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Short Review

Application of Anti-Thrombotic Method Based on Thrombosis Mechanism in Cardiovascular Grafts

Hao Tian#, Ziwei Xi#, Junjie Chen and Wen Zeng*

Department of Anatomy, State Key Laboratory of Trauma, Burns, and Combined Injury, National and Regional Engineering Laboratory of Tissue Engineering, State and Local Joint Engineering Laboratory for Vascular Implants, Key Lab for Biomechanics and Tissue Engineering of Chongqing, Third Military Medical University, Chongqing 400038, China

 # Equal Contribution

Abstract

Cardiovascular grafts often cause serious complications and risks due to thrombosis. The immune rejection and inflammatory response induced by the implantation of cardiovascular grafts often lead to platelet adhesion, activation, aggregation and chemotaxis of inflammatory cells and further lead to thrombosis. Among them, bioprosthetic blood vessels are the development trend of small-caliber vascular grafts that can be used for coronary artery bypass grafting, and they are typical representatives of cardiovascular grafts. Thrombosis is one of the largest obstacles clinical application of small diameter engineering blood vessels (TEBVs). At present, a series of anti-thrombotic methods based on the mechanism of thrombosis are mainly adopted, including the promotion of endothelialization of engineering blood vessels, topological modification of blood vessel surfaces, nano-modification, gene reprogramming and immune regulation. Inhibition of thrombosis will promote tissue engineering and the treatment of cardiovascular disease. This article starts with the mechanism of thrombosis and multiple strategies for anti-thrombotic, and reviews the advances in the field.

Introduction

In recent years, cardiovascular disease has gradually become the biggest threat of human health. On the basis of the World Health Report, there are about 15 million people die of cardiovascular disease each year around the world, and this number is estimated to increase by 50% by 2020 [1]. Replacement therapy has become the main way of cardiovascular disease, including heart valves, vascular valves, vascular stents, artificial blood vessels and so on. Large-caliber replacement vessels are currently more mature, but there are still no products available for small-caliber vascular grafts that can be used for coronary artery bypass grafts, peripheral vascular replacement, hemodialysis fistulas, etc. Currently, small-diameter replacement blood vessels commonly used in clinic include autograft blood vessels and tissue engineering blood vessels, but autograft blood vessels are often limited due to limited number and trauma to the body. Therefore, the importance of small diameter tissue engineering vessels in vascular replacement therapy is increasing, but there are still many problems in the research of small diameter tissue engineering vessels (< 6mm). As foreign bodies, TEBVs often have a high incidence of thrombosis due to chronic rejection of the graft due to innate immune response and chronic inflammation. Vascular transplantation treatment often fails due to early thrombosis. At present, there is no systematic review of the mechanism of thrombosis in cardiovascular grafts. How to prevent thrombosis in transplanted blood vessels is still being explored. In this article, the application of thrombus formation mechanisms and anti-thrombotic methods based on thrombosis mechanisms in cardiovascular grafts will be reviewed. It has certain reference significance for the development of tissue engineering.

***Corresponding author:** Wen Zeng, Department of Anatomy, Army Medical University, Gao Tan Yan Street, Shaping Ba District, Chongqing 400038, China Tel: +86 13647638478; E-mail: zengw0105@163.com

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Thrombosis Mechanism of Cardiovascular Grafts

The type of thrombosis caused by cardiovascular grafts

A thrombus is a solid mass formed in the heart and blood vessels of a living body, or in some parts of the blood, where solidification is formed. According to the pathological classification, it is divided into four types: white thrombus, mixed thrombus, red thrombus and transparent thrombus. Among them, transparent thrombus occurs in capillaries, and it is less involved in patients with cardiovascular grafts. It was found to occur in a Human Vascularized Composite Tissue Allografts (VCA) patient with acute rejection in a skin pathological biopsy [2]. According to the site of occurrence, it can be divided into arterial thrombosis and venous thrombosis. Classical venous thrombosis is caused by the coagulation cascade and meets virchow triad (endothelial injury, slowed blood flow, hypercoagulable state), while arterial thrombosis is relatively white due to a relative lack of red blood cells and more platelets, which meets other conditions (vWF Fixation, high shear force, sufficient platelets and vWF) [3]. The graft thrombus also forms a foreign body thrombus due to the foreign body reaction to form a temporary matrix [4].

The mechanism of thrombosis triggered by cardiovascular grafts

Platelet adhesion-activation-aggregation

Under normal circumstances, intact endothelial cells and their surface protective agents keep circulating platelets at rest. However,

when endothelial damage occurs, subendothelial collagen is exposed and vWF stored in the endothelium is released. Collagen binds to platelet GPVI and integrin α2β1, and vwf binds to GPIb-IX-V. In this process, vwf first binds to GPIb-IX-V, which slows down platelet movement and facilitates subsequent reactions with receptors with low binding kinetics. Vwf is also divided into different types. When they are fixed on the damaged endothelium or on the surface of the graft, they will allosteric and undergo binding with platelets. Among them, the large vwf multimer can enhance the potential of thrombosis. It is related to the promotion of thrombosis under arterial hemodynamic conditions. Collagen binds to GPVI and integrin α2β1 to mediate platelet activation. Platelet integrin changes from a low-affinity state to a high-affinity state from the inside-out or the outside-in signaling. Plasma fibrin and vwf bind to integrin αIIbβ in a high-affinity state and form a bridge between integrin αII2bβ3 heterodimers on adjacent platelets, resulting in platelet aggregation [5]. The activated platelets activate and release thromboxane A2, ADP, and other agonists to further amplify platelet adhesion, activation, and aggregation [6]. Under arterial hemodynamic conditions, sCD40L binds to platelets and stabilizes arterial thrombus by αII2β3 mediated mechanism [6].

