contains endothelial cells that manage the homeostasis of the wall by structural, metabolic, and signaling functions. The endothelium plays a role as a barrier to elements contained in the blood, but is also an active biologic interface between the blood and other tissues, regulating cellular and nutrient trafficking. It has several important functions such as keeping certain elements in blood separated from the vessel and maintaining a balance between pro-coagulant and anticoagulant activity, pro- and anti-inflammatory response, and contracted and relaxed vasomotor tone.

The endothelium produces antithrombotic molecules in order to prevent blood from clotting. Certain molecules such as heparin sulfate, thrombomodulin, and plasminogen rest on the endothelial surface

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whereas molecules such as prostacyclin and nitric oxide (NO) enter the blood. Endothelium can produce prothrombotic molecules when it encounters stressors; however, it normally maintains a balanced anticoagulant state, maintaining blood fluidity.

Endothelial cells also have an important function as a regulator of the immune response. In a normal situation without pathologic stimuli, endothelial cells are not capable to attract and bind patrolling leukocytes, thus maintaining an anti-inflammatory state. When local injury or infection initiates pathologic stimulation, endothelial cells respond by secreting chemokines that attract white blood cells to the injured area. Additionally, endothelium produces cell surface adhesion molecules, which recruit mononuclear cells to the endothelium and therefore promote their migration to the injury site. This response is important for the development of atherosclerosis.

Another function of endothelium is to modulate contraction of smooth muscle cells in the media by releasing substances such as vasodilators and vasoconstrictors. Vasodilators (e.g. NO, prostacyclin) and vasoconstrictors (e.g. endothelin) fine-tune the resistance of the vessel and subsequently alter the arterial blood flow. Endothelium normally maintains a state of net relaxed vasomotor tone with a predominance of vasodilators. Endothelium can also respond to various physical stimuli such as shear stress and can additionally dilate the blood vessel. The endothelium principally regulates such response through release of NO. This endothelial-dependent response is called flow-mediated vasodilation (FMD), which can be measured for clinical evaluation of endothelial function. For example, impairment of FMD is observed in the early stages of atherosclerosis. However, endothelial function tests are currently not recommended to be used for surrogate markers in clinical practice since the tests are technically challenging and the validation of clinical benefits in the evaluation of cardiovascular risk requires more evidence.

As mentioned earlier, endothelial cells can respond to or in other words get ‘activated’ due to changes in the local extracellular milieu. Examples of such changes are common stresses (e.g. shear stress and mild changes in temperature), transient infections and minor trauma. The term ‘endothelial cell activation’ (EC activation) refers to a change from the normal state, illustrated by loss of barrier function, pro-adhesive (leukocyte adhesion), vasoconstriction, and procoagulant properties. EC activation is not necessarily linked to disease and can be temporary and mild or permanent and severe.

In conclusion, the normal arterial endothelium consists of a dynamic interface with net anticoagulant properties, net relaxation of smooth muscle cells and anti-inflammatory characteristics. Endothelial cells may react to various changes in homeostasis and become ‘activated endothelial cells’.

Vascular smooth muscle cells

As mentioned earlier, smooth muscle cells have two functions, namely contractile and synthetic. Vasoconstriction and vasodilatation are regulated by various vasoactive substances such as angiotensin II, acetylcholine, NO and endothelin, which are released by endothelium. Another element of contractile function is the elasticity of the vessel, which is regulated by the lamina elastica. They are situated between the smooth muscle cells and are responsible for the stretching of the vessel during systole and diastole. This function is crucial in the pathogenesis of atherosclerosis, because it prevents the weakening of the vessel wall that can prevail as a complication of atherosclerosis. For example, aneurysm due to weakening of the vessel wall is a serious complication of atherosclerosis.

It is important to understand the synthetic function of smooth muscle cells since the dysfunction of it is thought to contribute to the pathogenesis of atherosclerosis. Normally the smooth muscle cells synthesize collagen, elastin and proteoglycans that form the connective tissue matrix of the vessel wall. Smooth muscle cells can also synthesize vasoactive and inflammatory mediators such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF- α). These mediators stimulate leukocyte

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migration and induce the endothelial cells to express leukocyte adhesion molecules as mentioned earlier. This synthetic function is found to be more dominant in case of an atherosclerotic plaque, which is illustrated in the next section (1.2). Although smooth muscle cells rarely divide in normal circumstances, it can proliferate in response to injury, which is an important sign of atherosclerotic plaque formation.

