AGING, ATHEROSCLEROSIS, AUTOIMMUNOINFLAMMATION, AND SYNERGISTIC PHENOMENON

Acad. ***Vasile ANESTIADI***

ETATE, ATEROSCLEROZĂ, AUTOIMUNOINFLAMAȚIE ŞI FENOMENUL "SYNERGISME"

În lucrare se analizează cele mai recente date privind rolul proceselor autoimune şi modificările de vârstă ale sistemului arterial în aterogeneză. Procesele de senescenţă contribuie la creşterea permeabilităţii arterelor, dereglarea barierei endoteliale, favorizând insudaţia componentelor plasmatice, inclusiv lipoproteinele, şi infiltraţia peretelui vascular cu monocite. Microscopia electronică cu baleiaj a suprafeţei interne a arterelor coronariene umane a demonstrat că cel mai precoce indice al leziunilor aterosclerotice este tumefierea endoteliocitelor. Sinergismul "aterogeneza-gerontogeneza" reprezintă un fenomen fundamental în evoluţia aterosclerozei, denumită şi "rugina vieţii". Este expus detaliat rolul mecanismelor autoimune în patomorfogeneza aterosclerozei. Inflamaţia imună în peretele arterial, ca reacţie la depunerea complexelor autoimune ce includ lipoproteinele modificate în calitate de antigen, este considerată un component important al aterosclerozei. Implicarea imunoinflamaţiei în mecanismele aterogenezei este apreciată drept o concepţie complet nouă, originală, descrisă recent în monografia lansată în cadrul International Academy of Pathology (Amsterdam, Montreal).

Президиум Российской Академии Медицинских Наук постановлением № 72 от 28 марта 2007 присудил авторам: Диплом премии им. А.И. Струкова, оценив как "лучшую научную работу по патологической анатомии".

În Federaţia Rusă premiat – Vladimir Nagornev; în RM premiaţi membrii A.Ş.M. – Vasile Anestiadi şi Eremia Zota.

The development of structural modifications of the arterial system, its modelling according to age-related and functional, especially haemodynamical parameters, its gerontogenesis plus *"injury"*, finally determine atherogenesis and pathomorphosis, named the *"life rust"*.

Age-related modifications in the artery substrate metabolism lead to braditrophism, evidentiating by aging. The primary factor, which changes the status of glycosaminoglycanes and enzyme systems'activity, contributes to hyperpermeability and breaking of the endothelial barrier, making easier the transport of high-molecular plasma components, including lipoproteins. *"Stigmata"* and *"stomata"*, alteration and desquamation of endothelium can be seen.

The accelerated increase of plasma insudation, accompanied with arterial wall infiltration, may contribute to atherogenesis. *Apo-beta* containing LDL, and VLDL accumulate mostly in intima, in GAG-complexes. Lipoprotein particle's electric potential influences LDL catabolism and is regarded as an important age-related factor. The *"injury"* phenomenon and the involution of the arterial substrate play the determining role in *atherosclerosis*' setting up and further development.

The synergy *"atherogenesis-senescence"* is evidentiating in a progressive and parallel mode during the aging process.

Arterial injury is manifested (a) by increased endothelial permeability, which leads to plasma and glucoprotein insudation and some monocyte infiltration into the innermost wall layers, (b) lamellar disintegration (fragmentation and fraying), and (c) variable medial myocyte destruction; *proliferative reaction* to the injury consists primarily of smooth muscle proliferation into the subendothelial (intimal) and, initially,some elastic neoformation by the proliferating myocytes; *lipid deposition* consists of (a) intracellular lipid accumulation in myocytes and immigrant monocytes that turns both cells into *"foam cells"*, and (b) extracellular amorphous lipid deposits, some of them apparently bound to the locally accumulated glucoprotein products (Paris Constantinides).

The studies of macroscopically intact surfaces of the intima of human coronary arteries by means of scanning electron microscopy have revealed the earliest signs of the atherosclerotic changes such as endothelium swelling. These phenomena are caused by the oedema of the subendothelial layer.

The endothelial cells from the oedematous zone prolapse into the arterial lumen, forming balloon-like or cone-like protrusions with the development of crater-shaped defects on the top. Endothelium is alterated - oedema serofibrinous and deformated glycocalix.

It is possible to note monocyte migration into

the intima through crater-shaped formations of the elongated endothelial cells, subsequent monocyte fixation and thrombocyte adhesion to such zones. There can also be noted a penetration of some non-identifiable cells. The role of monocytes is very important in the functioning of the *"scavenger"* mechanism of LDL catabolism and in foam cells formation.

