International Journal of Materials Science and Applications
2021; 10(2): 35-45
http://www.sciencepublishinggroup.com/j/ijmsa
doi: 10.11648/j.ijmsa.20211002.13
ISSN: 2327-2635 (Print); ISSN: 2327-2643 (Online)

Application and Manufacturing Method of Stent Material in Vascular Regeneration and Prevention of Vascular Restenosis

Wenqi Fan

Material Science and Engineering, Harbin Institute of Technology, Harbin, China

Email address:
fwqisabel@163.com

To cite this article:
Wenqi Fan. Application and Manufacturing Method of Stent Material in Vascular Regeneration and Prevention of Vascular Restenosis. *International Journal of Materials Science and Applications.* Vol. 10, No. 2, 2021, pp. 35-45. doi: 10.11648/j.ijmsa.20211002.13

Received: March 29, 2021; **Accepted**: April 14, 2021; **Published**: April 23, 2021

Abstract: With the development of biological tissue engineering, vascular stent materials have been greatly improved. Synthetic polyester polymers and bio-derived materials with excellent biocompatibility, biodegradability and mechanical strength have greatly improved. These are ideal tissue vascular scaffold materials. Vascular stents mainly play two roles in the body: vascular regeneration and prevention of vascular restenosis. In terms of vascular regeneration, the repair of common bone defects and the pulp regeneration require revascularization. This type of stent has production-promoting ability of adopting the multi-level microtubule structure. Different aperture induces different vascular behavior of making the adhered macrophages deforming correspondingly, promoting the infiltration of endothelial cells into the extracellular matrix and accelerating the formation of new blood vessels. In the treatment of atherosclerosis, stents can not only support blood vessels, but also prevent blood vessel from restenosis and keep blood vessels opening for a long time. To this aim, stents generally carry and controllable release of drugs of inhibiting the proliferation of smooth muscle cells. Such stents are called drug-eluting stents. Usual drugs are rapamycin and paclitaxel. This review intends to mix the nano-scale anticancer drug nanoenzymes with polymers on the surface of the stent and exert the sustained drug releasing function of the drug-eluting stent. This type of drug-eluting stent can not only prevent blood vessel restenosis, but also treat cancer by attacking tumor cells.

Keywords: Angiogenesis, Vascular Restenosis, Multi-level Microtubule Structure, Drug-eluting Stent, Nanoenzyme

1. Introduction

Tissue engineering refers to the acquisition of a small amount of living tissue from the body, using special enzymes or other methods to separate cells from the tissue for cultivation and expansion in vitro. Then the expanded cells are mixed with biomaterials of good biocompatibility, degradability and absorbability in a certain proportion, so that the cells adhere to the biomaterials to form cell-material complexes, and achieve the function of repairing wounds and rebuilding. At present, the main applications of biomaterials are vascular stents for the treatment of cardiovascular diseases and artificial bone stents, which are aimed to promote repair of broken bones. Cardiovascular disease was one of the main causes of death of the global population and has caused serious economic losses. Therefore, people have paid more and more attention to the treatment of cardiovascular disease. Cardiovascular disease is usually related to vascular stenosis or blockage. Coronary artery bypass grafting is considered to be the best choice for patients with revascularization. However, artificial blood vessels have limitations, such as low patency, intimal hyperplasia, and poor anastomotic elasticity [1]. Therefore, a vascular stent with a suitable caliber must have the ability to replace artificial blood vessels. The ideal vascular stent must have a certain degree of mechanical strength and can resist blood erosion; it must have a more convenient implantation method and easy to operate; it must have good biocompatibility of not inducing inflammation and immune rejection after implantation. In addition to treating cardiovascular diseases, the process of repairing damaged bones inevitably requires vascular regeneration. Bone regeneration scaffold is an important factor in the construction of bone tissue engineering, which plays an important role in regulating seed cell recruitment, angiogenesis and osteogenic

micro-environment [2]. Bone scaffold materials have different functions with different sizes of holes and pipe diameter structures. Experiments have proved that the multi-stage microtubule structure scaffold can better stimulate the adhesion and differentiation of bone marrow mesenchymal stem cells into osteoblast cell lines in vivo. Vascular stents can support the adhesion of endothelial cells and the migration and growth of smooth muscle cells, but there is no acellular matrix of endothelial cells on the surface of the lumen. When directly exposed to the bloodstream, there is a great risk of acute thrombosis [3], leading to the restenosis of implanted vessels. In order to guarantee the function of the stent for a long time and prevent vascular restenosis, immunosuppressant and chemo-therapeutic drugs are applied to the surface of the stent to make a drug-eluting stent. The materials currently applied to vascular stents include bio-derived materials, such as collagen, chitosan, and fibrin, and synthetic polymer materials, such as polyurethane, polylactic acid, and polycaprolactone. Different materials have their own advantages and disadvantages, and jointly promote developing stent materials.

2. Research Progress of Vascular Stent Materials

2.1. Bio-derived Scaffold Material

Bio-derived scaffold materials mainly include collagen, chitosan, fibrin, etc. They have good biocompatibility, degradable, and promote cell adhesion and reproduction on their surface. Bio-derived materials have a long history in the medical field. They have grown from vitro single cell culture to organ culture and transplantation, and possess a broad development prospects.

2.1.1. Collagen

Collagen is the most abundant protein in mammals, accounting for 25% to 30% of the total protein. It is widely present in all tissues from the body surface of lower vertebrates to the mammalian body. Collagen participates in the formation of the net structure of extracellular matrix fibrils and microfibrils, and it is the main scaffold of extracellular matrix [4]. Collagen has excellent biocompatibility, biodegradability, and permeability, rarely triggers immune rejection when implanted into the body. At the same time, collagen can also adjust the morphology of surrounding tissue cells and enhance the migration, adhesion, proliferation, differentiation of cells [5]. In terms of morphology, collagen can be processed into mesh, fibrous, and spongy shapes, and used in bioprosthetic heart valves and vascular transplantation nerve regeneration [6]. In addition, covered the surface with collagen can improve the toughness and mechanical strength of the materials. The double-layer vascular catheter prepared with collagen as raw materials has the maximum tensile strength 0.49MPa and the maximum elongation rate 84.88% under dry conditions; the tensile strength is 0.37MPa and the maximum elongation rate is 72.05% under wet conditions [7]. These data show that in terms of material mechanical strength, collagen can be well used in the manufacture of vascular stents as a biologically derived material. In the study, it was found that the increase in the mass ratio of collagen increased the tensile strength of this kind of vascular stent. However, after the collagen on the surface of the stent rapidly degenerates, it is very easy to cause the blood vessel to narrow again. Therefore, surface modification should be performed to prevent cardiovascular diseases when using collagen stents.

