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Some "Micro" and "Nano" Elements in the Surface Modification of Cardiovascular Biomaterials

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Introduction

Percutaneous Coronary Intervention (PCI) is the main approach for treating Coronary Artery Disease (CAD) [1]. Low surgical risk and short recovery time are the main advantages of PCI, and stent is the core in the PCI treatment. Stents are generally made from metals including 316L Stainless Steel (316L SS), nitinol and cobalt- chromium alloy, they are named as non-degradable metals [2]. The inherent metallic properties of Bare Metal Stent (BMS) surface are failed to encourage Re-endothelialization and further lead to in-stent thrombosis, and the metallic surface are limitations for effectively drug loading by ionic binding or direct absorption [3]. Based on the problems, Drug Eluting Stent (DES) coated with various biocompatible polymers contained different drugs is a normal choice to elevate the biocompatibility and treatment properties [1]. While the foreign metal stay in the tissue for a long term will lead to immunoreaction [4].

In recent years, the biodegradable metals, including magnesium-, zinc- and iron- based alloys, generally exhibit their advantages on implanted field, stent made of the biodegradable metals are named as Bioresorbable Stents (BRS) [5]. Contrary to BMS or DES, gradually degradation of BRS could not only reshape the vessel, but also disappear eventually to avoid the second operation and reduce long term antiplatelet therapy. Besides, BRS could decrease the inflammation and the late stent thrombosis problem for the drugs or factors on the surface [5]. However, the mechanical properties and unsuitable degradation period are the limitation of the application in coronary artery intervention field [6]. And consideration must also be given to the potentially harmful consequences of systemic delivery through stent.

Recent researches generally considered that formatting a continuous layer of Endothelial cells (ECs) is a better solution to prevent in-stent restenosis. Therefore, surface endothelialization has been a promising direction of implanted device surface modification. To increase the re-endothelialization rate on the device surface, simulating the natural micro-environment has attracted more and more attention. Creating a microenvironment similar to natural vessel may be a promising method to shorten the reendothelialization period, and the ECs will cover the implanted stent and isolate the implanted materials from blood stream to reduce the corrosion rate of BRS.

Cells are subjected to both the surface topography of the basement membrane and the mechanical load from the blood stream in vivo [7]. Simulating the biological microenvironment of the cells on the biomaterials surfaces in vitro may be an effective method to build a vessel structure with autologous EC monolayer [8]. Cells are sensitive to the morphological features of Extracellular Matrix (ECM), thus, fabricate the micro-/nano-patterned surfaces with ECM source material is meaningful to regulate the cell behavior [9]. The next generation of stents should be reendothelialized after implantation to specifically suppress the immune cell response by changing the surface patterns, which will reduce the attachment of immune cells and increase the recruitment, migration and growth of endothelial cells. In this section, bio-inspired "micro" and "nano" structure on stent surfaces is the main discussed topic.

Simulated physiological structure of normal blood vessel

Simulating the biological microenvironment of the cells on the biomaterials surfaces in vitro may be an effective method to build a vessel structure with autologous EC monolayer [8]. Cells are subjected to both the surface components and topography of the basement membrane *in vivo* [7]. Cells are sensitive to the morphological features of ECM, thus, fabricate the micro-/nano-patterned surfaces with ECM components is meaningful to regulate the cell behavior [9]. Geometric confinement caused by micropattern alignment can affect the architecture of F-actin and Microtubules (MTs) within aligned cells, thus regulating morphology and functions of cells [10]. The F- actin microfilaments are important to cells for the roles in cell adhesion, migration, and maintenance shape of cells [11]. For example, ECs could respond to blood flow and reshape actin stress fibers according to the direction of blood flow [12].

Because of the reasons above, changing the implanted surface morphology exhibits potential methods to induce the protein adsorption and directional distribution of cells. To imitate the natural environment, the substrates with engineered morphologies are developed to achieve cell alignment [13]. Compared with the traditional smooth surface, the microstructure surface showed better EC migration and diffusion properties. For example, on grooves with width of 22 μm, the migration of ECs was enhanced [14] and parallel grooves with width of 2 μm showed the highest cell affinity [15]. The complex vascular microenvironments, such as ECM, blood flow shear stress and SMC, could influence the function of ECs simultaneously. For example, a parallel groove stripes may guide cell growth along the grooves, which are similar to physiological EC status exposed to blood status [16].

