DOI: 10.15825/1995-1191-2020-1-86-96

BIODEGRADABLE SMALL-DIAMETER VASCULAR GRAFT: TYPES OF MODIFICATION WITH BIOACTIVE MOLECULES AND RGD PEPTIDES

E.A. Senokosova, E.O. Krivkina, L.V. Antonova, L.S. Barbarash
Research Institute for Complex Issues of Cardiovascular Diseases, Kemerovo, Russian Federation

The need for small-diameter grafts for replacing the damaged area of the blood pool is still very high. These grafts are very popular for coronary artery bypass grafting. Polymeric synthetic grafts are an alternative to autografts. A promising area of tissue engineering is the creation of a biodegradable graft. It can serve as the basis for *de novo* generation of vascular tissue directly in the patient's body. Optimization of the polymer composition of products has led to improved physicomechanical and biocompatible properties of the products. However, the improvements are still far from needed. One of the decisive factors in the reliability of a small-diameter vascular graft is the early formation of endothelial lining on its inner surface, which can provide atrombogenic effect and full lumen of the future newly formed vessel. To achieve this goal, grafts are modified by incorporating bioactive molecules or functionally active peptide sequences into the polymer composition or immobilizing on its inner surface. Peptide sequences include cell adhesion site – arginine-glycine-aspartic acid (RGD peptide). This sequence is present in most extracellular matrix proteins and has a tropism for integrin receptors of endothelial cells. Many studies have shown that imitation of the functional activity of the natural extracellular matrix can promote spontaneous endothelization of the inner surface of a vascular graft. Moreover, configuration of the RGD peptide determines the survival and differentiation of endothelial cells. The linker through which the peptide is crosslinked to the polymer surface determines the bioavailability of the RGD peptide for endothelial cells.

Keywords: tissue engineering, polymer graft, RGD peptides, endothelization, biocompatibility.

1. BACKGROUND

Cardiovascular diseases (CVDs) remain the main cause of mortality and disability for the population of most countries in the world [1]. According to WHO statistics, in 2015 CVDs caused the death of about 17.7 million people [2]. While analyzing this problem Mathers C.D. and Loncar D. estimated that by 2030 this number will be increased by 30% [3]. An unchallenged leadership among CVDs belongs to atherosclerosis, during the development of which atheromatous plaque develops and increases in the full thickness of the arterial walls [2]. This leads to an impairment in the vessel patency and consequently deterioration of the vascular supply to the tissues [2, 4–8].

In modern cardiovascular surgery during the treatment of the damaged vessel the choice lies between angioplasty and replacement by a vascular implant (vascular graft). Using the patient's own arteries and veins for implants presents an ideal option, however there are certain limitations in their use.

Auto-, xeno-, allotransplants

The patient's own arteries (thoracic and radial) and veins (great saphenous) can be used by many indications for transplants into the coronary bed [9]. The disadvantages of this type of transplants include: anatomic features of the vessel structure which prohibit its use for plastic material; limited number of arteries and veins; possible traumatization of both the vessel and the adjoining tissues during extraction; risk of ischemia development at the site of material sampling; age-related degeneration [10, 11]. At the same time allo- and xenografts are being developed. The leading problem related to allografts (homografts or transplants obtained from other people) and xenografts (transplants obtained from other animals) is foreign genetic material. The use of such grafts implies a carefully adjusted protocol of devitalization, aseptic processing and, if necessary, cryopreservation of the samples. Immune rejection, allergic reactions, infection process development and calcification – such complications may be expected in some cases when such implants are used [12–14].

Artificial transplants

Synthetic vascular grafts can be divided into 2 types: biostable and biodegradable. Biostable grafts are made from polytetrafluorethylene, polyethylene terephthalate, polyurethanes. Such prostheses are successfully used in reconstructive surgery for vessels over 6 mm in diameter. In case of an impaired vessel with a smaller diameter,

Corresponding author: Evgeniya Senokosova. Address: 6, Sosnovy Blvd, Kemerovo, 650002, Russian Federation.
Tel. (3842) 64-46-50. E-mail: sergeewa.ew@yandex.ru

the hemodynamics of which is characterized by a lower blood velocity, biostable grafts become inapplicable due to rapid hyperplasia of the neointima and thrombosis [15–17].

Biodegradable polymer vascular grafts are quite attractive. Their main special feature is imitation of the extracellular matrix structure with subsequent full replacement of the polymer matrix by the recipient's newly formed vascular tissue. The materials for manufacturing of such prostheses may include synthetic polymers, such as: polyglycolic acid, polylactic acid, polycaprolactone, polyglycerolsebacate, polyhydroxyalcanoates, etc. In order to produce tissue engineered vascular grafts various methods are used, such as solvent casting, phase separation, levigation from a polymer solution, 3D printing and electrospinning [18]. The latter may be considered a priority method. The electrospinning method may help achieve the stretching of the polymer solution into fibers the diameter of which varies between 10 microns to 50 nanometers, with the formation of various-sized and highly porous frames [19–21]. Also changing the manufacturing regimen and the solution formulation in the process of electrospinning enables to produce frames consisting of layers with different composition [22].

Improving biocompatibility of the synthetic material and modification types

Some polylactone type polymers demonstrate satisfactory mechanical properties, low toxicity and immunogenicity, however their highly hydrophobic nature and low surface energy limit the wetting properties of the material, adhesion and cell proliferation which are required for further tissue remodeling [23, 24]. Using a combination of synthetic and natural polymers (collagen, chitosan, fibrin, silk fibroin, polyhydroxybutyrate-covalerate etc.) can lead to the improvement of biocompatibility for the produced matrix [25–27]. Also the frame biocompatibility can be enhanced by means of using various polymers in the process of its manufacturing. Using a combination of polycaprolactone (PCL) with polyhydroxybutyrate-co-valerate (PHBV) demonstrated an increase in the biocompatibility of a matrix produced from these materials versus a sample made from only polycaprolactone [28].

At the stage of *in vivo* testing serious problems occur with biodegradable artificial prostheses: thrombogenesis, calcification, incompatibility of the physico-mechanical properties and compliance with the native vessel, inflammation process development, insufficient biocompatibility of the material [29]. Strategies aimed at overcoming such problems are focused, inter alia, on developing the biofunctional properties of the conduits.