2.1.2. Chitosan

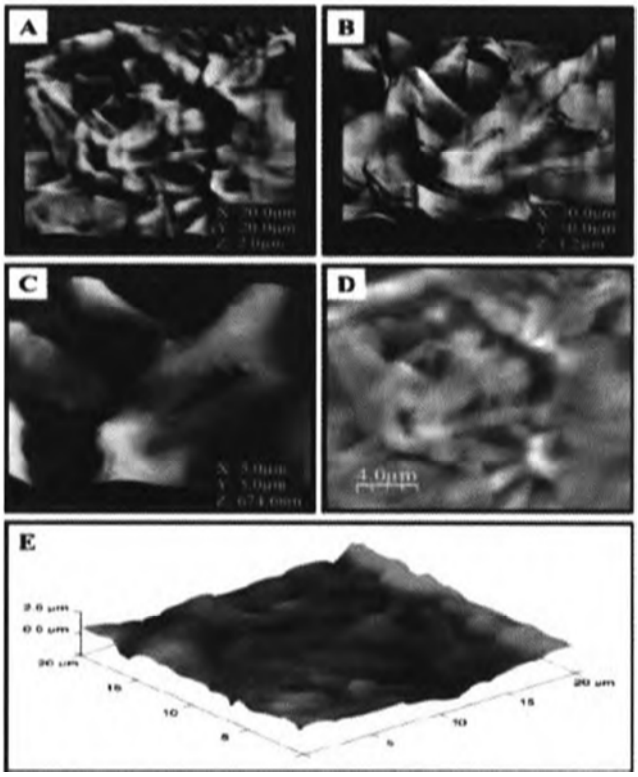

Figure 1. *AFM image of the inner surface of polycaprolactone/chitosan tubular stent Annotation: Ruler of Figure A=20μm; ruler of figure B=10μm; ruler of figure C=5μm Figure D is two-dimensional image of figure A; figure E is Three-dimensional image of PCL/CS sample.*

Chitosan is the product of natural polysaccharide chitin removed from part of the acetyl group. The amino group in the molecular structure of chitosan is more reactive than the acetylamino group in the chitin molecule, which makes the polysaccharide has excellent biological functions and can carry out chemical modification reactions. Chitosan has a variety of physiological functions such as biodegradability, biocompatibility, non-toxicity, antibacterial, anti-cancer, lipid-lowering, and immune enhancement. Therefore, it is considered as a functional biomaterial with greater application potential. For example, the double-layer tubular chitosan hydrogel composite scaffold prepared by the solvent casting-co-particle leaching method has a tensile strength of (95.81±11.00) kPa, an elongation of (112.5±13.0)%, and a porosity of 82%[8]. In vitro, degradation rate and fibroblast proliferation are enhanced, so it can be proved that chitosan-based scaffold materials have become ideal vascular scaffold materials. At the same time, observation under the

microscope [9] shows that the inner and outer surfaces of the chitosan scaffold have obvious ridges and valleys (Figure 1). The rougher outer surface is conducive to cell adhesion, proliferation, and has good biocompatibility. However, the low tensile strength and fast biodegraded rate of chitosan-based stents are problems that hinder the development of such materials.

2.1.3. Fibrin

Fibrin is the earliest coagulation factor discovered in humans. It is an elongated ellipsoid and a highly insoluble protein polymer. Fibrin is mainly derived from plasma protein with obvious blood and tissue compatibility, no toxic side effects and other adverse effects. It can also be used as a skeleton to promote cell growth and has a certain bactericidal effect. Therefore, fibrin can be used as a biological scaffold material in many fields. The fibrin vascular stents prepared by solvent casting have made co-culture with endothelial cells. Cell adhesion behavior can be observed after 2 hours, and a continuous monolayer of endothelial cells can still be seen on the surface of the scaffold after 15 days [10]. At the same time, a viable and dead cell staining experiment was performed. At any time, there were few dead cells that were stained. These two experiments prove that fibrin has good biological safety and certain potential in the preparation of tissue engineering vascular stents. However, the stability of fibrin is insufficient, which limits its application.

One type of fibrin is platelet-rich fibrin, which is a second-generation platelet-derived self-derived scaffold material. There is no need to add thrombin, anticoagulant, calcium chloride and other substances during preparation. Platelet-rich fibrin has a strong fiber network, superior mechanical properties, and can slowly release a variety of growth factors, which help stem cell to migrate, proliferate, differentiate and accelerate the tissue repair process. In addition, this fibrin is easier to meet the physiological coagulation process and has a natural structure. Therefore, it will bring less immunogenicity and cross-reaction [11]. Experiments have shown that platelet-rich fibrin plays an important role in the field of pulp revascularization. The patient's pulpitis symptoms disappear after 12-15 weeks. Root development, root apex closure, and pulp vitality test are similar to the adjacent lateral incision teeth [12]. This indicates that platelet-rich fibrin can promote the differentiation of dental pulp cells into odontoblasts and promote the formation of blood vessels.

2.2. Artificial Synthetic Scaffold Materials

Artificial synthetic scaffold materials' main feature is that they have biocompatibility without the participation of biological factors, for example, some polymers and the selected scaffold metal with good biological activity. Among them, polymers include polycaprolactone, polylactic acid, polyglycolide-lactide, etc. Compared with bio-derived materials, they have better mechanical properties, and degradation rate. Especially zinc can be completely degraded. And they can accurately control the microstructure and porosity during the production process [1] to meet the durable good mechanical properties better required by blood vessels.

2.2.1. Polycaprolactone

Polycaprolactone (PCL) is a polyester obtained by ring-opening polymerization of caprolactone monomers. It has good biocompatibility, high permeability to a variety of drugs. It is easy to load, blend and dope modification and can be mixed with a variety of polymers. The ester bond in the PCL chain can undergo non-enzymatic hydrolysis or intracellular degradation in the body. The decomposition products can generate water and carbon dioxide through the tricarboxylic acid cycle which are metabolically eliminated. Therefore, they are harmless to the human body and will not be accumulated. The process of synthesizing PCL is diversified. PCL can be produced by selecting different polymerization mechanisms, polymerization temperature, polymerization time with different molecular weight and polydispersity coefficient, so as to realize the control of its degradation behavior and mechanical strength. Therefore, PCL is widely used in the field of tissue engineering [13].

However, the cell affinity of PCL fiber scaffold is poor. Cell adhesion is the first step in the interaction between cells and the scaffold. Blood is mainly composed of water, cells, and various proteins. The hydrophilicity and hydrophobicity of the scaffold directly affect its surface adsorption of proteins and cells. Studies have shown that hydrophobic surfaces adsorb proteins stronger than hydrophilic surfaces, and hydrophilic surfaces will affect the conformation of proteins, so moderate hydrophilic modification can increase the affinity of cells. PCL is a hydrophobic substance. For surface modification, PCL can be blended with collagen, or can be used as the core and methacryloyl gelatin as the shell to make nanofiber scaffolds.

PCL has a high degree of crystallinity, which causes its degradation rate to be very slow [14]. As a tissue engineering scaffold, its degradation rate should match the rate of tissue regeneration, but the slow degradation rate of PCL fiber scaffolds may hinder the formation of new tissues. Lactide is easily hydrolyzed and polymerized, which can reduce the crystallinity of the copolymer. Therefore, the copolymerization of lactide and caprolactone monomers can obtain L-lactide-co-Σ-caprolactone (PLCL) [15], making the fiber scaffold increase water absorption rate and increase degradation rate in vitro. In addition, PCL has low mechanical strength, high elasticity and flexibility, and insufficient tensile strength. Therefore, carbon nanotubes or hydroxyapatite nanoparticles can be incorporated into PCL to increase the Young's modulus. The orientation of PCL can also be adjusted to increase molecular order and increase tensile strength.