Understanding the normal vessel structure is necessary for better design of the bionic graphics for Understanding the interaction between cells and topography [17]. In human vascular wall, the EC and SMC are the main components, and the ordered distribution of EC and SMC guarantee the normal physiological functions of the vascular environment [18]. ECs in a native vessel environment exhibit an elongated, cobblestone and aligned morphology and growth followed the blood flow direction. And each EC is attached to several surrounding ECs to continuously create an endothelial monolayer [1]. And the vascular endothelial matrix consists of the contractile SMC sublayer, which owns a direction perpendicular to the blood flow direction. Random surface topographies may promote VSMC proliferation, highly ordered structures can result in VSMC alignment, decreased proliferation and increased differentiation [3]. If the SMC layer with directional distribution was construct as the biomimetic vascular endothelial matrix, which may provide a basic surface for EC of rapid and complete reendothelialization process [19]. To sustain the normal function, including the anticoagulant properties and the release of inhibition proliferative biological functional factors, ECs need the support from the SMCs [20]. The effects of microstructures and nanostructures on SMC and EC are dependent on the size, orientation, and geometry of two and three dimensional systems [21]. For instances, highly ordered features on the surface may increase the VSMC alignment and differentiation, as well as reduced diffusion [17].

Except the vessel structure, the cell-material interactions at the interface affect reendothelialization processes on the stent. The first event happened after stent implanted is protein adsorption (albumin, immunoglobulin, fibrinogen, etc.), and then the interactions between the adsorbed protein layer and the blood are began, especially high levels of fibrinogen adsorption on the surface which may contribute to platelet adhesion and activation, and these activation will lead to thrombus formation within minutes or hours [22]. The adsorption process is affected by material surface properties and topography [23,24]. An increasing number of researchers are looking for new technological solutions to engineer the surface of biomaterial implant in a nanoscale to enhance biocompatibility and tissue regeneration. Surface properties such as surface chemistry, charge and wettability can be specifically optimized to induce the cell adhesion and proliferation. Some reports considered that the hydrophilic surfaces or surfaces with abundant hydroxyl groups could absorb water and have more resistant to protein adsorption, this kind of surface may suppress platelet adhesion by suppressing fibrinogen adsorption [25,26]. While some researchers found the hydrophilic surface may activate plasma coagulation [27,28]. For instance, fibrinogen can be adsorbed on the surface of modified nitinol alloys with a concentration dependent manner [29,30]. Thus, changing the surface characterizes and configuration is a complex method to influence the protein adsorption [31].

Biomolecules

There are two parts related to the surface modification of cardiovascular biomaterials: Biomolecules and micro-/nanopatterned type. In this section, modification biomolecules will be discussed.

Extracellular Matrix (ECM) is an acellular component present in all tissues and organs, which could provide the physical scaffolding for the cellular components and involving in initiating key biomechanical clues needed for tissue and cell morphogenesis, differentiation, and homeostasis [32]. The ECM is composed of two main kinds of macromolecules: Fibrous proteins and proteoglycans (PGs) [33]. Fibrous proteins consist of collagen, elastin, fibronectin and laminin. Proteoglycan (PG) consists of glycosaminoglycan (GAG) chains covalently attached to specific protein cores, except for hyaluronic acid (HA), and PG fills most of the extracellular space in the form of hydration gel [34]. ECM is an important aspect of functional expression and maintenance of biomimetic surfaces. The choose of modification material may similar to the natural ECM to obtain better biocompatibility.