In particular, stimulation of the graft inner surface endothelization may facilitate a decrease in the risk of thrombogenesis. The process of graft modification envisages including (incorporating into the nano size fibres of the polymer or surface immobilization) substances into the polymer matrix which promote adhesion retention, support the vital activity of the cells required for speedy formation of the endothelial lining and other *de novo* tissue formation. Such substances include a number of growth factors and chemoattractant molecules [30, 31]. At the same time, a significant scientific interest is related to surface modification of ready polymer matrixes by means of immobilizing functionally active peptides on their surfaces which are capable of selective adhesion to endothelial cells from the patient's system blood flow [32]. Such peptides include the arginine-glycine-aspartic acid (RGD) which is present in most of the extracellular matrix proteins [33]. The RGD sequence is one of the key ligands for integrins – receptors which are responsible for cell adhesion, migration, proliferation, differentiation and survival [34]. One of the key challenges in the development of devices with RGD-containing peptides is the choice of RGD configuration, as well as the ligand or linker by means of which the adhesive peptide will be immobilized on the polymer surface.

Currently the possibility of using RGD peptides for modification of the surfaces of constructions obtained by means of tissue engineering which come into contact with blood and require prompt surface endothelization is being studied simultaneously in many countries. Research groups carry out independent studies in this area, using their own protocols beginning with the synthesis of a certain peptide configuration and all the way through to a model of *in vivo* testing for a ready model. Therefore, according to existing literature data there is no evidence based opinion regarding a preferable configuration for an RGD peptide or the structure of a ligand/linker, which characterizes this area as under-investigated, and therefore quite attractive to be studied in regard to creating functionally active devices for the needs of cardiovascular surgery. The current review covers the main modern approaches used in the development of modified biodegradable prostheses with an emphasis on describing use of surface modification for small diameter vessel prostheses by means of RGD peptides.

Vascular endothelium

Vascular endothelium (VE) is a continuous highly differentiated monolayer of squamous cells of mesenchymal origin (endotheliocytes) which line the inner surface of each integral part of the cardiovascular and lymphatic systems [35]. Several distinctive features can be distinguished which emphasize the priority importance of achieving prompt and quality endothelization of the inner surface of a polymer vascular prosthesis. First of all, the endothelial monolayer is formed by endotheliocytes with various phenotypes the ratio of which depends on many factors: the amount of pressure in the vessel, the velocity,

the share stress force, a pulsing or constant flow, as well as peculiar features pertinent to the extracellular matrix [36, 37]. In other words, the endothelial lining of a vessel is a highly adaptive system which enables the vessels and cavities to support functioning under various conditions (types and length of the stimuli).

Secondly, the vascular endothelium has morphological and functional variations which match their specific location in the body [38]. The vascular endothelium produces a large amount of biologically active substances, from an inorganic molecule of NO to complex organic structures (C-type endothelial natriuretic peptides) [40, 41]. Thus, the VE is not only a barrier layer of cells between the blood (or lymph) and the subendothelial vascular tissues but also an active endocrine 'organ' which takes part in functional self-regulation, regeneration and remodeling of the vasculature, in direct metabolism of the tissues and organs, in transvascular substance and cell migration, for example leukocyte migration, as well as influencing the most important stage of the hemostasis system's work – coagulation [42–44]. The important contribution of the VE into the normal physiology of the body indicates that any disfunction in it may lead to a wide range of pathological conditions. The most socially significant and debatable ones among these are CVDs, sepsis and cancer [45–47]. Therefore, rapid formation of the endothelial monolayer on the inner surface of a biodegradable polymer prosthesis which replaces an impaired section of the vascular bed is a most important goal in the creation of biocompatible and functionally active vessel replacement devices. The speed and quality of the endothelization may determine the consistency of the tissue engineered prosthesis itself, its further remodeling, as well as the physiology of those tissues and organs (or organ systems) in the vascular pool of which it is implanted.

2. MAIN BIOLOGIGALLY ACTIVE SUBSTANCES USED FOR THE MODIFICATION OF TISSUE ENGINEERED VASCULAR PROSTHESES IN ORDER TO ACCELERATE THE INNER SURFACE ENDOTHELIZATION

Including substances capable to attract endothelial cells from the recipient's systemic blood flow, and to provide optimal conditions for their vital activity, into the tissue engineered matrix is one of the trends in creating biofunctional biodegradable vessel prostheses. Such substances include bioactive molecules which control polymer frame remodeling processes with a priority to rapid and quality endothelization of the inner surface. Much attention is devoted to growth factors – signal polypeptides which regulate cell survival, migration, proliferation and differentiation [48]. Due to the chemical instability of growth factors one of the common methods used to include them into the polymer matrix is incorporation. For example, in the process of two-phase electrospinning the biomolecules are enclosed into the polymer fibers which form the device, which ensures their structural integrity and prolonged release related to gradual degradation of the polymer fibre [49–51]. Another successful method which enables to ensure structural stability and increased lifespan for the molecules is the adsorption of growth factors to fibronectin, fibrin, gelatin, heparin, which in their turn are immobilized to the matrix surface. Speaking about tissue assimilation and remodeling at the polymer tube frame, the following fact should be taken into account: supporting vital activity for adhesive cells and future tissues is possible in case of availability of an extensive and branched vasculature [52]. Therefore the Vascular Endothelial Growth Factor (VEGF) as a modification component is quite interesting and indeed of prior importance, as it facilitates endothelization of the inner surface of the grafts as well as stimulating vascular network formation and growth on the transplant and capillary genesis throughout its thickness.