2.2.2. Polylactic Acid

Polylactic acid is a polyester polymer obtained by polymerization of lactic acid as the main raw material. It has good biodegradability and undergoes metabolic conversion by organisms to finally generate carbon dioxide and water. Polylactic acid has good mechanical, physical properties, the

best tensile strength and ductility. It is suitable for a variety of processing methods. Therefore, polylactic acid with different properties can be obtained by different synthesis methods which aim to make vascular stents with different requirements. ABUDULA [16] et al. used electrospinning to prepare polylactic acid/polybutyl succinate scaffold materials in different ratios and mixed them with fibroblasts. After a certain number of days, it can be observed that the cell coverage on the surface of the composite material is higher than that of the polylactic acid scaffold and the polybutyl succinate scaffold alone. Therefore, the composite scaffold promotes the fibrotic growth of cells. The results can confirm the biocompatibility of polylactic acid, which is very suitable to replace diseased blood vessels or as a vascular stent to maintain the normal working of blood vessels. However, polylactic acid is very brittle and usually mixed with other polymers to form composite materials to exert.

2.2.3. Poly(lactic-co-glycolic Acid)

Poly(lactic-co-glycolic acid) (PLGA) is an amorphous polymer formed by random copoly-merization of lactic acid and glycolic acid. Depending on the biological content of lactic acid and glycolic acid, the degradation time of the polymer and the materials' elasticity can be controlled. Different monomer ratios can produce different type of PLGA, and the degree of degradation varies with the monomer ratio. The more the glycolide from lactic acid polymerized, the easier it degrades. The polyester polymer, which PLGA belongs to, is metabolized and hydrolyzed by the organism. And the ester bond inside the polymer macromolecule can be broken and finally decomposed into lactic acid and glycolic acid. These small molecules are normal metabolites of the body, which can be decomposed into water and carbon dioxide through the tricarboxylic acid cycle and excreted from the body. Therefore, PLGA has good biocompatibility. In addition, PLGA can carry drugs and control drug releasing [17]. PLGA may be better than the currently commonly coating used polypropylene in terms of physical and chemical properties. PLGA has good hydrophilicity, and its degradation rate is faster than hydrophobic polypropylene polymer [18], so the body retention time is relatively short. This may facilitate the repair of blood vessels, thereby reducing the risk of advanced thrombosis.

Chen Ming [17] observed the feasibility and biocompatibility of PLGA as a stent coating in a porcine coronary artery injury model. This experiment used a two-layer structure design. The bottom layer of the stent is a chromium-cobalt alloy, the middle layer is a titanium-oxide material to increase the adhesion between the drug layer and the metal stent, and the surface layer is a mixture of PLGA and rapamycin. The degradability of PLGA controlled the release of rapamycin. The results showed that the endothelialization score of PLGA was similar to the bare metal stent, but the coverage rate of the new cell layer on the stent surface was smaller than the bare metal stent. This is because PLGA has good degradability. After the surface layer is absorbed, the titanium-oxide layer contacts the blood, which can reduce the adhesion of platelets and inhibit the formation of cells, finally improve the long-term biocompatibility of the stents. This experiment also revealed that the PLGA coating has good biocompatibility and blood compatibility, and can be used as an ideal choice for stent drug-carrying coatings.

2.2.4. Degradable Zinc

Even polylactic acid stents used widely, there were still some vascular compatibility problems [19], such as extremely late thrombosis during degradation, low implantation success rate, easy stent overlap, and impact on the thickness of the blood vessel wall. Unlike polymer stents, the mechanical properties and wall thickness of metal degradable vascular stents are close to traditional permanent stents, which can provide adequate mechanical support for damaged blood vessels in the early stage.

Zinc is one of the trace elements in the human body. It is directly involved in the synthesis of nucleic acid and protein, the differentiation, proliferation and metabolism of cells. Therefore, zinc is an essential life element in the important physiological processes of the human body [20, 21]. The standard electrode potential of Zn is -0.763 V, and the degradation rate is appropriate. Because the corrosion rate of degradable metal the applied vascular stents should be less than 0.2 mm/a. Also, it should be mechanically intact for 4 to 12 months after implantation, completely absorbed in 12 to 24 months, and the corrosion degradation mode is required to be uniform degraded [22]. The corrosion degradation rate and degradation mode of zinc alloys can meet the need to maintain the vascular support effect for 4-12 months.

The degradation mechanism of Zn in a body fluid environment with a pH of 7.4 is the simultaneous presence of oxygen absorption corrosion and hydrogen evolution corrosion. The mechanism is: $2Zn + O_2 + 2H_2O \rightarrow 2Zn(OH)_2 \rightarrow 2ZnO + 2H_2O$ and $Zn + 2H_2O \rightarrow Zn^{2+} + H_2 + 2OH^-$. Because of the precipitation of hydrogen, zinc-based alloys also have a certain anti-inflammatory function.

In addition to water and oxygen, proteins also accelerate the degradation of zinc. Protein can affect the degradation process of zinc by competing with other anions in the blood. For example, the adsorption process of serum albumin (BSA) occurs relatively quickly, which can reach a steady state within a few minutes, preferentially occupying the active sites and hindering the adsorption of anions. Besides, BSA will weaken the protective effect of the adsorption layer and accelerate charge transfer. As the immersion time is prolonged, the higher BSA is concentrated, and the more obvious effects on zinc degradation are accelerated [23].

3. Angiogenesis Factor

3.1. Small Molecule Active Peptide

Small molecule active peptide is a kind of biochemical substance between amino acid and protein, generally composed of 2 to 15 amino acids. With simple structure of small peptide and small molecular weight, it can directly enter

cells for efficient absorption, transformation and utilization. It also can adjust the physiological functions of various systems and cells in the body. Even small molecule peptides have excellent biocompatibility. The biological materials used in the bone transplantation process, such as hydroxyapatite, are lack of osteo-inductive properties. Therefore, growth factors such as active peptides are needed to be modified on the surface to regulate the process of osteoangiogenesis.

3.1.1. Angiogenic Peptide

Vascular endothelial growth factor (VEGF) has the effects of promoting increased vascular permeability, degeneration of extracellular matrix, migration, proliferation and angiogenesis of vascular endothelial cells. In a hypoxic environment, VEGF binds to the VEGF receptor on the endothelial cell membrane, causing autophosphorylation of the receptor, realizing the mitogenic properties of VEGF, and inducing endothelial cell proliferation. VEGF can also increase the expression of plasminogen activator (PA) and plasminogen activator inhibitor-l (PAI-1) mRNA, which can increase the activity of plasminogen activating factor, and promote extracellular proteolysis, finally promote the formation of new capillaries.