Some biomolecules have been researched for fabricate nanopattern, including HA, collagen I, phosphatidyl choline, and the mixtures of fibronectin [18,35-39], most materials are components of ECM. HA and is the key component of ECM and could trigger signaling pathways associated with cell adhesion (plaque kinase (FAK)), proliferation, migration (extracellular regulatory

kinase (ERK1/2)) and differentiation through specific HA cell surface receptors (CD44 or RHAMM) [40-44]. The existence of -OH group in the chemical construction is related to its high water retention ability and swelling ability [45]. Besides, HA is a negatively charged polysaccharide with simple and linear chemical structure, the negative charge of HA could combine with the different cations (Mg^{2+}, Zn^{2+}, Ca^{2+}) give the polysaccharide high water retention property to the polysaccharide [46]. And HA can only induce a weak immune response as an implanted material [41]. Some research found that the High Molecular Weight Hyaluronic Acid (HMW-HA) inhibits cell adhesion and related to cell differentiation and anti-inflammatory effects [47], while Low Molecular Weight Hyaluronic Acid (LMW-HA) promotes cell adhesion [48,49]. And the regulator between the two weights is hyaluronidase (HAa) [50]. Using this characterize, the HA could regulate the cell adhesion [18]. Therefore, HA is a potential material to manufacture the structure on the surface.

Except the HA biomolecules, collagen is another possible material to format the structure on the surface. Collagen, accounting for 30% of the total protein mass of multicellular animals, is the most abundant fibrous protein in ECM. Collagen could provide tensile strength, regulates cell adhesion, and supports chemotaxis and migration, and direct tissue development [51,52]. There are 28 kinds of collagen have been identified [53], including that, collagen type I involves a number of enzymatic post- translational modifications, collagen types IV, VI, VIII, and X are involved in forming various kinds of networks [54]. According to the aim of the surface, different collagen could be chosen to fabricate nano structure.

"Micro" and "Nano" elements

Normal drug release system on the stent surface is focus on the drugs' properties. The release drugs could regulate the vessel cell's behavior by controlling the cell cycle. While in vivo, the blood stream is also an important element which could influence the cell adhesion and proliferation on the stent surface. Due to the blood flow around the implanted stent, coatings may delaminate under Flow Shear Stress (FSS) which would cause complications downstream. And the ECs monolayer under the FSS may change the morphology of ECs [55].

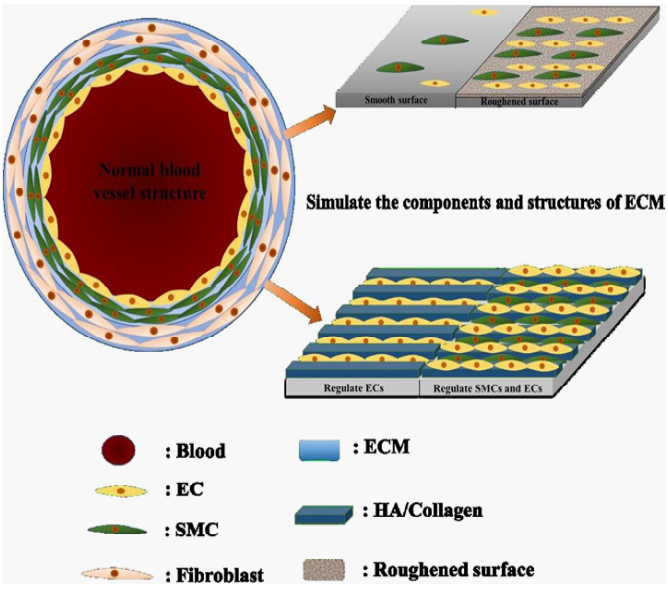

Figure 1: The micro-/nano-structure on the stent surface which simulate the normal blood vessel structure to regulate the cell orientation, adhesion and proliferation.

Considering this, some researches have altered the original surface of stents to create optimally interact with cells. Figure 1 demonstrates the normal vessel components and structure, and the how micro-/nano-surface on stent regulate the cell's behaviors by simulating the vessel structures. The Some initial researchers found that the metals with random nanostructured surface could increase the vascular cell responses, which was a promising strategy to improve stent efficacy [52]. Recent approaches have centered on modifying stent surface by unique nanometer topographies which mimic the natural vascular tissue, including nanostructure surface and nanoparticles coating [3,56,57]. Therefore, micro-cartography has been widely used to simulate the structure of natural ECM to regulate the cells behaviors.

