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NANOPARTICLES AS AGENTS FOR TARGETED DELIVERY IN THE TREATMENT OF VASCULAR PATHOLOGIES

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Abstract

Inflammation in the pathogenesis of cardiovascular diseases. Inflammation is the cornerstone of CVD. Systemic inflammation can lead to activation of the endothelium characterized by increased expression of endothelial adhesion molecules and chemokines (e.g., vascular adhesion molecules [VCAM] and monocyte chemotactic protein [MCP-1]), as well as reduced expression of anti-atherogenic molecules. Statins are the most effective treatment for hyperlipidemia and remain the gold standard for the treatment of vascular inflammation and CVD.

New strategies and approaches to targeted delivery of drugs. These approaches are mainly based on two main aspects: 1) pharmaceutical composition which allows to encapsulate therapeutic agents; 2) surface functionalization with the help of a target agent (i.e., antibodies and small molecules) for drug delivery to endothelium. Nanostructured mesoporous silicon vectors (MSV) charged with 10-nm polymer micelles are used as a tool for the treatment of chronic heart failure. Another approach is the development of carriers that are analogues of natural adhesion molecules (CAM) or selectin ligands.

The strategy of treatment of cardiovascular diseases with preparations based on nanoparticles. For the visualization of atherosclerotic plaques, nanoparticles conjugated with indium (111In) based on antibodies bound to LOX-1 receptors of low density were used in mice.

New ideas and opportunities for drug development. 1) development of carrier-based microorganisms (such as bacteria or viruses), or cells (e.g. leukocytes, erythrocytes, platelets and stem cells); 2) development of nanoparticles with analogues of biologically active molecules that bind to cell membranes. Additional approaches include lacto-glycolic acid polymers (PLGA). Another approach to delivering drugs to the endothelium is to create a nanocapsule based on high molecular weight polymers with a nucleus containing a drug substance. This may allow switching from a three-compartment pharmacokinetic model to a one-cell model.

Key words: inflammation of blood vessels; nanoparticulate drug delivery systems; C- reactive protein; NF-kB; endothelium.

Introduction.

Currently, cardiovascular diseases (CVD) are the leading cause of urgent hospitalization and the leading cause of death in many industrialized countries. A single point of view on the causes of these diseases at the moment, not fully formulated, but experimental and clinical studies indicate a pivotal role of endothelial dysfunction in their pathogenesis [1, 2].

Cardiovascular diseases are multifactorial complex pathologies, which is usually associated with hypercholesterolemia, diabetes, smoking, hypertension and aging. It is known that each of these states contributes to damage of the vascular endothelium and the development of pathology. It should be noted that the presence of overweight contributes to the development of metabolic syndrome, inflammation of blood vessels and

progression of atherosclerosis. For example, nearly one-third of American children are overweight or obese, which contributes to the initiation they have vascular lesions. In patients with obesity, the number of macrophages, free fatty acids (FFA) and proinflammatory mediators (e.g., tumor necrosis factor-α (TNF – α), interleukin 6 (IL-6), C-reactive protein (CRP) and leptin) increases proportionally with increasing amount of visceral fat, whereas anti-inflammatory factors (adiponectin) have an inverse relationship. Free fatty acids activate a nuclear enhancement factor of Kappa-light chain of activated b cells (kappa B), which leads to the development of TNF-α. In turn, activates lipolysis, TNF – α, which increases the recruitment of macrophages and induced the synthesis of IL-6, which stimulates the production and secretion of CRP. The interaction between macrophages and adipocytes significantly increases hepatic production of CRP and may increase its level, which is one of the key risk factors for cardiovascular disease [2, 3, 4, 5, 6, 7, 8].

Inflammation in the pathogenesis of cardiovascular diseases.