The VEGF molecule can ensure migration of already mature forms of the endothelial cells towards the polymer matrix from anastomosis zones and attract endothelial cell precursors from the blood [53]. The VEGF-A 165 isoform is most active in angiogenesis stimulation (prevailing numerically), being bound to the VEGFR2 receptor on the endothelial cell it provides most significant functional signals [54–56]. V.V. Sevostianova et al. (2018) published data describing the character of inner surface endothelization for polycaprolactone grafts with incorporated VEGF which have been implanted into the abdominal part of the aorta to laboratory rats for 1, 3, 6 months. Thus, PCL/VEGF grafts demonstrated better short-term (75% vs 50%) and long-term (100% vs 75%) permeability as compared to non-modified analogues. Due to VEGF use on the inner surface of the transplants already one month after implantation a large number of immature $CD31^+$ $CD34^+$ endothelial cells has been identified which during follow-up by the time of the implantation time into the abdominal part of the rats' aorta formed a monolayer with a prevalence of mature cells with $CD31^+CD34^-$ phenotype. Non-modified PCL grafts were not so successful [57]. Similar results have been obtained with co-polymer PHBV/PCL grafts modified by the same growth factor [58]. Research carried out by Henry, J.J.D. et al. (2017) showed that after implantation of vascular grafts from polylactic acid (PLLA – poly-l-lactide acid) into the carotid artery of laboratory rats and PLLA/PCL variation modified by VEGF in each case already two weeks later active angiogenesis has been noted: on the inner surface of 82% of the samples endothelial cells have been identified, while in non-modified graft this rate was 2 times lower [59]. Other bioactive factors make a less pronounced contribution to the endothelization process, acting more indirectly.

The basic fibroblast growth factor (bFGF) has an impact on many physiological and pathological processes: cell survival, differentiation, proliferation, angiogenesis, adhesion, as well as skeletogenesis and wound healing [60, 61]. BFGF angiogenesis is based on mature endothelial cell stimulation to proliferation and organization into tube structures [62, 63]. Both in *in vitro* and in *in vivo* experiments successful EC adhesion and viability results have been obtained. During cultivation of human microvascular endothelial cells (HMECs) and peripheral blood canine endothelial progenitor cells (CEPC) on the surface of a decellularized carotid artery of a pig covered with bFGF under conditions of blood flow imitation, more successful EC retention has been demonstrated on bFGF-modified samples (60%) [64]. Owing to the procedure of venous transplant wrapping in a bFGF-containing hydrogel sheet their structural and physiological properties have been improved, EC survival during implantation to laboratory mice has been improved vs. non-modified veins [65].

Many other growth factors and chemoattractant molecules are also used as agents for artificial polymer vascular graft modification. In particular the platelet-derived growth factor (PDGF) is interesting due to its participation during the embryonal and postnatal periods in differentiation, proliferation, migration of mesenchymal origin cells, in the formation and stabilization of blood vessels, in tissue regeneration [66–68]. The transforming growth factor beta (TGF-beta) when secreted into the extracellular environment by various cell types performs a number of functions, including cell proliferation and differentiation control as well as angiogenesis stimulation [69].

The stromal cell-derived factor – 1 alpha (SDF-1α) is a chemoattractant molecule which performs a number of important functions both in the embryonal period and in an adult body. SDF-1α controls migration of various cell types, attracts and takes part in the proliferation of endothelial progenitor cells from the bone marrow [70, 71]. Implantation of grafts made from polyester with SDF-1α into the carotid artery of sheep has shown stem cell attraction, improved endothelization, decreased intimal hyperplasia and thrombosis frequency [73].

During modification of low diameter synthetic vessel substitution devices several types of biologically active molecules can also be used to launch various effects stimulating and supporting endothelization, facilitating remodeling of vessel tissues with the formation of all the appropriate tissue layers found in a true vessel. Thus, layered incorporation of the VEGF, bFGF and SDF-1α complex into a biodegradable vessel graft made of PHBV/PCL promoted 100% permeability and early full graft endothelization in *in vivo* experiments vs samples with each factor incorporated separately [73]. It has been proved that bFGF and SDF-1α molecules supported sustainable VEGF-induced formation of quality endothelial lining on the inner surface of the vessel prostheses. High primary permeability during 12-month implantation to rats provided for the formation of vascular tissues in the place of the biodegradable matrix with simultaneous calcification intensity decrease and no immune rejection signs [74].

3. SURFACE RDG PEPTIDE MODIFICATION

A large number of methods aimed at the modification of the vessel substituting inner surface are being developed in order to get a functionally active endothelial monolayer. *In vitro* graft endothelization by autologous cells is an effective, however rather controversial method. In this case the time for producing a cell-colonized vessel graft and its cost are increased [75]. Such a graft can not be used in emergency cardiovascular surgery. In emergency cases a cell-less biodegradable graft which forms a microenvironment to attract cells that take part in the endothelization process can be a more successful option. Another area actively developed in tissue engineering is surface modification of polymer vascular prostheses which implies creation of a biomimetic surface the architectonics and functionality of which would be similar to that of the natural extracellular matrix.

The extracellular matrix and integrin receptors

The extracellular matrix (ECM) consists of a compound protein complex of various structure and configuration which is characterized by specificity of the ratio of the main glycoprotein – collagen – to other glycoproteins, proteoglycans and hyaluronic acid for each tissue type [76]. The main functions of the ECM are: forming borders between cell groups, creating a media for cell migration; regulating cell behaviour by means of growth factors and proteins containing cell adhesion sites. The combination of these functions also enables the ECM to support structural hierarchy in tissue organization [77]. Interaction between the ECM and the cells is carried out via integrin mediated cell adhesion. An integrin receptor is a heterodimer consisting of α- and β-subunits. Human cells have altogether 18 α-subunits and 8 β-subunits in different variations which represent 24 types of transmembrane receptors. Integrin reorganizes signals from the ligand to the cell; also reverse transmission of the intercellular signals towards the ligand takes place which in turn regulates the correlation affinity and the force of interaction [78–80]. As a result a large number of signal molecular cascades are activated which lead to structural and physiological changes in the cells responsible for supporting focused adhesion, proliferation, indirect cell cycle regulation [81]. In the process of fibrin matrix inner surface endothelization in the vessel replacing device both precursor cells and mature endothelial cells take part which circulate in the blood flow and mig-

rate from the anastomosis ends with the native vessel [82–84]. ECs express 13 types of integrins; among these the ones taking most active part in the process of adhesion with subsequent endothelization are the β1, αvβ3 и αvβ5 subfamilies [85]. An emphasis on protein ligands conjugated with certain integrin receptors and their cell adhesion sites lays the basis for the development of inner surface modification of tissue engineered vessel replacement devices made of porous artificial material and for the stimulation of accelerated endothelization. For β1-integrins the ligands will be collagen and laminin, and the binding site – the Asp-Gly-Glu-Ala (DGEA) peptide sequence; additional recognition sites for laminin are Tyr-Ile-Gly-Ser-Arg (YIGSR), Arg-Gly-Asp (RGD) and several others. The αvβ3 and αvβ5 integrins possess an affinity to fibronectin, von Willebrand factor, fibulin, osteopontin, vitronectin with RGD adhesive peptide sequence [86–88]. The RGD-peptide may be considered a general integrin binding motive. RGD's representative versatility on the ECM makes it a maximally eligible factor for surface modification of biodegradable polymer matrixes. Research is being carried out to study peptide sequences both obtained in the course of extraction from natural materials and artificially synthesized. The latter have certain advantages: the risk of immune response is decreased as well as infections related to an insufficient degree of material cleansing. Comparison of the functional properties of natural RGD-containing proteins and their artificial analogs has shown that the latter are more efficient [89].