"Micro" and "Nano" particles

The main strategy of "micro" and "nano" particles is encapsulating anti-restenosis medicine in nanocarriers (majorly of polymeric or nature MVs) and then coated the nanocarriers on stents. Cells can incorporate particles varying from 50 to 300 nm in diameter based upon a variety of different internalization pathways including non- specific and receptor-mediated endocytosis [58,59]. Nanoparticle (NP) -mediated Drug Delivery Systems (DDS) are a promising transform plat. The NP-eluting biomaterial stent provides an efficient transform plat than dip-coating stent, for its better and more prolonged delivery ability.

The nanocarriers applications on atherosclerotic plaques began in the research of nano-suspensions. While the nano-suspensions utilized as a clinically medicine which inject straight into veins may affect the body system, the targeted delivery by a stent is an efficient way to solve the problem [60]. Westedt et al. used the balloon catheter delivery systems to infusion of drug-loaded micro-/nano-carriers to increase a sustained drug release at the site of angioplasty [61]. Besides, immobilization the natural nanoparticle on the surface is an innovation strategy to increase the biocompatibility and regulate the cell interaction to the surface. Thus, facilitate suitable particles suspension and choose immobilization method are the main points in the nanocarriers applications on metallic material. Song et al. used an ex-vivo model utilizing dog carotid arteries to evaluated the uptake of polymeric Nanoparticles (NPs) with anti- restenosis drugs [62]. They found that the arterial uptake is a size dependent process, which means 100 nm NPs penetrating better than 266 nm NPs. Other researchers [63] found that the NPs was taken up rapidly by endothelial cells and was localized in the cytoplasm. Besides, an research depicted an effective uptake of PEO-PCL nanoparticles, which efficiently encapsulate both PTX and CER, by VSMCs with a significant anti- proliferative effect [64].

To promote the adhesion of structure on the surface, amine functionalization (- NH_2) or Layer-by-Layer assembly (LBL) are frequently-used methods. Liu et al. develop a time-ordered heparin/poly l-lysine nanoparticle (NP), and then deposit this NPs on a polydopamine-coated titanium surface [65,66]. This coating owns high anticoagulant activity and could selective inhibition of SMC and increase the EC proliferation. The feature of this coating is the drug release stages could be controlled to regulate the cells behavior [66]. Li et al. deposited a dopamine and hexamethylenediamine (PDA/HD) coating onto 316 L SS surface to adhesion HA with gradients of MW. The HA with high MW (1×105, and 5×105 Da) restrained the adhesion and proliferation of vascular SMCs (VSMCs) and macrophages(MA), and suppressed the platelet activation/aggregation and thrombosis

[67]. The in vivo results demonstrated that the surface with HA of 1×10^5 Da created a friendly microenvironment to induce the reendothelialization and stimulation reducing restenosis of cardiovascular biomaterials. Thus, the MW of the HA have different regulation effects on different cells.

"Micro" and "Nano" structures

Creating nanostructure on stent surfaces is another method to regulate the cell adhesion. Nanostructure always made of nano-topography (carved out of the stent material itself or provided by a coating of nanostructures), and may or may not be loaded with anti-restenosis drugs on the surface. Changing the interface roughness by pores, pits, grooves, pillars maybe affect the protein adsorption and cell adhesion on the implanted surface, and create a fast regeneration of the tissue by promoting adhesion and proliferation of cells by influencing the protein adhesion. The main parameters which reflect the roughness is the water contact angle, some research found that the nano-surface is hydrophilic, while micron/nano-surface is hydrophobic [68,69]. Several engineering techniques have been utilized to create a micro/nano-meter scale surface on implanted material. The techniques are devised into two forwards: Remove part of the surface, including anodization, chemical corrosion and laser treatment; add material on the surface, like biomolecule modification.

Removing part of the surface

Micron-scale and nanoscale surface features could change the surface roughness which directly associated with changing adhesion by special three-dimensional morphology. Many methods have been researched to change the micro/nanostructure of the surfaces, such as acid etching, sand blasting, anodic oxidation and laser texturing [70-72].