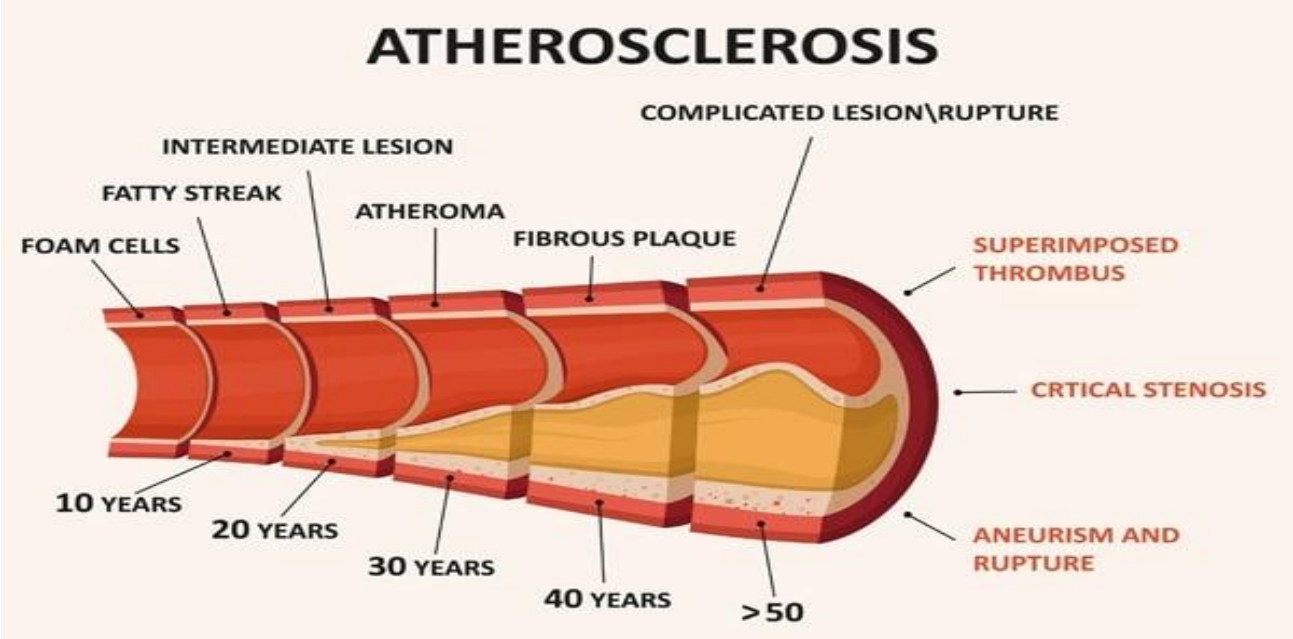
Extracellular matrix

Vascular extracellular matrix in the media consists of elastin, proteoglycans and fibrillar collagen, which are principally synthesized by smooth muscle cells as mentioned earlier. With the provision of flexibility by elastin and biomechanical strength by fibrillar collagen, the arterial vessel is able to maintain the structural integrity despite high pressure within the lumen.

Three pathologic stages of atherogenesis

Atherogenesis can be divided into five key steps, which are 1) endothelial dysfunction, 2) formation of lipid layer or fatty streak within the intima, 3) migration of leukocytes and smooth muscle cells into the vessel wall, 4) foam cell formation and 5) degradation of extracellular matrix. Via these consecutive steps, an atherosclerotic plaque is formed. The formation of the plaque can also be divided into three major stages namely 1) the fatty streak, which represents the initiation 2) plaque progression, which represents adaption and 3) plaque disruption, which represents the clinical complication of atherosclerosis.