Artificial synthesis enables to obtain various configurations of the RGD peptides which possess various potential of interacting with cells. The overall number of studied configurations can be divided into 2 groups: non-cyclic (linear) and cyclic forms. It has been shown that cyclic RGD peptides are the ones to be bound to αvβ3 integrins [90]. The ligand may be either of natural origin or synthesized (linker). Control of the specific interactions between cell receptors and ECM ligands is a critical aspect in tissue engineering as it ensures the effectiveness of cellular migration and adhesion [91]. It has been shown that it is the length of the ligand that ensures bioavailability of the RGD peptides for integrin mediated interaction with the cell and further regulation of the adhesion force and migration speed [92]. The number of 'polymer composition – linker – RGD peptide' is quite large, therefore currently the issue regarding priority RGD peptide modification of polymer vascular prostheses is open.

RGD configuration types and ligands/markers conjugated with them

Synthesized GRGDDSP peptides immobilized on a PCL graft by means of water resistant bioadhesive mussel fp-151 protein (MAP) has shown its efficiency when implanted into rabbits' carotid arteries. Such a coating improved endothelization of the MAP-RGD graft surface by means of active attraction of mature and progenitor endothelial cells which ensured monthly patency in nearly 70% of all cases [93]. An emphasis has been made in this work on the MAP linker: an artificially synthesized form produced from natural components turned out to be more biocompatible and quite simple in obtaining as compared to existing commercial samples [94].

A study performed by Cutiongco M.F.A. et al. (2015) included *in vitro* and *in vivo* comparison of the cyclic cRGD peptide form (CRRGDWLC) and the non-cyclic RGDS peptide cross-linked by means of PVA grafts (poly(vinyl alcohol) hydrogel) with the help of a linker produced by interphase polyelectrolyte complexing (IPC): fibre formation from chitosan and alginate. In the course of this study fibronectin and heparin performed the role of alternative modifying agents [95]. Viability of human umbilical vein endothelial cells (HUVEC) on polymer films with fibronectin coating, RGDS and cRGD showed a positive tendency towards improvement of cellular survival as compared to non-modified analogues. At the same time, modification with heparin was considered ineffective due to decreased adhesion and endothelial cell proliferation. In the course of haemocompatibility assessment samples modified by fibronectin were also excluded due to platelet activation. Polymer films with non-cyclic RGDS demonstrated platelet activation to a lesser degree than films with fibronectin. Samples with cyclic cRGD activated individual platelets that were only partly attached by pseudopodia, which indicated low platelet activation and presented this modification as most fitting for further *in vivo* testing [96].

In one of the studies by Samantha Noel et al. (2015) synthesized peptide sequences CGGRGD, CGGYIGSR and CGGREDV were studied which were immobilized via a polyethyleneglycol linker (PEG) on the surface of polyethylene terephthalate with the purpose of increasing the athrombogenic properties of the artificial material. The effectiveness of modified polymer film versions was evaluated by adhesion indicators as well as by HUVEC cell culture viability. The grafted REDV peptide did not improve endothelial cell adhesion while RDG peptide and YIGSR peptide significantly increased the metabolic activity of the cell culture. The authors noted that co-immobilization of RGD and YIGSR peptides improved HUVEC metabolic activity even further, which indicated synergism between two sequences [97]. Choi W.S. et al. (2016) performed surface modification of a polymer frame produced from a combination of polyurethane (PU) and elastomer (Pellethane) with heparin, adhesive GRGDS and YIGSR peptides via a PEG linker. *In vitro* experiment showed that the effect of RGD peptide on HUVEC cell culture adhesion and proliferation was somewhat higher than for YIGSR peptide or for the sample with co-immobilization of both peptides. Implantation

of non-modified grafts as well as those modified by heparin and by two adhesive peptides was performed for rabbits for a period of up to 2 months. The results of the experiment showed 71.4% patency in modified samples vs 46.2% in non-modified analogues [98].

In one of the works performed by the research group headed by Antonova L.V. (2015) and devoted to biodegradable graft modification by adhesive peptides the GRGDG configuration has been studied [99]. Surface modification was compared to PHBV/PCL grafts with incorporated VEGF. According to the results of short term and long term implantation of grafts with RGD or VEGF into the abdominal aorta of laboratory rats the authors noted no significant differences in cellularity evolution during the formation of endothelial monolayer which was functionally more mature as compared to non-modified grafts. Both types of modification proved to be sufficiently effective [100]. Further on, in 2019 the same research group presented the results of *in vitro* and *in vivo* studies where the results of modification by various configurations of RGD peptides and linkers immobilized on the surface of PHBV/PCL grafts were compared. The studied adhesive peptide sequences were as follows: non-cyclic RGDK and AhRGD, cyclic c[RGDFK] peptide. Cross-linking of the peptides with polymer materials was performed via linkers of different length and chemical content: short 1,6-hexamethylenediamine and long 4,7,10-trioxa-1,13-tridecanediamine. Same as in the study performed by Cutiongco M.F.A. et al. (2015) the most optimal configuration was the cyclic form c[RGDFK], however the length of the linker group made a significant impact on the bioavailability of the molecule both *in vitro* and *in vivo*. Colony-forming human endothelial cell adhesion on graft samples modified by c[RGDFK] via the 4,7,10-trioxa-1,13-tridecanediamine linker exceeded that demonstrated in comparison with other RGD-modified samples. Also it has been possible to achieve a better endothelial monolayer on the inner surface of the grafts implanted to laboratory rats, as well as 100% graft permeability at different times after implantation (1 and 3 months). At the same time hemocompatible properties of such material were higher in comparison with samples modified by the same cyclic RGD peptide but cross-linked with the polymer surface by a short linker – 1,6-hexamethylenediamine [101].