VEGF-derived peptide QK peptide has been identified an angiogenic potential comparable to recombinant VEGF [24], and can promote the proliferation of human umbilical vein endothelial cells (HUVECs) [25]. Exenatide (Ex-4) can promote the expression of VEGF in cells which further strengthen the proliferation of endothelial cells and blood vessels. It is a synthetic product of glucagon-like peptide-1 (GLP-1) analogue exendin-4, also a GLP receptor agonist, and an approved diabetes treatment drug. The use of Ex-4 in mouse experiments promoted the healing of back wounds in diabetic mice [26], at the same time, enhanced the proliferation, differentiation of HUVECs and the expression of VEGF in human keratinocytes. Kang [27] et al. found that Ex-4 improved the hemodynamics of mice with hindlimb ischemia, reduced local tissue damage of muscles, and increased the staining area of adhesion molecules in platelet-endothelial cells of hindlimb defects. Besides, it promoted the expression of angiogenic factors. These experimental results can prove that the iogenesis ability of Ex-4. Prominin-1 derived peptide (PR1P) was a newly designed polypeptide containing 12 amino acid sequences [28]. This ability is characterized by directly binding to VEGF, promoting the binding of VEGF to vascular endothelial cells, VEGF receptors and neuropilin. However, the defect of PR1P is that it can only work with VEGF to promote the expression of VEGF. But PR1P cannot promote angiogenesis when it works alone. In corneal experiments, without the corneal cells containing endogenous VEGF, the alone injection of PR1P peptide into the cornea did not increase the formation of new blood vessels; while the injection of PR1P peptide and VEGF into the cornea together promoted the formation of corneal new blood vessels.

3.1.2. Arg-Gly-Asp (RGD)

RGD peptide is the shortest amino acid sequence of fibronectin that promotes cell adhesion and is widely present in a variety of extracellular matrix proteins. RGD peptides have been shown to promote osteoblast cell lines in the adhesion and osteogenic differentiation of human mesenchymal stem cells (MSCs) on a variety of bioactive materials [29]. The relationship between the adhesion, different level of some cells and the properties of RGD peptide has been discovered. For example, the adhesion level of cells is positively correlated with the density and mobility of RGD peptides on the surface of the material. Moreover, the concentration of the peptide also affects the shape of the cell. The greater the RGD concentrated is, the longer the cell is, and the lower the roundness is [30].

Collagen mimetic peptides are derived peptides of collagen, which can combine with cell membrane integrins to promote cell adhesion. In order to evaluate the adhesion-promoting effect of collagen mimic peptides, studies have compared RGD peptides with collagen I-derived peptides DGEA [31]. The results showed that DGEA peptides have lower cell adhesion effects than RGD peptides, but stronger osteogenic effects. Heparin is a natural anticoagulant substance in animals, and it can bind with the transmembrane proteoglycan to complete the adhesion of osteoblasts with extracellular matrix [32]. Experiments have compounded RGD peptides and heparin-binding peptides to simulate the synergy among the extracellular matrix, integrin and proteoglycan receptors. The extracellular matrix has a complex network composed of a variety of macromolecules, mainly containing collagen, non-collagen, elastin, proteoglycan and aminoglycan. Integrin is heterophilic cell adhesion molecules that depend on Ca^{2+} or Mg^{2+}, promoting mutual recognition and adhesion between cells and cells, cells and extracellular matrix. Therefore, it plays the role of linking the external effects of cells with the internal structure of cells. The results show that the combination of RGD peptide and heparin-binding peptide can significantly promote the adhesion, proliferation and differentiation of osteoblasts. But it does not show a significant synergistic effect on cell adhesion and proliferation. The cell culture results showed that the acceleration of cell adhesion and proliferation produced by RGD peptide and heparin-binding peptide alone was better than the combination of the both.

3.2. Multistage Microtubule Structure Bone Stents Carrier

For the repair of bone defects, there are two commonly methods: boneless graft and bone graft. Boneless transplantation slowly performs bone traction after osteotomy to activate the body's bone regeneration potential and achieve bone repair. However, long-term slow bone traction brings great discomfort and inconvenience to the patients [33]. Bone grafting accelerates and simplifies the healing process by implanting natural bone, including the use of autologous bone grafts, allogeneic and xenogeneic bone grafts. However, the source of autologous bone is limited and can cause complications. Allogeneic bone may spread infectious diseases, and xenogeneic bone may cause animal-derived virus-transmitted diseases [34, 35]. Thus these points limited the clinical application of bone transplantation.

Bone growth stent is an important factor in the construction of bone tissue engineering. It plays an important role in regulating seed cell recruitment, angiogenesis and osteogenic microenvironment. Bone stents with multi-level microtubules can load bone morphogenetic proteins and chemokines, also control their release timing, so that the biological activities of these growth factors can be maintained, and couple time and space with osteogenic differentiation induction. Micro-nano hierarchical structure materials can effectively regulate cell adhesion, migration, proliferation and differentiation [36]. Cells can rearrange with the micro-topological structure of the material surface. In turn, they can also control individual molecules in the cells to control their own response to the material topological structure. The current common artificial bone scaffold uses hydroxyapatite-collagen biomimetic composite fiber [37], which has a porous structure from nanometer to centimeter scale. In vitro, the experiments have proved that pore sizes smaller than 10 microns are easily immersed in tissue fluid to provide more cell adsorption sites and regulate the osteogenic differentiation of mesenchymal stem cells. At the same time, the fiber has a large surface area, which promotes the adhesion of macrophages and accelerates the migration of cells from the fiber surface to the inside. The pore size greater than 100 microns provides sufficient space for osteogenesis and angiogenesis [38]. In vivo, the experiments have shown that the multi-level microtubule structure accelerates the release of growth factors from endogenous mesenchymal stem cells, which can accelerate the healing of tissues and the differentiate into osteoblastic cell lines [39].

Bone regeneration materials with good osteogenesis effect must have rapid vascularization support in order to achieve excellent bone repairing effects. Angiogenesis is the process of sprouting new blood vessels from original blood vessels, including the proliferation and migration of endothelial cells, the expression and regulation of proteolytic enzymes, the rupture and reconstruction of extracellular matrix, and the formation of endothelial lumen. It involves the activation of a series of signal transduction pathways. There are angiogenesis promoters and inhibitors around the endothelial cells of new blood vessels. And the content of these two biological factors is in a dynamic balance. Among them, the promoting factor can accelerate the hydrolysis of the macromolecular protein network in the extracellular matrix by proteolytic enzymes in the endothelial cells, so that the endothelial cells infiltrate into the extracellular matrix, forming new capillaries and gathering into a vascular network. The structure of multi-level microtubules can cause corresponding deformation of the attached macrophages, resulting in increasing skeletal tension. Meanwhile, macrophages also transform to M2 type [40]. M2 type can regulate the expression of endothelial growth factor and further regulate the formation of blood vessels. Different tube diameters can induce different macrophage behaviors and even suppress immune rejection. Relevant vitro experiments have confirmed that the multi-stage microtubule structure can promote the adhesion of mesenchymal stem cells and can differentiate into osteocytic cell lines [39]. For the differentiation of human bone marrow mesenchymal stem cells, exogenous osteogenic factors need to be added.