Changing roughness of the surface is an important method to regulate the cell's behavior. Increased surface roughness may promote ECs proliferation. The electron beam deposition was utilized to manufacture different scales surface on titanium stents and the nanometer and submicron features remained better endothelial layer intact under flow conditions [73]. Hydrothermal technique under alkaline conditions is a popular method to remove part on the surface and format uniform nanostructures (RMS 0.14-0.41 nm) on the surface of 316 L SS. The nanostructured surfaces exhibited normal clotting times, minimal platelet aggregation, and minimal hemolysis; however, no significant differences were observed between the nanostructured surfaces and the control material [74].

Laser treatment is a useful method to remove part of the surface. The micro/nano structure greatly promotes the cell adhesion and proliferation [69]. Different pattern could be controlled by adjusting the laser energy density (irradiation energy per unit area and scan patterns). Utilizing the femtosecond laser, a periodic nanostructures on the TiO_2 film surface were manufacture, the period and height of the structures were about 230 nm and 150 nm, which could increase the cell spreading [75]. Base on this result, the team further studied the applicability of hierarchical periodic micro/nano- structures on the surface modification of nitinol and found this pattern seem to regulate the ECs to spread along the nanometer scale, and the pinning effect from the periodic micro-structures shifted the water contact angles to more hydrophobic values, which decreased the platelet adhesion on the surface [70]. The different behavior of ECs and platelets maybe relate to the volume difference in the cells, which means the periodic micro-structure larger than of 2 μm can influence the results [70,75]. Except the normal groove structures, some bionic structure was developed to obtain special function. Micron-level grooves inspired by shark skin structure were obtained by laser treatment on Ti-6Al-4V [76]. Using "Layer-by-Layer" (LBL) methodology to manufacture an HA-Chitosan (CHI) coating on the grooves could increase the bio function [76].

Nanotubes can be utilized for vascular stent applications for increasing the motility of ECs. And the solution-based approach is suitable for the implanted devices with a complex shape (like cardiovascular stent). Moreover, the nanotubes (NTs) could delivery and release of various drugs to enhance the functions of cells [77-79]. Therefore, Nanotubes are a promising candidate to regulate the cell behaviors. The TiO_2 nanotube array is formed by anodic oxidation. The ECs on the nanotube matrix are elongated, which also effect of increased proliferation, migration speed and extracellular matrix production, while the VSCMs the nanotubes were decreased, and the α-SMA expression on the nanotube were increased, which reflected the VSCM tend to contractile phenotype [80]. Titanium dioxide nanotube arrays (TNTAs) with the diameter of 30~90 nm which could be regulated by anodic oxidation parameters. TNTA with smaller diameter own better blood and cell compatibility compared with that of larger sizes [81]. Heat treatment is an indispensable process after anodic oxidation to change the phase. The Titanium Dioxide Nanotube (TNT) coating annealed at 450^0C may obtain better platelet behavior for forming more anatase [82]. Therefore, the combination of crystalline phase and TNT's size controls the cell and blood behavior [82]. Besides, the chitosan-heparin nanoparticles could be loaded in TiO_2 nanotubes to regulate the cell-biomaterials interaction and blood compatibility [83]. TiO_2 nanotubes could restrict the size of SMC but not EC at a certain structure. The 5-layer polydopamine (PDA) were deposited on the interface of the TNT to functionalize the nanotube arrays which endowed high bioactivity of TNT [84], which could regulate the behavior of ECs and SMCs, and reduce the SMCs adhesion and proliferation on the surface of TNT [85]. Fabricating two-scale micro/nano structures on titanium surfaces regulate the adhesion proteins and microfilaments of SMCs [86].

Dry etching technique based on plasma is an innovation method to fabricate a surface consisting of periodic arrays grooves range from 750 nm to 100 μm, which inducing ECs arranged similar to the natural endothelium in vessels, In vitro rat aortic endothelial cell adhesion and growth tests demonstrated the endothelial cell coverage on nanometer-scale Ti patterns was increased compared with micrometer-scale Ti patterns [15].