CONCLUSION

A lot of attention is devoted to growth factors and adhesive peptide sequences, in particular RGD, in various areas of development based on selective binding to target cells. Biologically active molecules – VEGF, bFGF and some others integrated into the vascular prosthesis material, have shown to be efficient in *in vitro* and *in vivo* studies. Use of several growth factors for the modification of biodegradable vessel replacement items may lead to more optimal neogenesis of true blood vessel tissues at the implant site. Affinity to endothelial cells makes RGD peptides and their configurations ideal agents for surface modification of tissue engineering constructions which contact with blood and require prompt surface endothelization. The speed of spontaneous endothelization which should be inititated during implantation of a small diameter artificial blood vessel will depend directly on the RGD peptide bioavailability which may be ensured by means of a linker of a certain length.

The authors declare no conflict of interest.

REFERENCES

1. World health statistics 2016. Monitoring health for the SDGs, sustainable development goals. *World Heals Organization*. WHO Press. 2016; 64.
2. World health statistics 2017: monitoring health for the SDGs, Sustainable Development Goals. Geneva: World Health Organization; 2018.
3. *Mathers CD, Loncar D.* Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med*. 2006; 3 (11): 2011–2030.
4. *Cahill PA, Redmond EM.* Vascular endothelium – Gatekeeper of vessel health. *Atherosclerosis*. 2016; 248: 97–109.
5. *Gimbrone MA, Garcia-Cardena G.* Endothelial cell dysfunction and the pathobiology of atherosclerosis. *Circ Res*. 2016; 118 (4): 620–636.
6. *Yurdagul AJr, Finney AC, Woolard MD, Orr AW.* The arterial microenvironment: the where and why of atherosclerosis. *J Biochem*. 2016; 473 (10): 1281–1295.
7. *Bentzon JF, Otsuka F, Virmani R, Falk E.* Mechanisms of plaque formation and rupture. *Circ Res*. 2014; 114: 1852–1866.
8. *Wilson CJ, Clegg RE, Leavesley DI, Pearcy MJ.* Mediation of biomaterial-cell interactions by adsorbed proteins: a review. *Tissue Eng*. 2005; 11: 1–18.
9. *Rocco KA, Maxfield MW, Best CA, Dean EW, Breuer CK*. *In vivo* applications of electrospun tissue-engineered vascular grafts: a review. *Tissue Eng*. Part B: Reviews. 2014; 20 (6) 628–640.
10. *Shah SA, Chark D, Williams J, Hessheimer A, Huh J, Wu YC et al.* Retrospective Analysis of Local Sensorimotor Deficits After Radial Artery Harvesting for Coronary Artery Bypass Grating. *J Surg Res*. 2007; 139 (2): 203–208.
11. *Tara S, Rocco KA, Hibino N, Sugiura T, Kurobe H, Breuer CK et al.* Vessel bioengineering. *CIRC J*. 2014; 78 (1): 12–19.
12. *Gatto C, Giurgola L, D'Amato Tothova J.* A suitable and efficient procedure for the removal of decontaminating antibiotics from tissue allografts. *Cell Tissue Bank*. 2013; 14 (1): 107–115.
13. *Palumbo VD, Bruno A, Tomasello G, Damiano G, Lo Monte AI.* Bioengineered vascular scaffolds: the state of the art. *Int J Artif Organs*. 2014; 37 (7): 503–512.
14. *Sankaran KK, Subramanian A, Krishnan UM, Sethuraman S.* Nanoarchitecture of scaffolds and endothelial