Inflammation is the cornerstone of CVD. Chronic inflammation may contribute to the development of coronary atherosclerosis. The link between inflammation and coronary events, most likely related to the exacerbation of local inflammatory process in coronary plaques. Systemic inflammation can lead to activation of the endothelium characterized by increased expression of endothelial adhesion molecules and chemokines (e.g., vascular adhesion molecules [VCAM] and monocyte chemotactic protein [MCP-1]), as well as reduced expression of anti-atherogenic molecules (nitric oxide and prostacyclin). Systemic inflammation alters the blood clotting mechanism and increase platelet activation, creating a procoagulant state. Endothelial activation due to systemic inflammation may be a symptom of end-stage cardiovascular diseases such as congestive heart failure with elevated levels of circulating inflammatory cytokines (TNF-α, IL-6, CRP) [9, 10, 11, 12, 13, 14].

Proinflammatory cytokines reduce the concentration of lipoprotein cholesterol low-density particles (LCNP) and increase the concentration of triglycerides, which in turn increases the adverse lipid profile associated with cardiovascular events. In addition, it is believed that LHCP becomes more atherogenic by oxidation, and when it is stored in the subendothelial space. In the wall of the inflamed vessel, there is increased generation of reactive oxygen species (ROS), which penetrate into immune cells and activate vascular cells. Accumulated oxidized LHCP absorbed by the resident macrophages, stimulating the immune cells with the formation of inflammatory cytokines and chemokines. Set a positive feedback loop and increases the expression of adhesion molecules on endothelium to facilitate adhesion of monocytes. The endothelium is particularly vulnerable to this process in areas of low shear stress such as bends or bifurcations or downstream of stenoses. Thus, the beginning and the spread of atherosclerosis depends on activation of the endothelium and vascular inflammation, which lead to the initiation of atherogenesis, the progression of the formation and rupture of plaques and thrombosis [15, 16, 17, 18, 19, 20].

For the treatment of LDL the most effective and widely used group of drugs are the statins. Numerous clinical trials have proven the benefits of statins and their effect on LDL. Statins possess significant anti-inflammatory effects that may inhibit kappa B activity by reducing the activation of genes regulating adhesion of endothelial permeability and prothrombin response. Statins also reduce the level of C-reactive protein in the blood, reducing the risk factor of cardiovascular diseases [11, 21].

Along with statins there are other classes of drugs. Quite common fibrates, angiotensin converting enzyme inhibitors (IAF), receptor blockers angiotensin, aspirin, also in the literature there are data on the use of L-arginine, resveratrol and losartan potassium. Fibrates facilitate the reverse transfer of cholesterol, inhibit the expression of TNF-α and inhibit the activation of kappa B. Antiplatelet effects of aspirin are mainly beneficial for the cardiovascular system, but also prevent the development of proinflammatory and vasoconstrictor products of cyclooxygenase I (COX-1). The beneficial effects of angiotensin-converting enzyme inhibitor is due to inhibition of the formation and retention of angiotensin II and bradykinin, which increase vasodilation, the IAF exhibit anti-inflammatory effects. For example, angiotensin II stimulates the infiltration and proliferation of monocytes and is a potent activator of NADPH oxidase in the vascular wall. This enzyme system is one of the main causes of generation of reactive oxygen species that oxidize LDL and inhibit nitric oxide, thereby cancelling the effect of this vasodilator endothelial factor [22, 23, 24, 25].

The study of anti-inflammatory therapy for the treatment of cardiovascular diseases is a promising area for the treatment of cardiovascular diseases. The development of approaches for delivery of drug in the bloodstream in order to avoid systemic side effects is the preferred choice when studying the treatment of vascular diseases.

New strategies and approaches to targeted delivery of drugs.

Currently there are many drugs effective for the treatment of cardiovascular diseases. The use of new biologically active agents in the therapy of these diseases remains difficult due to their low stability in systemic administration and absence of effective methods of delivery to the affected area. In the modern realities are being developed for the creation of specialized vectors that facilitate the delivery of biological preparations to the most effective molecular targets in a desired tissue. The result was formed a few approaches to drug delivery in different sizes, classified by form and content. These approaches are mainly based on two main aspects:

1) pharmaceutical composition which allows to encapsulate in itself, therapeutic agents;

2) functionalization surface using a targeted agent (i.e., antibodies, aptamers and small molecules) for drug delivery to endothelium [26, 27].