4. The Drug-Eluting Stent

The drug-eluting stent (DES) is a bare metal stent platform carrying anti-vascular intimal hyperplasia drugs, locally controlled releasing and eluting in the blood vessel [41], which effectively inhibits the intimal hyperplasia of the stent and prevents restenosis of the vessel at the implantation site. The reasons of vascular restenosis can be divided into the following categories: thrombus formation, elastic contraction of blood vessel walls, inflammatory reactions, and formation of new membranes. The stent can solve the problem of elastic contraction of the blood vessel wall, and the eluted drug can avoid the formation of new membrane [42]. Therefore, the effective application of drug-eluting stents can greatly reduce the incidence of restenosis and re-intervention. Bare stents are generally made of stainless steel or cobalt-chromium. The preparation of the polymer drug-loading layer covering the surface of these stents involves permanent, degradable and polymer-free drug-loading coating technology. Commonly used polymers are polylactic acid (PLA), polylactic acid (PLLA), polylactic acid (PDLA), PGA, polyethylene glycol (PEG), polycaprolactone(PCL), etc.[43], containing the drugs, such as paclitaxel and rapamycin.

The key to the design of DES lies in the polymer drug-loaded coating technology, the influence of the inner coating on the adhesion of the stent. Some questions should be considered, for example, how the drug-loaded coating contains drugs, and how the outer coating controls the drug release rate. Permanent polymer drug-loaded coating technology is the basic technology for drug-eluting stents. Drug-eluting stents have high requirements for permanent polymers, such as, good biocompatibility, and slight inflammation. The drug in the permanent polymer coating is released by the dissolution of microparticles, and then enters the blood vessel wall by passive diffusion. It can also be stored in the polymer film in the form of a solution or directly dissolved in the polymer matrix. The degradable polymer drug-loaded coating releases the drug through the dual pathways of drug dispersion and polymer degradation, in which monomers produced by polymer degradation may cause complications such as inflammation to the body. Polymer-free drug-loaded coating technology includes: Drug is poured into blind or nano-pores on the surface of the stent wire; The drug is dissolved in a bioabsorbable carrier on the surface of no-polymer drug-loaded stent; The drug substance combine with covalently bonds or attach to the stent surface in the form of crystals and chemical precipitation. This method can completely eliminate the sensitization and inflammation caused by the polymer drug-loaded coating in the drug-eluting stent, at the same time, does not affect the repair, healing and coverage of the stent intima. It can also eliminate the cracking, exfoliation and accumulation of the polymer drug-loaded coating phenomenon to maintain the integrity of the stent surface.

4.1. Drug-eluting Stent Carrying Paclitaxel/Chitosan

Paclitaxel is a diterpene alkaloid compound with anticancer activity. Its mechanism of action is by disrupting the dynamic balancing between tubulin dimers and microtubules, promoting tubulin polymerization. It inhibits the depolymerization of microtubules and keep tubulin stable, resulting in cells failing to form spindles and spindle filaments during mitosis, cell division and proliferation, so that Paclitaxel has exerting anti-proliferation and anti-cancer effects [44, 45]. Clinical studies have shown that paclitaxel can effectively prevent or inhibit the proliferation and migration of smooth muscle cells, thereby reducing vessels restenosis [46]. There are a large number of hydroxyl and amino groups in the structure of chitosan, which can form hydrogen bonds with glycoproteins in mucus. Besides, the positive charge on chitosan interacts with the charge on the mucosa, thereby increasing the residence time of the drug in a specific area, to achieve the purpose of stable release of drugs and improvement of drug efficacy. In addition, the polysaccharide chains on chitosan can be used for targeting, which can open cell channels and greatly increase the probability of drugs absorbed by cells. Different from other biodegradable materials, these properties make chitosan an excellent choice for drug carriers [47-49]. Regarding the assembly feed ratio of paclitaxel and chitosan, Tang Jing [50] conducted experiments and found that when the concentration of paclitaxel aggregates is 1 mg/mL and the concentration of chitosan solution is 2 mg/mL, it can make an uniform Slender nanofibers (Figure 2).

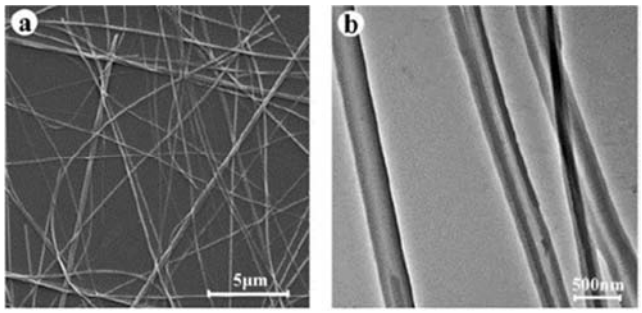

Figure 2. *SEM image (a) and TEM image (b) of the assembly formed by chitosan at 2 mg/mL and paclitaxel at 1 mg/mL.*

In the study of drugs' sustained release, the sample is dispersed in phosphate buffer solution, with a dialysis bag, immersed in phosphate buffer solution, and placed in a shaker (set temperature is 37°C). The results showed that 62% of the drug was released after 21 days (Figure 3). This result indicated that the paclitaxel/chitosan assembly had slow drug release in vitro. This is because the drug-eluting stent coated with paclitaxel/chitosan core-shell nanofibers achieves sustained drug release by breaking non-covalent bonds. The specific principle may be that ultrasound is used to promote the aggregation of paclitaxel molecules under the π-π stacking effect, hydrophobic effect and form a paclitaxel core. Then, under the synergistic effect of hydrogen bonds and van der Waals forces, the chitosan fibers gradually wraps around the paclitaxel core to form a chitosan shell [50]. The chitosan shell has two main functions: the shell inhibits the excessive lateral growth of the paclitaxel core and the chitosan macromolecular flexible chain promotes the axial growth of the paclitaxel core. Thus, a paclitaxel/chitosan flexible nano-core-shell structure nano-long fiber is formed to control the release of the drug.

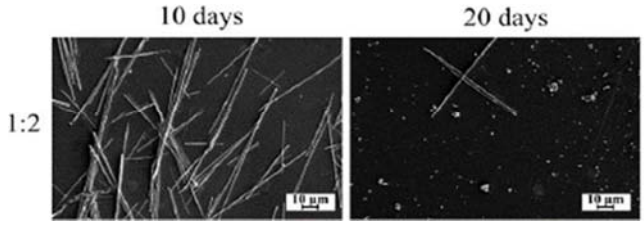

Figure 3. *SEM images of paclitaxel/chitosan (1:2) assembly after 10 days and 20 days during the determination of sustained drug release.*

In addition, Yinyi® Microblind Coronary Stent is a polymer-free paclitaxel drug stent. The stent is packed with micron-level honeycomb pits on the surface, and the medicine is directly packaged in the pits to realize the carrying and slow release of the medicine. This drug-carrying structure can effectively prevent restenosis in the stent. At the same time, it avoids the late inflammation of the local blood vessel wall which is caused by the polymer itself or the degraded monomer, thus, reducing the occurrence of thrombotic events in the stent [51].

4.2. Drug-Eluting Stent Carrying Polymer/Rapamycin

Rapamycin (RAPA) is a new type of macrolide drugs, lipophilic and very slightly soluble in water, which is a new type of immunosuppressant with good curative effect, low toxicity and no nephrotoxicity. It is now often used as a drug to maintain the immunity of transplanted organs (especially kidney transplants) to slow down the immune rejection after organ transplantation. The mechanism of action is that it highly binds to the receptor FKBP12 (a cytoplasmic binding protein) and inhibits the growth of vascular smooth muscle cells by preventing the transition from G1 to S phase in the cell cycle [52]. Rapamycin has its unique advantages as a DES drug coating, mainly appearing in that it only has an inhibitory effect on the excessive proliferation of smooth muscle cells, but little effect on the re-endothe lialization of vascular lesions. It also has a certain inhibitory effect on inflammation [53].