cells in engineering small diameter vascular grafts. *Biotechnol J*. 2015; 10 (1): 96–108.
15. *Wang X, Lin P, Yao Q, Chen C.* Development of small-diameter vasculargrafts. *World J Surg*. 2007; 31: 682–689.
16. *Jaspan VN, Hines GL.* The current status of tissue-engineered vascular grafts. *Cardiology in Review*. 2015; 23 (5): 236–239.
17. *Tresoldi C, Pellegata AF, Mantero S.* Cells and stimuli in small-caliber blood vessel tissue engineering. *Regen Med*. 2015. 10 (4): 505–527.
18. *Ravi S, Chaikof EL.* Biomaterials for vascular tissue engineering. *Regen Med*. 2010; 5: 107–120.
19. *Doshi J, Reneker DH.* Electrospinning process and applications of electrospun fibers. *J Electrostat*. 1995; 35 (2–3): 151–160.
20. *Dhandayuthapani B, Yoshida Y, Maekawa T, Kumar DS.* Polymeric scaffolds in tissue engineering application: A review. *Int J Polym Sci*. 2011; 1–19.
21. *Rim NG, Shin CS, Shin H.* Current approaches to electrospun nanofibers for tissue engineering. *Biomed Mater*. 2013; 8: 014102.
22. *Greenwald SE, Berry CL.* Improving vascular grafts: the importance of mechanical and haemodynamic properties. *J Pathol*. 2000; 190: 292–299.
23. *Babayan AL.* Poverkhnostnaya energiya polimerov (elastomernykh kompozitsiy): sravnitel'nyy analiz znacheniy poverkhnostnoy energii s parametrami defektnosti polimerov. *Nauchnyy zhurnal KubGAU*. 2017; 131 (07).
24. *Shen H, Hu X, Yang F, Bei J, Wang S.* Combining oxygen plasma treatment with anchorage of cationized gelatin for enhancing cell affinity of poly (lactide-co-glycolide). *Biomaterials*. 2007; 28: 4219–4230.
25. *Meinhart JG, Schense JC, Schima H, Gorlitzer M, Hubbell JA, Deutsch M et al.* Enhanced endothelial cell retention on shear-stressed synthetic vascular grafts precoated with RGD-cross-linked fibrin. *Tissue Eng*. 2005; 11 (5e6): 887–895.
26. *Fernandez P, Bareille R, Conrad V, Midy D, Bordenave L.* Evaluation of an *in vitro* endothelialized vascular graft under pulsatile shear stress with a novel radiolabeling procedure. *Biomaterials*. 2001; 22 (7): 649–658.
27. *Feugier P, Black RA, Hunt JA, How TV.* Attachment, morphology and adherence of human endothelial cells to vascular prosthesis materials under the action of shear stress. *Biomaterials*. 2005; 26 (13): 1457–1466.
28. *Antonova LV, Sevostyanova VV, Seifalian AM, Matveeva VG, Velikanova EA, Sergeeva EA et al.* Comparative *in vitro* testing of biodegradable vascular grafts for tissue engineering applications. *Complex issues of cardiovascular diseases*. 2015; (4): 34–41. [In Russ, English abstract]. doi: 10.17802/2306-1278-2015-4-34-41.
29. *Anderson JM.* Biological responses to materials. *Annu Rev Mater Res*. 2001; 31: 81–110.
30. *Lee KW, Johnson NR, Gao J, Wang Y.* Human progenitor cell recruitment via SDF-1α coacervate-laden PGS vascular grafts. *Biomaterials*. 2013; 34 (38): 9877–9885.
31. *Gong W, Lei D, Li S, Huang P, Qi Q, Sun Y et al.* Hybrid small-diameter vascular grafts: anti-expansion effect of electrospun poly ε-caprolactone on heparin-coated decellularized matrices. *Biomaterials*. 2015; 76: 359–370.
32. *Ren X, Feng Y, Guo J, Wang H, Li Q, Yang J et al.* Surface modification and endothelialization of biomaterials as potential scaffolds for vascular tissue engineering applications. *Chem Soc Rev*. 2015; 44 (15): 5680–5742.
33. *Wang F, Li Y, Shen Y, Wang A, Wang S, Xie T.* The functions and applications of RGD in tumor therapy and tissue engineering. *Int J Mol Sci*. 2013; 14 (7): 13447–13462.
34. *Harburger DS, Calderwood DA.* Integrin signalling at a glance. *J Cell Sci*. 2009; (122): 159–163.
35. *Gomazkov OA.* Endothelium – "Endocrine Tree". *Nature*. 2000; 5: 38–46.
36. *Kotsovolis G, Kallaras K.* The role of endothelium and endogenous vasoactive substances in sepsis. *Hippokratia*. 2010; 14 (2): 88–93.
37. *Babichev AV.* Rol' endoteliya v mekhanizmakh gemostaza. *Pediatr*. 2013; 4 (1): 122–127.
38. *Petrishchev NN.* Disfunktsiya endoteliya. Patogeneticheskoe znachenie i metody korrektsii. SPb.: IITs VMA, 2007: 296.
39. *Li H, Wallerath T, Forstermann U.* Physiological mechanisms regulating the expression of endothelial-type NO synthase. *Nitric Oxide*. 2002; 7: 132–147.
40. *Bae CR, Hino J, Hosoda H, Arai Y, Son C, Makino H et al.* Overexpression of C-type Natriuretic Peptide in Endothelial Cells Protects against Insulin Resistance and Inflammation during Diet-induced Obesity. *Sci Rep*. 2017; 7 (1): 9807.
41. *Hagensen MK, Vanhoutte PM, Bentzon JF.* Arterial endothelial cells: still the craftsmen of regenerated endothelium. *Cardiovascular Res*. 2012; 95 (3): 281–289.
42. *Pi X, Xie L, Patterson C.* Emerging Roles of Vascular Endothelium in Metabolic Homeostasis. *Circ Res*. 2018; 123 (4): 477–494.
43. *Mas M.* A Close Look at the Endothelium: Its Role in the Regulation of Vasomotor Tone. *Eur Urol Suppl*. 2009; 8: 48–57.
44. *Gimbrone MA, Garcia-Cardena G.* Endothelial Cell Dysfunction and the Pathobiology of Atherosclerosis. *Circ Res*. 2016; 118 (4): 620–636.
45. *Franses JW, Drosu NC, Gibson WJ, Chitalia VC, Edelman ER.* Dysfunctional endothelial cells directly stimulate cancer inflammation and metastasis. *Int J Cancer*. 2013; 133 (6): 1334–144.
46. *Kotsovolis G, Kallaras K.* The role of endothelium and endogenous vasoactive substances in sepsis. *Hippokratia*. 2010; 14 (2): 88–93.
47. *Briggs T, Arinzeh TL.* Growth factor delivery from electrospun materials. *J Biomater Tissue Eng*. 2011; 1 (2): 129–138.
48. *Sevostyanova VV, Golovkin AS, Antonova LV, Glushkova TV, Barbarash OL, Barbarash LS.* Modification of polycaprolactone scaffolds with vascular endothelial growth factors for potential application in development of tissue engineered vascular grafts. *Genes & Cells*. 2015; 10 (1): 84–90.
49. *Spano F, Quarta A, Martelli C, Ottobrini L, Rossi RM, Gigli G et al.* Fibrous scaffolds fabricated by emulsion