For delivery of medicinal substances vascular system is a natural way of delivery to the lesion. However, the vasculature has a major drawback because the therapeutic agents cannot be delivered to a localized area due to system distribution. Recently, the endothelial layer was identified as a potential target for pharmaceutical intervention because of its active participation in the pathogenesis of cardiovascular diseases. Vascular inflammation and increased permeability of the endothelium is a common mechanism involved in the development of atherosclerosis, heart failure, diabetic vascular disease, trauma and ischemia-reperfusion. These endothelial changes could facilitate the delivery into the tissues with the help of special agents focused on tokens allocated to the damaged site. For example, nanostructured mesoporous silicon vectors (MV), in the form of 10-nm polymeric micelles have been used for the treatment of chronic heart failure. A team of researchers in their works have shown that DCA is accumulated in myocardium after intravenous administration, indicating improved cardiac permeability and retention effect. Thus, contrast agents, nanosensors or therapeutic agents can be selectively delivered to the myocardium in prophylactic, diagnostic or therapeutic purposes [28, 29, 30, 31].

An alternative approach is the development of carriers with a functionalized surface, or on the basis of selectieve ligands focused on markers of excessive cell adhesion (MIKA), and on the basis of the antigen-lymphocyte function-related receptors low-density lipoprotein. These approaches have led to the development of biologicaly to the data target. When inflammation of the endothelium actively allocated leukocytes regardless of the damage. Biomimetic carriers follow leukocyte tropism and selectively deliver a medicinal substance to the affected tissue. It was discovered that MICK focused on the Fe3O4SiO2 nanoparticles with multifunctional core-shell, mainly absorbed by inflamed endothelial cells in comparison with untargeted nanoparticles liposomes MIKA, who was used in experiments on the model of atherosclerosis in mice, and demonstrated a pronounced therapeutic effect [32, 33, 34, 35].

The strategy of treatment of cardiovascular diseases with preparations based on nanoparticles.

For targeted delivery of pharmaceutical compositions in the endothelium are used in various types of biologicaly. For example, researchers have developed a carrier-based chloromethylketone and micelle-based nanoparticles with high affinity to blood clots. Chloromethylketone base was associated with the nanoparticles, perfluorocarbons, and micelles with anticoagulant. Both approaches showed a significant antithrombotic effect. Nanoparticles associated with indium having a surface functionalized with antibodies associated with receptors LHCP was used for visualization of atherosclerotic plaques in mice. Using a variety of approaches to the delivery of particles into the endothelium, it is possible to investigate nanoparticles in the circulatory system, to demonstrate translirovalis and track their accumulation in the inflamed tissue and excretion through the lymphatic system. Such studies provide important information that complements the study of their therapeutic efficacy [34, 36, 37, 38].

New ideas and opportunities for drug development

The design of the surface of the media fragments that mimic the natural ligands, can provide selective targeting, precise delivery of therapeutic agents in diseased tissue. However, sequestration of nanoparticles in the mononuclear phagocytic system unable to adequately assess the biological barriers that hinders their clinical application. New biomimetic development is mainly based on two strategies:

1) top-down approaches, i.e. development of carrier-based microorganisms (such as bacteria or viruses), or cells (e.g. leukocytes, erythrocytes and platelets);

2) bottom-up approaches such as the conjugation of the nanoparticles surface with analogues of biologically active molecules that specifically bind to

the markers and selektine or coating of synthetic particles cell membranes. Additional approaches include polymers of lactic acid-glycolic acid (PLGA) – coated cells of platelets, which are mainly studied on the model of coronary restenosis rats [33, 39, 40, 41].