This kind of DES is usually a metal stent covered with a polymer, and the polymer carries rapamycin. The polymer can be selected from bio-inert polysulfone-polyethylene glycol copolymer (PSF-PEO) or biodegradable polylactic acid. The surface of PSF-PEO material has a microphase separation structure, which can improve blood compatibility. Li Qiyun et al.[54] used PSF-PEO with 30% polyethylene glycol coating to mix with rapamycin, and sprayed with 316L stainless steel bare metal stent by ultrasonic atomization. The experimental results showed that in the control group without rapamycin, the official cavity area was small. The neoplastic membrane

area was large. The graded area stenosis rate was high. Besides, the synthesis phase specific marker PCNA located in the smooth muscle cell nucleus was positive and the stent was covered with intact vascular endothelium. The stent coated with rapamycin also inhibited the formation of new membrane. Although few endotheliums were covered, more leukocytes were accumulated, which proved to be a mild inflammatory reaction.

PLGA is a copolymer formed by the polymerization of monomers of lactic acid and glycolic acid. Different types of PLGA can be prepared by controlling different monomer ratios, so that the degradation rate can be controlled. The degradation rate is mainly related to the ratio and relative molecular weight of the two monomers: lactic acid and glycolic acid. Generally, the greater the proportion of glycolic acid, the faster the degradation rate. Therefore, the degradation time of PLGA with different molecular weights or monomer ratios can be selected to change the sustained release performance of the stent drug coating. Sun Yuanke [55] used electrophoretic deposition in a stable colloidal system to prepare polylactic acid eluting stents with rapamycin. Because the drug-loaded nanoparticle deposition solution must have good stability, the drug-loaded nanoparticles in this deposition solution can continuously and stably deposit and grow a film on the surface of the stent to form a uniform drug-loaded coating. The carrier PLGA is capped by carboxyl (-COOH), and the surface emulsifier PAA is an anionic surfactant. The prepared RAPA-PLGA-NPs are negatively charged in the colloidal liquid, so the anode deposition method is used to prepare the stent drug-carrying coating. The best effect is when the deposition voltage is 6-7V, for 20-30min, and the concentration of deposition solution is 1.2-1.4mg/ml. (Figure 4)

Drug release is divided into swelling type and erosion type. The swelling matrix system mixes the drug in the carrier polymer, which is swellable and generally non-degradable. In the process of drug release, the polymer can absorb a large amount of liquid and the volume increases. After the liquid enters the matrix, the drug gradually dissolves and diffuses out of the expanded matrix. The drug release rate largely depends on the swelling rate of the polymer, the dissolution and diffusion rate of the drug in the liquid. The erodible drug carrier is generally a degradable polymer. While the drug diffuses from the carrier polymer, the polymer itself is gradually degraded. The drug release rate is mainly related to the dissolution and diffusion rate of the drug. Also, the degradation rate of the carrier is connected. The drug carrier PLGA is a degradable polymer. In theory, at the initial stage of drug release, the polymer has not begun to degrade, and the polymer swells because of water absorption. The drug release is mainly based on dissolution and diffusion. At this occasion, the drug release mode is similar to swelling controlled release type. As the sustained release progresses, PLGA begins to conduct a hydrolysis reaction and gradually degrades, and the drug is released with the degrading carrier. At this occasion, the drug release mechanism is biased towards the controlled erosion releasing drug mode [55].

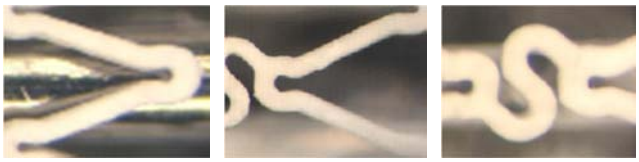

Figure 4. *The stent coating morphology when the deposition voltage is 6-7V, the deposition is 20-30min, and the deposition solution concentration is 1.2-1.4mg\ml*

5. Summary and Outlook

Stent materials can combine the good compatibility of bio-derived scaffolds with the good mechanical properties of artificial composite materials. Such artificial composite materials containing natural ingredients will be a popular direction pursued by researchers. The role of stents on blood vessels is reflected in two aspects: implantation of stents in the wound site, the carried growth factors promoting vascular regeneration, implantation in atherosclerosis or tumor tissue blood vessels, which can inhibit endothelial cells by releasing drugs Adhesion, restenosis of blood vessels, and even tumor cells. At present, most stents can carry growth factors and simulate the growth environment of blood vessels to repair damaged tissues. They can also be coated with polymers containing drug components by methods such as electrophoretic deposition to work as drug-eluting stents. Cancer is one of the main threats to human health. When worse changes occur in advanced esophageal cancer, bowel cancer, and cholangiocarcinoma, the natural ducts are blocked due to tumor growth and the lumen is blocked. Therefore, the patient always loses the opportunity for surgery because of the late tumor stage. Under such conditions, the luminal stent can be implanted into the blocked position by interventional means to maintain the patency of the lumen. However, it faces the problem of tumor tissue growth and the lumen will be blocked again. A stent, which not only can prevent the blocked lumen but also has an anti-tumor effect, is the new type of stent we are looking forward to.

Can the coated drugs be changed from rapamycin and paclitaxel, which inhibit vascular restenosis, to those that have stronger and more effective killing of tumor cells? Drugs used to treat cancer are generally nano-sized molecules. Nanotechnology is an emerging field. In terms of stent synthesis, it is known that nanoparticles can be added to the polymer covering of the metal stent surface to adjust the mechanical properties. For example, adding hydroxyapatite to the polyethylene fiber to improve the Young's model Quantity [13]. Then the hydroxyapatite nanoparticles used here can also be replaced with nanoenzymes. Nanoenzyme is a kind of mimic enzyme with catalytic function, which can catalyze the chemical reaction inside tumor cells to achieve endogenous cell killing effect. Stents coated with rapamycin and paclitaxel cannot have anti-tumor effects on all types of malignant tumor cells. Therefore, we need to find a chemical reaction which will inhibit all tumor cells and achieve anti-tumor effects. This chemical reaction can be carried out by all tumor cells and cannot occur in normal cells. This kind of endogenous

chemical kinetic killing of cells not only has obvious therapeutic effect, but also has little damage to surrounding tissues. It is a new way to treat tumors, avoiding the shortcomings of chemotherapeutics that are only effective for one type of cancer.

The high metabolism of tumor cells requires more glucose and oxygen to maintain aerobic glycolysis, which results in hypoxia and acidic environment around tumor cells. Under this condition, aerobic respiration produces a large amount of intermediate product hydrogen peroxide, and the final product is reactive oxygen species ROS. Although the strong oxidizing properties of ROS can kill cells, in order to survive, tumor cells will choose to oxidize glucose into water molecules, so that the surrounding hydrogen peroxide content is limited, and the converted ROS is not enough to kill tumor cells. Therefore, we can consider a sequential catalytic reaction: the scaffold carries both glucose oxidase and Fe_3O_4 nanoparticles. First, glucose oxidase can convert glucose in cells into hydrogen peroxide, and then Fe_3O_4 is used as a catalyst for the hydrogen peroxide reaction to accelerate the generation of a large amount of ROS to achieve the purpose of tumor killing. In terms of drug transportation, Fe_3O_4 nanoparticles with a diameter of 7nm can be synthesized through the water-oil phase [56] and put into silica gel balls together with glucose oxidase. The synthesized silica balls have a diameter of about 100 nm. The polymer covered on the stent surface can be considered as a negatively charged polylactic acid - polyglycolic acid copolymer, and the drug coating is prepared by anodic deposition [55]. It is the hope that in the future vascular stents can be perfectly combined with tumor treatment to provide new methods for the rehabilitation of cancer patients.