electrospinning: from hosting capacity to *in vivo* biocompatibility. *Nanoscale*. 2016; 8 (17): 9293–9303.
50. *Antonova LV, Matveeva VG, Velikanova EA, Khanova MY, Sevostyanova VV, Tsepokina AV et al. In vitro* activity of bioactive molecules incorporated into poly (3-hydroxybutyrate-co-3-hydroxyvalerate)/poly(ε-caprolactone) scaffolds. *Complex Issues of Cardiovascular Diseases*. 2018; 7 (2): 89–101. [In Russ, English abstract]. doi: 10.17802/2306-1278-2018-7-2-89-101.
51. *Novosel EC, Kleinhans C, Kluger PJ.* Vascularization is the key challenge in tissue engineering. *Adv Drug Deliv Rev*. 2011; 63 (4–5): 300–311.
52. *Chen X, Wang J, An Q, Li D, Liu P, Zhu W et al.* Electrospun poly(L-lactic acid-co-ε-caprolactone) fibers loaded with heparin and vascular endothelial growth factor to improve blood compatibility and endothelial progenitor cell proliferation. *Colloids Surf*. B: Biointerfaces. 2015; 128: 106–114.
53. *Maes C.* Impaired angiogenesis and endochondral bone formation in mice lacking the vascular endothelial growth factor isoforms VEGF164 and VEGF188. *Mechanisms of Development*. 2002; 111 (1–2): 61–73.
54. *Potente M, Gerhardt H, Carmeliet P.* Basic and therapeutic aspects of angiogenesis. *Cell*. 2011; 146: 873–887.
55. *Miettinen M, Rikala MS, Rysz J, Lasota J, Wang ZF.* Vascular endothelial growth factor receptor 2 (VEGFR2) as a marker for malignant vascular tumors and mesothelioma – immunohistochemical study of 262 vascular endothelial and 1640 nonvascular tumors. *Am J Surg Pathol*. 2012; 36 (4): 629–639.
56. *Sevostyanova VV, Antonova LV, Velikanova EA, Krivkina EO, Glushkova TV et al.* Endothelialization of Polycaprolactone Vascular Graft under the Action of Locally Applied Vascular Endothelial Growth Factor. *Bull Exp Biol Med*. 2018; 165 (2): 264–268.
57. *Antonova LV, Sevostyanova VV, Kutikhin AG, Mironov AV, Krivkina EO, Shabaev AR et al*. Vascular Endothelial Growth Factor Improves Physico-Mechanical Properties and Enhances Endothelialization of Poly(3-hydroxybutyrate-co-3-hydroxyvalerate)/Poly(ε-caprolactone) Small-Diameter Vascular Grafts *In vivo*. *Front Pharmacol*. 2016; 7: 230.
58. *Henry JJD, Yu J, Wang A, Lee R, Fang J, Li S.* Engineering the mechanical and biological properties of nanofibrous vascular grafts for *in situ* vascular tissue engineering. *Biofabrication*. 2017; 9 (3): 035007.
59. *Compagni A, Wilgenbus P, Impagnatiello MA, Cotten M, Christofori G.* Fibroblast growth factors are required for efficient tumor angiogenesis. *Cancer Res*. 2000; 60: 7163–7169.
60. *Itoh N, Ornitz DM*. Evolution of the FGF and FGFR gene families. *Trends Genet*. 2004; 20: 563–569.
61. *Yun YR, Won JE, Jeon E, Lee S, Kang W, Jo H et al.* Fibroblast growth factors: biology, function, and application for tissue regeneration. J. Tissue Eng. 2010; 1 (1): 218142.
62. *Liu F, Li G, Deng L, Kuang B, Li X.* The roles of FGF 10 in vasculogenesis and angiogenesis. *Biom Res*. 2017; 3: 1329–1332.
63. *Conklin BS, Wu H, Lin PH, Lumsden AB, Chen C.* Basic Fibroblast Growth Factor Coating and Endothelial Cell Seeding of a Decellularized Heparin-coated Vascular Graft. *Artificial Organs*. 2004; 28 (7): 668–675.
64. *Haraguchi T, Okada K, Tabata Y, Maniwa Y, Hayashi Y, Okita Y.* Controlled Release of Basic Fibroblast Growth Factor From Gelatin Hydrogel Sheet Improves Structural and Physiological Properties of Vein Graft in Rat. *Arterioscler Thromb Vasc Biol*. 2007; 27: 548–555.
65. *Ghil JS, Chung HM.* Evidence that platelet derived growth factor (PDGF) action is required for mesoderm patterning in early amphibian (Xenopus laevis) embryogenesis. *Int J Dev Biol*. 1999; 43 (4): 329–334.
66. *Caplan AI, Correa DJ.* PDGF in bone formation and regeneration: new insights into a novel mechanism involving MSCs. *J Orthop Res*. 2011; 29 (12): 1795–1803.
67. *Delgado JJ, Sanchez E, Baro M, Reyes R, Evora C, Delgado A.* A platelet derived growth factor delivery system for bone regeneration. *J Mater Sci Mater Med*. 2012; 29 (8): 1903–1912.
68. *Yuan SM, Wang YQ, Shen Y, Jing H.* Transforming growth factor-β in graft vessels: histology and immunohistochemistry. *Clinics*. 2011; 66 (5): 895–901.
69. *Sevastianov VI, Kirpichnikov MP.* Biosovmestimye materialy. M.: MIA, 2011: 544.
70. *Lewellis SW, Knaut H.* Attractive guidance: how the chemokine SDF1/CXCL12 guides different cells to different locations. *Semin Cell Dev Biol*. 2012; 23 (3): 333–340.
71. *De Visscher G.* Improved endothelialization and reduced thrombosis by coating a synthetic vascular graft with fibronectin and stem cell homing factor SDF-1α. *Acta Biomaterialia*. 2012; 8 (3): 1330–1338.
72. *Antonova LV, Sevost'yanova VV, Kutikhin AG, Velikanova EA, Matveeva VG, Glushkova TV i dr.* Vliyanie sposoba modifitsirovaniya trubchatogo polimernogo matriksa biomolekulami BFGF, SDF-1α i VEGF na protsessy formirovaniya *in vivo* tkaneinzhenernogo krovenosnogo sosuda malogo diametra. *Vestnik transplantologii i iskusstvennykh organov*. 2018; 20 (1): 96–109.
73. *Antonova LV, Sevostyanova VV, Mironov AV, Krivkina EO, Velikanova EA, Matveeva VG et al. In situ* vascular tissue remodeling using biodegradable tubular scaffolds with incorporated growth factors and chemoattractant molecules. *Complex Issues of Cardiovascular Diseases*. 2018; 7 (2): 25–36.
74. *McAllister TN, Maruszewski M, Garrido SA, Wystrychowski W, Dusserre N, Marini A et al.* Effectiveness of haemodialysis access with an autologous tissueengineered vascular graft: a multicentre cohort study. *The Lancet*. 2009; 373 (9673): 1440–1446.
75. *Kleinman HK, Philp D, Hoffman MP.* Role of the extracellular matrix in morphogenesis. *Curr Opin Biotechnol*. 2003; 14 (5): 526–532.
76. *Watt FM, Hogan BL.* Out of Eden: stem cells and their niches. *Science*. 2000; 287: 1427–1430.
77. *Shimaoka M, Springer TA.* Therapeutic antagonists and conformational regulation of integrin function. *Nat Rev Drug Discov*. 2003; 2: 703–716.