Figue 1



Initiation and formation of atherosclerotic plaque

The earliest visible signs of atherogenesis are the fatty streak and pre-existing lesions of adaptive intimal thickening. Fatty streak is a yellow discoloration on the surface of the artery lumen, which is flat or slightly elevated in the intima and contains accumulations of intracellular and extracellular lipid. At this stage of initiation, the fatty streak doesn't protrude substantially into the artery wall nor impedes blood flow. This process is already visible in most people by the age of 20. At this stage, there are no symptoms and this lesion may even diminish over time. Initiation of fatty streak development is most likely caused by endothelial dysfunction, since it involves entry and

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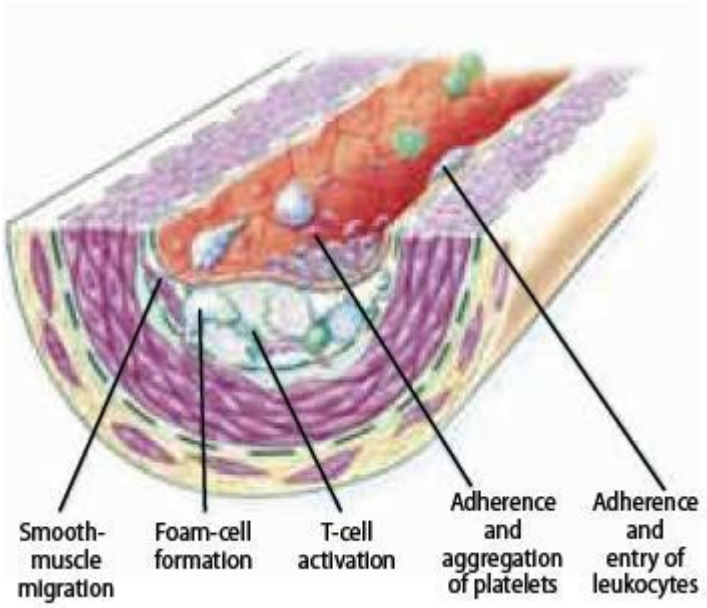
modification of lipids within the subintima. This modified layer of lipids creates a proinflammatory environment and initiates the migration of leukocytes and formation of foam cells (Figure 5). Intimal thickening mainly contains smooth muscle cells and proteoglycan-collagen matrix with a few or no infiltrating inflammatory cells.

Figue 2



Lipoprotein entry and modification

Disruption of the integrity of endothelial barrier due to endothelial dysfunction allows the passage of circulating lipoproteins (low-density lipoprotein, LDL) into the intima. By binding to proteoglycans, LDL particles start to accumulate. This accumulation is a critical process in atherogenesis since LDL may undergo chemical modifications while residing longer in the intima. It is needless to say that an elevated circulating LDL concentration strongly contributes to this accumulating process. Another major risk factor for this process is hypertension since it causes augmented vessel wall stress. Elevated vessel wall stress influences smooth muscle cells to synthesize proteoglycans in the intima, promoting LDL-binding with proteoglycans and therefore contributing to "trapping" of lipoproteins and lipid accumulation within the intima. At this point, macrophages adhere to dysfunctional endothelial cells and transmigrate into the intima. These macrophages are called 'foam cells' after they have taken up lipids.

As mentioned earlier, chemical modification occurs with LDL when chronic accumulation takes place inside the intima. There are several types of chemical modification that may occur. One is called oxidation and it results from the chemical reaction of reactive oxygen species and pro-oxidant enzymes produced by endothelial or smooth muscle cells, or macrophages penetrating the intima. This type of oxidative stress leads to cellular dysfunction and damage in endothelial cells and macrophages. Furthermore chronic hyperglycemia can stimulate glycation of LDL that may ultimately alter LDL into an antigenic and proinflammatory molecule. This explains why diabetes mellitus is a major risk factor for atherosclerosis. The biochemical modification of LDL into a proinflammatory molecule contributes to the inflammation process established by endothelial dysfunction. Furthermore, the oxidized LDL molecule induces tissue damage, which can initiate