Adding material on the surface

Adding material on the surface is another way to create nanostructure in the surface modification of cardiovascular biomaterials. Several kinds of biomolecule pattern have been manufactured, including groove stripes, round micro-domains, micro-networks and micro-tips [87-89]. The adding biomolecule and pattern are two basic elements in this section. As discussed before, HA is a suitable molecule for its biological function. Utilizing HA and dopamine (PDA) to prepare a multi-coating on 316 L SS, which gave the surface properties of increasing the ECs proliferation relied on the HA changed. And the 2.0 mg/mL HA enhance the ECs behavior obviously in vitro and this HA coating demonstrated excellent tissue compatibility [90].

The naturally formed titanium oxide film on titanium's surface is the source of its biocompatibility [91]. Developing the quality of natural titanium oxide films (about 10 nm) is a promising method to enhance its biocompatibility [92]. Based on these theories, Huang and his team [31,93] using Plasma Immersion Ion Implantation And Deposition (PIIID), and sputter deposition technology formatted crystalline titanium oxide films. The results showed that the lower interface energies and semiconducting nature of the titanium oxide films are the main reasons for better hemocompatibility. And this titanium oxide films have been apply to Helioos stent, which was one kind of heart stent made by Chinese technology. This stent uses the L605 alloy as the metal and titanium oxide films as coating, the sirolimus as the releasing drug. The Helioos stent have been used for almost decade in world wide.

The relationship between the ECs morphology and the cytokine secretion on parallel micro-stripes of High Molecular Weight Hyaluronic Acid (HMW-HA) coatings made on the TiOH surface [87]. The Nitric Oxide (NO), prostacyclin (PGI2), fibronectin (Fn) release and thrombomodulin (TM), Tissue Factor Pathway Inhibitor (TFPI), E- Selectin expression were increased with the L/B index enhanced of ECs on the surface [87]. Besides, the elongation of the ECs increased the anticoagulation property. From this research, the different sizes of micro-patterns of the coatings could regulate the ECs morphology-related function [87]. The HAa could change the HA from High Molecular Weight (HMW) to The Low Molecular Weight (LMW) [18]. Thus, Li et al. prepared a parallel micro-stripe with high molecular weight hyaluronic acid (HMW-HA) on NaOH-activated Ti surface. The stripes size was 25 μm wide ridges and 25 μm wide grooves [18]. The SMC were firstly cultured on the nanostructure surface made of HMW-HA, which can effectively adjust the shape and behavior of SMC. After cultured for a while, HMW-HA degraded to LMW-HA by HAa, and then cultured ECs on the regulated SMC, which could increase the adhesion ability and NO release of EC. This model is named as 'SMCs-HAa-ECs' system [18].

The subsequent work of parallel micro-stripes induce the proliferation of SMC and ECs further elucidated the proliferation of 'SMCs-ECs' collaboration system. The type IV collagen (ColIV) is the main component of the endothelial cell ECM thus, in their nest studied, an innovate co-culture model named "SMCs-ColIV-ECs" was developed and found that the HUVEC on the "SMCs-ColIV-ECs" model was large than that of on 'SMCs-HAa-ECs' system, and could release more PGI_2 and NO, for the fiber network structure of ColIV enhance the adhesion and diffusion of HUVEC on the surface [94]. Besides, the spread of HUASMCs were inhibited by HMW-HA and behavior were controlled by the stripes [94]. Besides, To further investigated the effect of cell number on the "SMCs-ColIV-ECs" model, Li et al. utilized 1×10^5 cells/ml EC and 2.5×10^4 cells/ml SMC to build a novel model on previous work to perfect the co-culture micro- environment [95]. The results showed that the HUVECs could covered the micro- patterned HUASMCs completely at this rate, and the anticoagulation function of the HUVECs was increased compared with in previous models. The series researches on nondegradable metal demonstrated that the HUASMC could increase the release of NO, TGF-β1 and other factors from EC, and these factors influence the phenotype and adhesion of SMC in reverse.