78. *Rosso F, Giordano A, Barbarisi M, Barbarisi A.* From cell-ECM interactions to tissue engineering. *J Cell Physiol*. 2004; 199: 174–180.
79. *Hynes RO.* Integrins: versatility, modulation, and signaling in cell adhesion. *Cell*. 1992; 69: 11–25.
80. *Xiao Y, Truskey GA.* Effect of receptor-ligand affinity on the strength of endothelial cell adhesion. *Biophys J*. 1996; 71: 2869–2884.
81. *Talacua H, Smits AI, Muylaert DE, van Rijswijk JW, Vink A, Verhaar MC et al. In situ* Tissue Engineering of Functional Small-Diameter Blood Vessels by Host Circulating Cells Only. *Tissue Eng*. Part. A. 2015; 21 (19–20): 2583–2594.
82. *Melero-Martin JM, Khan ZA, Picard A, Wu X, Paruchuri S, Bischoff J. In vivo* vasculogenic potential of human blood-derived endothelial progenitor cells. *Blood*. 2007; 109 (11): 4761–4768.
83. *Hsia K, Yao CL, Chen WM, Chen JH, Lee H, Lu JH.* Scaffolds and cell-based tissue engineering for blood vessel therapy. *Cells Tissues Organs*. 2016; 202 (5/6): 281–295.
84. *Ruegg C, Dormond O, Mariotti A.* Endothelial cell integrins and COX-2: mediators and therapeutic targets of tumor angiogenesis. *Biochim Biophys Acta*. 2004; 1654: 51–67.
85. *Berman AE, Kozlova NI, Morozevich GE.* Integrins as a potential target for targeted anticancer therapy. *Biochem*. 2013; 59 (3): 239–248. [In Russ, English abstract].
86. *Weber LM, Hayda KN, Haskins K, Anseth KS.* The effects of cell-matrix interactions on encapsulated beta-cell function within hydrogels functionalized with matrix-derived adhesive peptides. *Biomaterials*. 2007; 28 (19): 3004–3011.
87. *Tashiro K, Sephel GC, Weeks B, Sasaki M, Martin GR, Kleinman HK et al.* A synthetic peptide containing the IKVAV sequence from the chain of laminin mediates cell attachment, migration, and neurite outgrowth. *J Biol Chem*. 1989; 264 (27): 16174–16182.
88. *Hsu SH, Chu WP, Lin YS, Chiang YL, Chen DC, Tsai CL.* The effect of an RGD-containing fusion protein CBD-RGD in promoting cellular adhesion. *J Biotechnol*. 2004; 111 (2): 143–154.
89. *Liu J, Cheng X, Tian X, Guan D, Ao J, Wu Z et al.* Design and synthesis of novel dual-cyclic RGD peptides for αvβ3 integrin targeting. *Bioorg Med Chem Lett*. 2019; 29 (7): 896–900.
90. *Discher DE, Mooney DJ, Zandstra PW.* Growth factors, matrices and forces combine and control stem cells. *Science*. 2009; 324 (5935): 1673–1677.
91. *Wu S, Du W, Duan Y, Zhang D, Liu Y, Wu B et al.* Regulating the migration of smooth muscle cells by a vertically distributed poly (2-hydroxyethyl methacrylate) gradient on polymer brushes covalently immobilized with RGD peptides. *Acta Biomater*. 2018; 75: 75–92.
92. *Kang TY, Lee JH, Kim BJ, Kang JA, Hong JM, Kim BS. In vivo* endothelization of tubular vascular grafts through in situ recruitment of endothelial and endothelial progenitor cells by RGD-fused mussel adhesive proteins. *Biofabrication*, 2015; 7 (1): 015007.
93. *Hwang DS, Gim Y, Yoo HJ, Cha HJ.* Practical ecombinant hybrid mussel bloadhesive fp-151. *Biomaterials*. 2007; 28 (24): 3560–3568.
94. *Cutiongco MF, Choo RK, Shen NJ, Chua BM, Sju E, Choo AW et al.* Composite Scaffold of Poly (Vinyl Alcohol) and Interfacial Polyelectrolyte Complexation Fibers for Controlled Biomolecule Delivery. *Front Bioeng Biotechnol*. 2015; 3: 3.
95. *Cutiongco MF, Anderson DE, Hinds MT, Yim EK. In vitro* and *ex vivo* hemocompatibility of off-the-shelf modified poly (vinyl alcohol) vascular grafts. *Acta Biomater*. 2015; 25: 97–108.
96. *Noel S, Hachem A, Merhi Y, De Crescenzo G.* Development of a Polyester Coating Combining Antithrombogenic and Cell Adhesive Properties: Influence of Sequence and Surface Density of Adhesion Peptides. *Biomacromolecules*. 2015; 16 (6): 1682–1694.
97. *Choi WS, Joung YK, Lee Y, Bae JW, Park HK, Park YH et al.* Enhanced Patency and Endothelialization of Small-Caliber Vascular Grafts Fabricated by Coimmobilization of Heparin and Cell-Adhesive Peptides. *ACS Appl Mater Interfaces*. 2016; 8 (7): 4336–4346.
98. *Sedaghati T, Jell G, Seifalian A.* Investigation of Schwann cell behaviour on RGD-functionalised bioabsorbable nanocomposite for peripheral nerve regeneration. *New Biotechnol*. 2014; 31: 203–213.
99. *Antonova LV, Seifalian AM, Kutikhin AG, Sevostyanova VV, Matveeva VG, Velikanova EA et al.* Conjugation with RGD Peptides and Incorporation of Vascular Endothelial Growth Factor Are Equally Efficient for Biofunctionalization of Tissue-Engineered Vascular Grafts *Int J Mol Sci*. 2016; 17 (11): 1920.
100. *Antonova L, Silnikov V, Sevostyanova V, Yuzhalin A, Koroleva L, Velikanova E et al.* Biocompatibility of Small-Diameter Vascular Grafts in Different Modes of RGD Modification. *Polymers*. 2019; 11 (1): 174.

The article was submitted to the journal on 9.07.2019