The *"injury"* phenomenon, in connection with the age-determined involution of the arterial substrate, instigates the synergism *"atherogenesis-gerontogenesis"* - the fundamental phenomenon in disease's maleficent advancement dynamics.

The remission reflects the *pathomorphosis* of the regression of *atherogenesis*.

Lipoproteins have a wide spectrum of regulatory effects, which change during aging and atherogenesis, influenting upon the vascular status. The atherosclerotic process affects also the microcirculation.

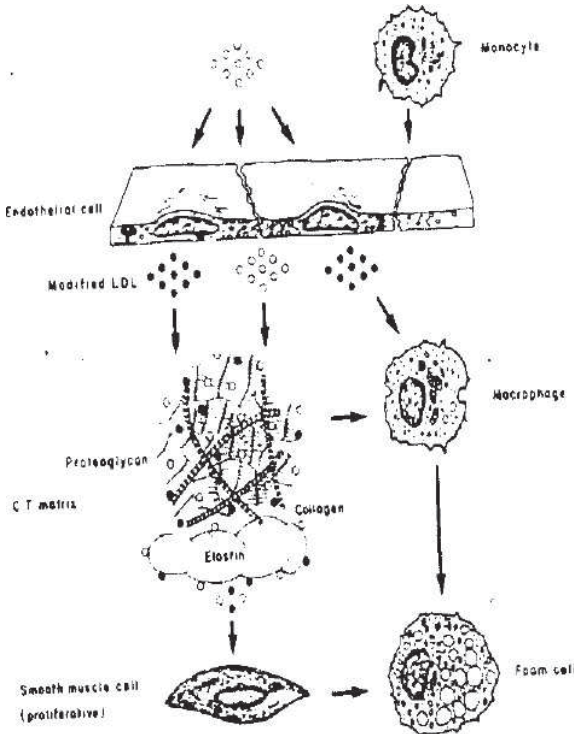

Figure 1. ***Schema illustrates the potential mechanisms of arterial proteoglycans and lipid accumulation***

Note. Native lipoproteins are modified during their pass through endothelium. The components of the connective tissue matrix (CT), especially proteoglycans are trapping die native and modified low density lipoproteins, building a complex. A part of this complex can be grasped by monocyte - derived macrophages (possibly, also by proliferating smooth muscle cells), which subsequently transform into foam cells (after Radhakrishnamurthy B. et al., 1990).

During initial and progressing stages of atherogenesis, the sedimentation of *apo*-B-containing LP, IgG, C3-fraction of the comple ment takes place in the same zones of the aortal and coronary walls, both in human and in experimental modeles.

In 1981, in Anichkov Atherosclerosis laboratory in Saint-Petersburg, there has been discovered immunomorphologically an "immune complex", more precisely - its components.

A vast importance during aging and athero sclerosis is attributed to local humoral regulatory factors, the capability to maintain the tissue trophies, their potential and, conversely, the progressive diminishing of their potential. A special role is attributed to the endothelium function.

There was studied the role of the immune inflammation in the set-up and the development of atherosclerosis, both in experimental material and in samples, obtained during surgical operations.

There has been conducted a study of human arteries from 250 coronary patients. The material has been studied by ultrastructural and immunohistochemical methods. An universal approach to atherosclerosis pathogenesis has been elaborated, according to which humoral factors, first of all modified lipoproteins, and cells of the vascular wall are considered an entity. The arterial wall is regarded as a target organ effectuating the main pathogenetic factors. The process in the arterial wall appears as a triggered chain of ceil reactions resulting in the formation of the atherosclerotic plaque.

The immune inflammation, which develops in the vascular wall as a response to the deposition or formation of the autoimmune complex that includes a modified lipoprotein as an antigen, is considered as an integral part of atherogenesis. Arterial pro teoglycans and lipid accumulation - potential mechanisms are demonstrated on *figure 1*.

V.Nagornev and E.Zota have illustrated the possible ways of autoantigen formation in arterial intima and immune inflammation development during initial phases of atherogenesis *(figure 2)*.