References

[1] Yang Lei, Li Xiafei, et al. Small-caliber tissue engineering vascular scaffold: how to produce a material with physiological remodeling activity [J], Chinese Tissue Engineering Research, 2019.

[2] Ye Haimin, Ding Linghua, Kong Wei, et al., Multi-level microtubule structure bone scaffold carrier promotes osteogenesis and angiogenesis and its mechanism [J].

[3] Huang Shupei, Liang Yuanfeng, Hao Junhai, et al. The effect of heparin grafting on the structure and anticoagulant effect of vascular acellular scaffolds [J], Guangdong Medicine, May 2019, Vol. 40, No. 10.

[4] Liu Yi, Zhou Qingzhu, Gong Zhuo, et al. The characteristics and manufacturing technology of collagen/inorganic materials to construct tissue engineering bone [J].

[5] DONG C, LVY. Application of collagen scaffold in tissue engineering: recent advances and new perspectives. Polymers (Basel).2016; 8 (2): 42-62.

[6] KANG L, JIA W, LI M, et al. Hyaluronic acid oligosaccharide-modified collagen nanofibers as vascular tissue-engineered scaffold for promoting endothelial cell proliferation. Carbohydr Polym. 2019; 2 (23): 106-115.

[7] ZHOU J, YING H, WANG M, et al. Dual layer collagen-GAG conduit that mimic vascular scaffold and promote blood vessel cells adhesion, proliferation and elongation. Mater sci Eng C Mater Biol Appl. 2018; 92: 447-452.

[8] BADHE RV, BIJUKUMAR D, CHEJARA DR, et al. A composite chitosan-gelatin bi-layered, biomimetic microporous scaffold for blood vessel tissue engineering. Carbohydr Polym. 2017; 157: 1215-1225.

[9] REZ MFA, BINOBAID A, ALGHOSEN A, et al. Tubular Poly/Chitosan Nanofibrous Scaffold Prepared by Electrospinning for Vascular Tissue Engineering Applications. J Bioma Tissue Eng. 2017; 7 (6): 427-436.

[10] PANKAJAKSHAN D, PHILIPOSE LP, PALAKKAL M, et al. Develpment of a fibrin composite-coated poly scaffold for potential vascular tissue engineering applications. J Biomed Mater Res B Appl Biomater. 2010; 87B (2): 570-579.

[11] Chen Leyi, Lu Xiaolin, Xu Wenan, Application of scaffold materials in pulp regeneration and revascularization [J], Chinese Tissue Engineering Research.

[12] KESWANI D, PANDEY RK. RevascuIarization of an immature tooth with a necrotic puIp using pIateIet-rich fibrin: a case report. Int Endod J. 2013; 46 (11): 1096-1104.

[13] Wu Xiaotong, He Er, Liu Laijun, et al. Research progress of tissue engineering scaffolds based on polycaprolactone fibers [J], Chinese Journal of Biomedical Engineering, October 2020, Volume 39, Issue 5.

[14] Chen Dairui, Bei Jianzhong. Wang Sheng guo. Polycaprolactone microparticles and their biodegradation [J]. Polym Degrad Stab, 2000, 67 (3): 455-459.

[15] Garkhal K, Verma S, Jonnalagadda S, et al. Fast degradable poly microspheres for tissue engineering: Synthesis, characterization, and degradation behavior [J]. J Polym Sci Pol Cem, 2007, 45 (13): 2755-2764.

[16] ABUDULA T, SAEED U, MEMIC A, et al. Electrospun PHEA-PLA/PCL Scaffold for Vascular Regeneration: A Preliminary in Vivo Evaluation, Transplantation Proceedings 2017; 49 (4): 716-721.

[17] Chen Ming, Peng Hongyu, Huo Yong, etc., a new type of biodegradable polymer coating. Effect of rapamycin-eluting stent on neointimal hyperplasia of porcine coronary arteries [J], Journal of Cardiopulmonary and Vascular Disease, Vol. 29, Issue 4, July 2010.

[18] Commandeur S, Van Beusekom H M, Van Der Giessen, W J. Polymers, drug release and drug-eluting stents. J Interv Cardiol. 2006, 19: 500-506.

[19] Zhou C, Li H F, Yin Y X, et al. Long-term in vivo study of biodegradable Zn-Cu stent: A 2-year implantation evaluation in porcinecoronary artery [J]. Acta Biomater., 2019, 97: 657.

[20] MENG Y, LIU L J, ZHANG D W, et al. Initial formation of corrosion products on pure zinc in saline solution [J], Bioactive Materials, 2019, 4 (1): 87-96.

[21] WEISS J H, SENSI S L, KOH J Y. Zn(II): a novel ionic mediator of neural injury in brain disease [J], Trends in Pharmacological Sciences, 2000, 21 (10): 395-401.

[22] Liu Lijun, Study on the corrosion behavior and mechanical behavior of pure zinc in simulated body fluids [J], University of Science and Technology Beijing.

[23] Qian Yi, Yuan Guangyin, Research status, challenges and countermeasures of biodegradable zinc alloy vascular stents [J], Acta Metallurgica Sinica, March 2021, Vol. 57 No. 3.

[24] Capasso D, Di Gaetano S, Celentano V, et al. Unveiling a VEGF-mimetic peptide sequence in the IQGAP1 protein [J]. Mol Biosyst, 2017, 13 (8): 1619-1629. DOI: 10.1039/c7mb00190h. Yang Y, Yang Q, Zhou F, et al. Electrospun PELCL membranes loaded with QK peptide for enhancement of vascular endothelial cell growth [J]. J Mater Sci Mater Med, 2016, 27 (6): 106. DOI: 10.1007/s10856-016-5705-6.

[25] Yang Y, Yang Q, Zhou F, et al. Electrospun PELCL membranes loaded with QK peptide for enhancement of vascular endothelial cell growth [J]. J Mater Sci Mater Med, 2016, 27 (6): 106. DOI: 10.1007/s10856-016-5705-6.

[26] Seo E, Lim JS, Jun JB, et al. Exendin-4 in combination with adipose-derived stem cells promotes angiogenesis and improves diabetic wound healing [J]. J Transl Med, 2017, 15 (1): 35. DOI: 10.1186/s12967-017-1145-4.

[27] Kang HM, Sohn I, Jung J, et al. Exendin-4 protects hindlimb ischemic injury by inducing angiogenesis [J]. Biochem Biophys Res Commun, 2015, 465 (4): 758-763. DOI: 10.1016/j.bbrc.2015.08.080.