Other biomimetic nanoparticles based on the endogenous carriers such as LDL and HDL, was designed to include the nucleic material and the delivery of therapeutic and diagnostic molecules, low-density lipoproteins, which are also used as contrast agents in combination with gold nanoparticles. Methods of modification of endogenous proteins and the encapsulated delivery of lipophilic drugs continue to be studied and expanded, indicating their potential efficacy in selective targeting of drugs for the treatment of cardiovascular diseases [42, 43, 44].

In addition to the platforms and strategies referred to above, the group of Molinaro et al. recently published a new method that combines ascending and descending approaches to the Assembly of hybrid biomimetic nanovesicles. This combined approach represents an evolution of the coating process previously used for functionalization of the lipid vesicles. In this case, the membrane proteins are distinguished from infiltration of immune cells and restored biocompatible choline-based phospholipids in liposomes and form nanovesicles called leucosome. Leukocytopenia properties were grafted into leucosomes through the integration of more than 300 membrane proteins in their status after the lipid bilayer. Among these properties, proteomic analysis revealed the presence of receptors that enhance adhesion to the activated vascular lakocom network, which revealed their autotolerance and the ability to evade the immune cleaning [45].

Despite the use of these platforms on the model of localized inflammation in mice, a description of the conservation of molecular pathways involved receptors and dynamic interactions between key cell types during the inflammatory process opens the possibility of using lakocom for the treatment of cardiovascular diseases where inflammation plays an important role in the activation of endothelial dysfunction. In sum, all of these biomedcode represent the next generation of nanomedical therapy, as they provide an alternative solution to evade mononuclear phagocytic system and transport through the endothelial wall of the vessel.

Also worth mentioning is a new approach to drug delivery to the endothelium, through the creation of nanocapsules on the basis of high molecular weight polymers with a core in the form of medicinal substances. Was formulated transfer theory three-compartment pharmacokinetic model in a single model. Based on the obtained in our laboratory experimental data on endotheliopathy activity of some compounds was hypothesized that nanocapsules with a certain size range can penetrate into the bloodstream and not go beyond it, which will greatly reduce the necessary concentration of the medicinal substance for the treatment of cardiovascular diseases. Samples nanocapsule L-arginine, losartan potassium and resveratrol based on xanthan gum and konjak Gunma Prefecture, obtained in the framework of this approach have dimensions of from 20 to 180 nm and greatly reduces the coefficient of endothelial dysfunction (CED) in an experiment with laboratory rats on the model of LNAME – induced endothelial dysfunction. These studies showed that nanocapsules reduce the CAD to a comparable level with the introduction of the original medicinal substances substances while the dosage of the studied drugs was 4 times less than the reference drug [46-57].

Conclusions

A new platform for drug delivery can encapsulate a variety of molecules and deliver them selectively to areas of inflammation of the endothelium. For the affected endothelial drugs can be sent using the classical approaches based on antibodies and other ligands using new generation systems biomimetics. These systems are based on the unique biology of some of the phenotypes of the cells that have the ability to recognize and overcome the inflammation of the endothelial barrier. In particular, it is possible to develop a delivery system of nanoparticles that can be used to preserve some properties of immune cells such as macrophages, leukocytes and T-cells. Using exceptional ability of these cells to detect, recognize and penetrate inflammatory tissue, was created by alternative platforms that can selectively deliver therapeutic and diagnostic products in the field of interest in various pathological conditions associated with local inflammation of the vascular bed. Together these findings reveal three potential areas for further research:

1) understanding of the pathophysiology of cardiovascular diseases as a result of exploring ways of inflammation,

2) development of therapeutic agents that passively or actively delivered to the inflamed endothelium

3) overcoming the limitations of available drugs with serious side effects and unwanted toxicity in healthy tissues.

New developments in the field of production of nanoparticles, combined with an understanding of the inflammatory processes of the endothelium in the pathogenesis of cardiovascular diseases may soon to ensure the development of targeted delivery of novel therapeutic agents in the place of inflammation of the blood vessels, which will lead to greater efficiency and reduced systemic side effects.

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