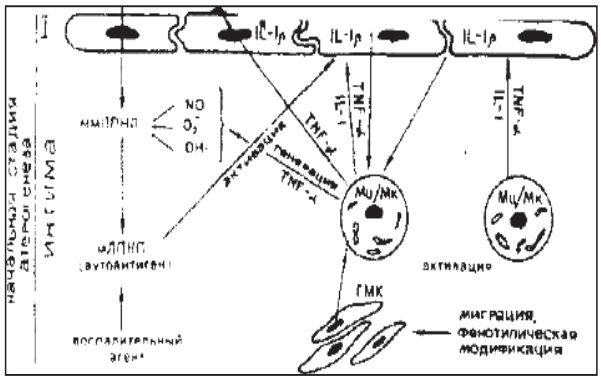

Figure 2. ***Schema illustrates the possible ways of immune inflammation during initial phases of atherogenesis***

The synergistic phenomenon "atherogenesis-gerontogenesis" manifests itself as an important factor in the complicity of mechanisms, that contribute to the acceleration of the process of biological involution. The functional-structural deviations in the cardiovascular system are determined by certain circumstances, of which the association of the immune inflammation becomes decisively oriented towards regression or progression, including atherosclerotic plaque formation.

It has been shown by injury zones, that in the earliest and in the progressing stages of the atherogenesis, both in human aorta and coronary vessels, and also in rabbits with experimental atherosclerosis, a sedimentation of *apo-B*-containing lipoproteins, immunoglobuline G, C_3-complement fraction takes place in one and the same zones.

The central place of any inflammation is occupied by the adhesion of blood leukocytes on the endothelial surface. We have shown that in the earliest stages of human atherosclerosis the focal adhesion of monocytes and lymphocytes occurs,on the intact endothelium.Leucocyte adhesion is noted over the zones of intimal accumulation of modified low density lipoproteins in the places of IL-1 and IL-8 prodiction by endotheliocytes.

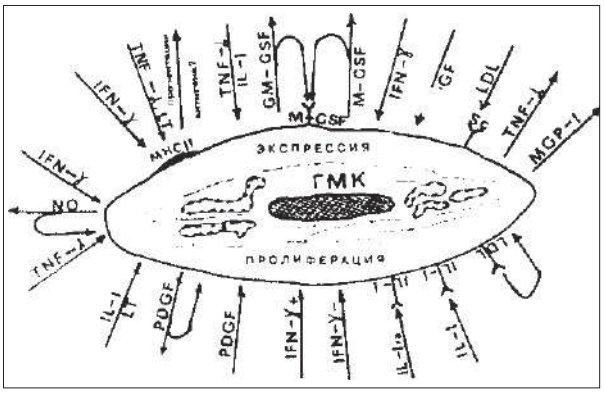

Figure 3. ***Schema illustrates the possible ways and conditions of smooth muscle cells; participation in the reaction of immune inflammation***

Note. IFN-g - interpherone-g; TNF-a - interleukin-a; LT - lymphotoxine (TNF-b); MHC II - main histocompatibility complex of the class II; IL-1 -interleukin-1; M-CSF, GM-CSF - macrophagal and granulocyte - macrophagal colonystimulating factor; PDGF - platelet-derived growth factor; Sc-scavegner-receptor; MCP1-monocyte chemotacritic protein; LDL-low density lipoproteins; IL-1b ra-IL-1 receptor antagonist; NO-nitrous oxide.

After adhesion, the monocytes and the lymphocyte actively penetrate (migrate) through the endothelium into the intima. We classify three phenotypes of macrophages, that have different functions in the atherosclerotic plagues. First phenotype is represented by the macrophages, thet have migrated through endothelium into the zone of sedimentation and/or formation *in situ* of modified low density lipoprotein, participate in scavenger-trapping of the latter and transform into foam cells.

Second phenotype is represented by the population of macrophages, that are localized in superficial and in deep zones of the atherosclerotic plaques and do not transform into foam cells, in spite the fact that they are surrounded by foam cells. Third phenotype is represented by a population of cells which also do not transform into foam cells, produce only TNF-a and are localized deep into the plaques, among cholesterol crystals and cell decay. This macrophage type we denote as cytotoxic. From blood-originating cells there are also present T-lymphocytes (CD4+, CD8+). We consider that the T-cells are activated during the immune inflammation in the arterial wall. Modified low density lipoproteins constitute the trigger mechanism of these processes. Peroxidated modified low density lipoproteins increase the DNA synthesis, HLA-DR and IL-2 expression in T-cells. The stimulating effect of mLDL on the T-cells is not direct, but is mediated via monocytes, which being influenced by LDL, express IL-1 and TNF-a, which activate the lymphocytes. Thus, the morphogenesis of atherosclerosis is linked in equal measure with modified LDL and with immune inflammation reactions, which develop in the vascular wall. Intimal cells induce

chemokines and cytokines, which make possible the adhesion and migration of blood-originating non-granular leucocytes and media-originating smooth muscle cells into the arterial intima. The following focal proliferation and cell interaction, with the participation of inflammation mediators, contribute to the formation of arterial plaques.