[28] Adini A, Adini I, Chi ZL, et al. A novel strategy to enhance angiogenesis in vivo using the small VEGF-binding peptide PR1P [J]. Angiogenesis, 2017, 20 (3): 399-408. DOI: 10.1007/s10456-017-9556-7.

[29] Chen Tianhong, Li Jingfeng, Research progress of small molecule active peptides in bone tissue engineering [J], International Journal of Biomedical Engineering, Vol. 43 No. 5, October 2020.

[30] Jonkheijm P. Guiding hMSC adhesion and differentiation on supported lipid bilayers [J]. Adv Healthc Mater, 2017, 6 (3): 201600862. DOI: 10.1002/adhm.201600862.

[31] Mehta M, Madl CM, Lee S, et al. The collagen I mimetic peptide DGEA enhances an osteogenic phenotype in mesenchymal stem cells when presented from cell-encapsulating hydrogels [J]. J Biomed Mater Res A, 2015, 103 (11): 3516-3525. DOI: 10.1002/jbm.a.35497.

[32] Ravanetti F, Gazza F, D'arrigo D, et al. Enhancement of peri-implant bone osteogenic activity induced by a peptidomimetic functionalization of Titanium [J]. Ann Anat, 2018, 218 (218): 165-174. DOI: 10.1016/j.aanat.2018.01.011.

[33] BALDWINP, LIDJ, AUSTONDA, et al. Autograft, Allograft, and Bone Graft Substitutes: Clinical Evidence and Indications for Use in the Setting of Orthopaedic Trauma Surgery. J Orthop Trauma. 2019; 33 (4): 203-213.

[34] GRIGORIAN SHAMAGIAN L, MADONNA R, TAYLORD, et al. Perspectives on Directions and Priorities for Future Preclinic Studies in Regenerative Medicine. Circ Res. 2019; 124 (6): 938-951.

[35] ORYAN A, ALIDADI S, MOSHIRI A, e al. Platelet-rich plasma for bone healing and regeneration. Expert Opin Biol Ther. 2016; 16 (2): 213-232. HOLTHAUS MG, STOLLE J, TRECCANI L, et al. Orientation of humanosteoblasts on hydroxyapatite-based microchannels. Acta Biomater. 2012; 8 (1): 394-403 WEINER S, WAGNER D. The Material Bone: Structure-Mechanical Function Relations. Annu Rev Mater Res. 2003; 28: 271-298. WANG XJ, LOU T, ZHAO WH, et al. The effect of fiber size and pore size on cell proliferation and infiltration in PLLA scaffolds on bone tissue engineering. J Biomater Appl. 2016; 30 (10): 1545-1551.

[36] HOLTHAUS MG, STOLLE J, TRECCANI L, et al. Orientation of humanosteoblasts on hydroxyapatite-based microchannels. Acta Biomater. 2012; 8 (1): 394-403.

[37] WEINER S, WAGNER D. The Material Bone: Structure-Mechanical Function Relations. Annu Rev Mater Res. 2003; 28: 271-298.

[38] WANG XJ, LOU T, ZHAO WH, et al. The effect of fiber size and pore size on cell proliferation and infiltration in PLLA scaffolds on bone tissue engineering. J Biomater Appl. 2016; 30 (10): 1545-1551.

[39] WON JE, LEE YS, PARK JH, et al. Hierarchical microchanneled scaffolds modulate multiple tissue-regenerative processes of immune responses, angiogenesis, and stem cell homing. Biomaterials. 2020; 227: 119548.

[40] PAN HH, XIE YT, ZHANG ZQ, et al. Immunomodulation effect of a hierarchical macropore/nano surface on osteogenesis and angiogenesis. Biomed Mater. 2017; 12 (4): 045006.

[41] Chen Li, Wang Wu, Application and progress of surface modification in neuro-interventional therapy materials [J], Journal of Interventional Radiology, July 2020, Vol. 29, Issue 7.

[42] Guo Jingtao, Ma Changsheng, Zhang Shuliang, et al. Application of drug elution in coronary multiple stents, China Medicine, June 2007, Vol. 2, No. 6.

[43] Zhu Y, Zhang H, Zhang Y, et al. Endovascular metal devices for the treatment of cerebrovascular diseases [J]. Adv Mater, 2019, 31: e1805452.

[44] X. Sun, Z. Pang, H. Ye, B. Qiu, L. Guo, J. Li, J. Ren, Y. Qian, Q. Zhang, J. Chen, X. Jiang. Co-delivery of pEGFP-hTRAIL and paclitaxel to brain glioma mediated by an angiopep-conjugated liposome [J]. Biomaterials. 2012, (33): 916-924.

[45] W. Zhang, Y. Shi, Y. Chen, J. Ye, X. Sha, X. Fang. Multifunctional Pluronic P123/F127 mixed polymeric micelles loaded with paclitaxel for the treatment of multidrug resistant tumors [J]. Biomaterials. 2011, (32): 2894-2906.

[46] J. Yang, Y. Zeng, C. Zhang, Y. Chen, Z. Yang, Y. Li, X. Leng, D. Kong, X. Wei, H. Sun, C. Song. The prevention of restenosis in vivo with a VEGF gene and paclitaxel co-eluting stent [J]. Biomaterials. 2013, (34): 1635-1643.

[47] C. K. S. Pillai, W. Paul, C. P. Sharma. Chitin and chitosan polymers: Chemistry, solubility and fiber formation [J]. Progress in Polymer Science. 2009, (34): 641-678.

[48] J. Grant, H. Lee, R. C. W. Liu, C. Allen. Intermolecular Interactions and Morphology of Aqueous Polymer/Surfactant Mixtures Containing Cationic Chitosan and Nonionic Sorbitan Esters [J]. Biomacromolecules. 2008, (9): 2146-2152.

[49] P. Kandra, H. P. J. Kalangi. Current understanding of synergistic interplay of chitosan nano particles and anticancer drugs: merits and challenges [J]. Applied Microbiology and Biotechnology. 2015, (99): 2055-2064.

[50] Tang Jing, Preparation of paclitaxel/chitosan co-assembled nanofibers and their application in drug-eluting stents [J].

[51] Zhang Zhiping, Ge Hua, Anti-vascular smooth muscle

proliferation and migration drug coating and restenosis after stent placement [J], Chinese Tissue Engineering Research, Vol. 16, No. 12, March 2012.

[52] Venkatraman S. Boey F Release profiles in drug-elut}ng stents: iseuesand uncartaintjes. J Control Release. 2007; 120 (3): 149-160.

[53] Wang X, Venkatraman SS, Boey FY, et al. Controlled release of sirolimus from a multilayered PLGA stent matrix. Biomaterials·2006: 27 (32): 5588-5595.

[54] Li Qiyun, Chen Zhong, Gu Xingzhong, A novel polymer carrying rapamycin-eluting vascular stent to inhibit intimal hyperplasia [J], Chinese Tissue Engineering Research and Clinical Rehabilitation, January 2009, Vol. 73, No. 4.

[55] Sun Yuanke, Process research on preparation of vascular stent nanoparticle drug-carrying coating based on electrophoretic deposition method [J].

[56] Xu Pengqi, Preparation of mitochondrial-targeted Fe_3O_4 nanoparticles and evaluation of its in vitro magnetocaloric efficacy [J].