Compared with nondegradable metals, the degradation rate of biodegradable metals is a limitation on surface modification. Direct coating degradable material with biomolecules usually carries the risk of local defects, for helping in building electrochemical corrosion units and elevating corrosion rates [96]. In order to enhance the corrosion of biodegradable metals, different surface passivation approaches have been explored, which basic principle is to block the ionic pathway [97]. Using NaOH and HF are popular to format a passivation layer to increase the corrosion rate and create a suitable surface for further modification. Besides, the coating directly deposited on the metals is another choose. Chen et al. [96] using liquid phase deposition technology to deposit the TiO_2 coating on Mg with PDA film, and inhibit the corrosion rate of magnesium. Magnesium, iron and zinc and their alloys have been identified as potential candidates for biodegradable metal implants, and they are all essential elements for body and involved in many metabolic reactions [98-101]. Li et al. developed a series of PDA/HA coatings with range HA molecular weight (MW, 4×10^3, 1×10^5, 5×10^5 and 1×10^6 Da) onto the NaOH passivated Mg-Zn-Y-Nd alloy surface. The coatings with HA MW of 1×10^5 and 1×10^6 Da increased the corrosion resistance of Mg alloy, and the two kind of HA also enhance the hemocompatibility, pro-endothelialization, anti-hyperplasia and anti-inflammation functions compared with the alloy without the HA coating [35].

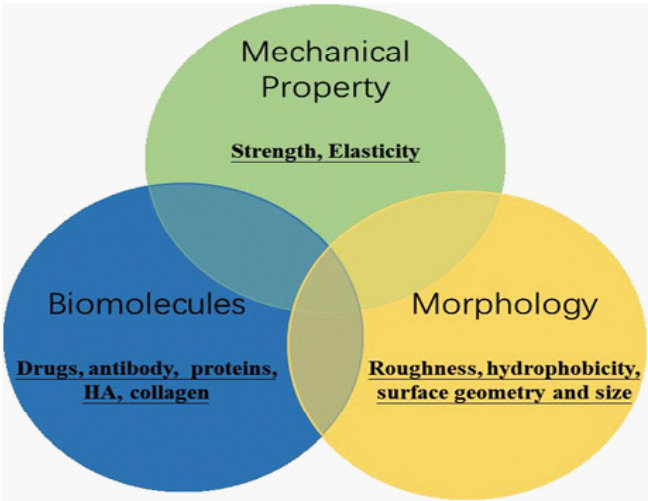

Figure 2: The micro-/nano-structure of stent surface inspired by ECM are make up by three factors: Mechanical properties, biomolecules and morphology.

Conclusion

Reendothelialization of implanted stent surface has been considered as a promising strategy to solve some clinical problems. To realize reendothelialization, directly reducing coagulation and thrombosis, repairing endothelium and inhibit the proliferation of SMCs by fixed drugs, proteins and antibody on the stent surface. While clinical application of cardiovascular stent may lead to thrombi, embolism, intimal hyperplasia, or late lumen loss. Although loaded drugs may confer immediate and significant therapeutic effects, cannot be guaranteed the long-term healing effects. The normal release surfaces are lack of a natural cardiovascular tissue, including morphology, structure and biological factors, more importantly, lacking ECM and SMC to immobilize EC. Therefore, providing a physiological microenvironment for reendothelialization can maintain the structural and functional stability of the endothelium. Based on this accept, manufacturing biomimetic matrix is an innovation strategy to create a stability of endothelial structure and function. Figure 2 showed that the micro-/nano-structure of stent sure inspired by ECM are make up by three factors: Mechanical

properties, biomolecules and morphogy. The Bio-mimetic surfaces on stent materials are a challenging direction to regulate the cell by a more bionic. Bring biomolecules from ECM on surface or remove some material from stent could create micro-/nano-structure to mimetic the natural structure of vessel. In this review, reasonably designed micro-/nano-structure that regulate the direction and adhesion of cells are summarized. Appropriate micro-/nano-size characteristics and biomolecules are the main factors to build the artificial bionics to construction of vascular endothelial matrix and further enhance the reendothelialization.

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