Î" M'CSF. IL-Q

ELAM-t. VCAM-I. ICAM-I. MCP-

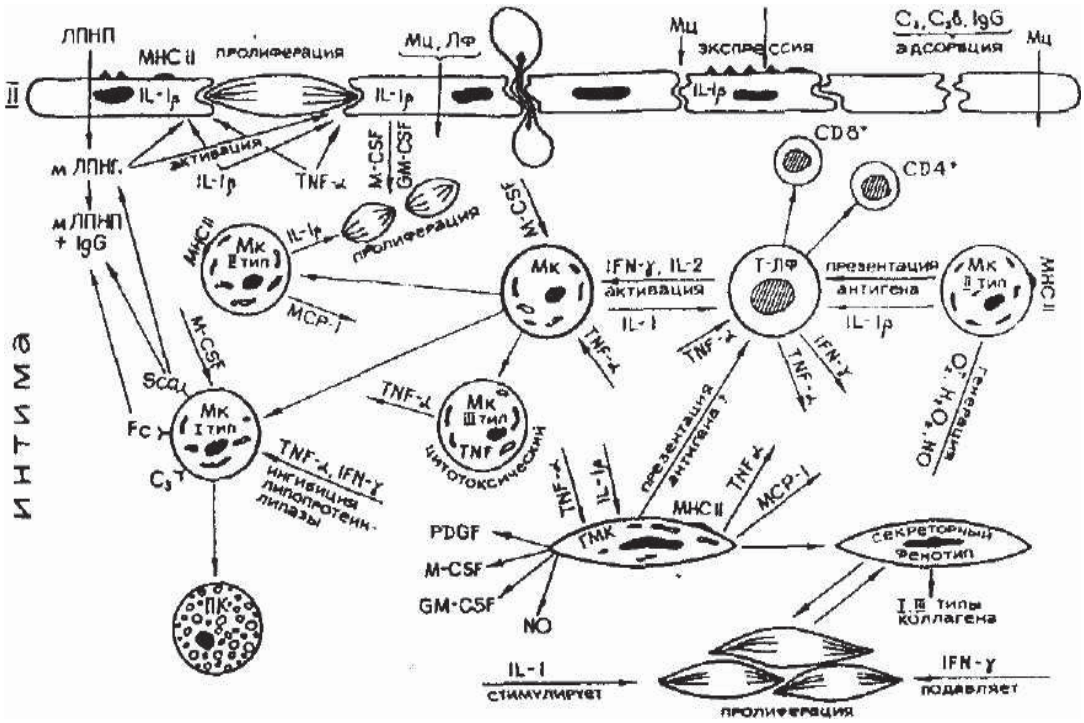

Figure 4. ***Scheme illustrates cell kinetics in the vascular wall and the role of the inflammation mediators in the process of atherosclerotic plaques formation***

Note. TNF-a (tumor necrosis factor - a): 1 - induces IL-1 production in monocytes /macrophages and endothelial cells; 2 - induces realization of M-CSF and GM-CSF in smooth muscle cells and endothelial cells; 3 - induces1L-6,IL-8production and realization;4 - induces ELAM-1 expression in endothelial cells; 5 - inhibits MHC II expression; 6 - inhibits lipoprotein lipase production in foam cells; 7 - has a cytotoxic effect on surrounding cells and tissues. Interpheron-g (INF): 1-induces MCHII expression in macrophages, smooth muscle cells, endothelial cells; 2 - activates macrophages; 3-suppresses the synthesis and secretion of lipoprotein lipase in foam cells; 4 - inhibits the expression of ICAM-1 in endothelial cells; 5 - suppresses cell proliferation.

The *"injury"* phenomenon, in connection with the age-determined involution of the arterial substrate, instigates the synergism "atherosclerosis - gerontogenesis" - the fundamental phenomenon.

The systematic pathobiological study reveals and demonstrates the most important process: the *inclusion of immunoinflammation into the mechanisms of the atherogenesis* – a totally new concept, described in the monograph launched at *International Academy of Pathology*.