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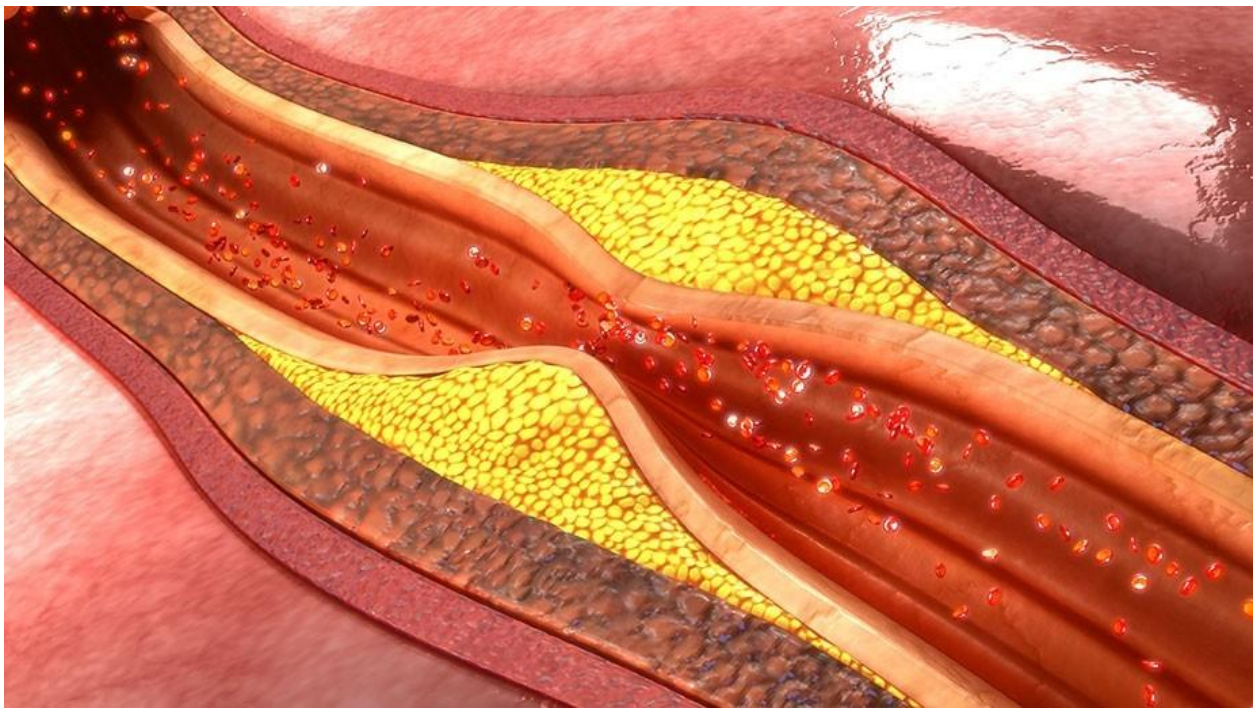
angiogenesis, forming new vasa vasorum in the plaque. It also induces leukocyte recruitment and foam cell formation in the fatty streak throughout the plaque development.

Leukocyte recruitment

Leukocyte recruitment to the arterial wall is another key step in atherogenesis, which is dependent on two important factors; expression of leukocyte adhesion molecules (LAM) on the endothelial wall and chemoattractant signals that direct diapedesis (intruding of molecules through the intact vessel wall). These two factors mainly direct monocytes to the atherosclerotic lesion. T lymphocytes that play a central role in the immune system reside within plaques at all stages of atherogenesis, mainly producing cytokines.

As mentioned earlier, modified LDL can maintain leukocyte recruitment by inducing LAM and chemokine expression. It can also stimulate endothelial and smooth muscle cells to produce proinflammatory cytokines. These proinflammatory cytokines can also induce LAM and chemoattractant cytokine expression, equivalent to the working of modified LDL. In conclusion, modified LDL can directly or indirectly promote leukocyte recruitment and atherogenesis.

Figue 3



Foam cell formation

When monocytes enter the intima, they differentiate into phagocytic macrophages. These phagocytic macrophages may become foam cells when they absorb lipoproteins. They don't phagocyte LDL with a classic cell surface LDL-receptor, since it does not recognize modified LDL, but with a family of 'scavenger' receptors that do bind and internalize modified LDL. Uptake by scavenger receptors avoids negative feedback inhibition from the high cholesterol content unlike the classic LDL-receptors, and allows the macrophages to imbibe cholesterol-rich lipid that results into the formation of foam cells. This uptake seems to be beneficial at first sight, since it absorbs the inflammatory modified-LDL, however since these foam cells have impaired trafficking, they will be locally

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accumulated in the plaque and encourage the plaque progression by serving as a source of proinflammatory cytokines.

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