After implantation, endothelial cells were damaged, the stent was re-endothelialized incompletely, endothelial dysfunction, and the local environment of the blood vessel was under hypoxic stress. In drug-eluting scaffold DES, the expression level of NO synthase in endothelial cells was significantly decreased, and ROS production was also significantly increased [7]. Cardiovascular grafts also alter local hemodynamics, and both insufficiency and dislocation of the stent will produce regions of high shear rate and promote thrombosis. Under high shear rate, the spherical vWF is stretched into a linear shape to shorten the platelet activation time [3].

The involvement and role of immune cells

Immune cells also play a role in graft thrombosis. Platelet-dependent neutrophil-mediated thrombosis may have three mechanisms: first, neutrophils can transfer the tissue factor TF to platelets; second, neutrophils can generate NETs, which are directly related to thrombosis; and In particular, neutrophils play a procoagulant role by inactivating key anticoagulant systems and inhibiting ADAMTS13-mediated vWF inactivation [8,9].

In patients undergoing angioplasty and stenting, Monocyte-Platelet Aggregates (MPA) is formed [10]. Increased circulating MPA in high-risk patients is associated with atherosclerotic thrombosis [11]. The combination of platelet-neutrophil complex and platelet-monocyte complex with activated endothelial cells and platelets further exacerbates the self-reinforcing thrombotic inflammatory cycle [12]. M1 macrophages have high antigen-presenting ability and can promote Th1 differentiation of lymphocytes. These cells produce toxic reactive oxygen intermediates and exacerbate pro-inflammatory reactions to damage neighboring cells in the microenvironment, leading to severe FBR, granulomatosis and Fibrous cysts [13].

In addition to classic inflammatory reactions, allergic reactions are also involved in thrombosis [14]. Eosinophils can directly stimulate the coagulation pathway and promote platelet activation. Eosinophil chemokines may regulate macrophage function and participate in the activation and recruitment of mast cells [15]. Macrophages can produce Matrix Metalloproteinases (MMPs) and induce atheroma to rupture and form thrombus [16]. Eosinophil cationic protein ECP can up-regulate adhesion factor-1 to allow monocytes to adhere to the surface of endothelial cells, and monocytes release TF to promote thrombosis [15]. Mast cells release mediators such as specific protein chymase and tryptase cause matrix degradation, apoptosis, and increased recruitment of inflammatory cells and induce leakage and bleeding of fragile neovascularization, leading to intra-plaque hemorrhage and plaque rupture and thrombosis [17].

Grafts also produce Damage-Associated Molecular Patterns (DAMP) and Extracellular Vesicles (EV). DAMP and EV can stimulate multiple innate immune signaling pathways and coagulation cascades, and even cause systemic inflammation and thrombotic complications [18].

Effect on cell reconstruction in cardiovascular grafts

The best way to combat cardiovascular grafts is to reconstruct the structure and function. Natural blood vessels consist of thin layers of healthy endothelial cells, connective tissue, SMC and elastin. Synthetic polymer scaffolds are usually hydrophobic and may induce non-natural conformation of proteins to inhibit endothelial progenitor cell attachment and viability. Grafts also damage endothelial cells resulting in tight junction opening and promote migration of inflammatory cells [7]. In addition, stent-induced "new atherosclerosis" promotes the continued activation of regenerating endothelial cells towards proinflammatory manifestations [19]. SMC is vital in maintaining vascular homeostasis, especially in terms of vascular reactivity, and DES can also inhibit smooth muscle cell migration.

Grafts trigger thrombus inflammation after formation of thrombus, which is characterized by leukocyte recruitment, activation of Vascular Smooth Muscle Cells (VSMC), and formation of cytokines, reactive oxygen species and growth factors in the vessel wall. Subsequent vascular remodeling involves the deposition of matrix proteins and EC, VSMC return to rest [20]. The normal inflammatory response is conducive to the regeneration and repair of blood vessels. For example, myofibroblasts can not only migrate to promote the formation of new intima during vein bypass surgery, but also cause negative (internal) remodeling of the blood vessel wall.

However, in persistent chronic inflammation, synthetic VSMCs can lead to neointimal hyperplasia NIH, myofibroblasts can cause organ fibrosis, and PMN can weaken the elasticity of blood vessel walls [20,21]. High plasma inflammation markers and acidosis have also been associated with failed revascularization [22,23].

Proper inflammatory regulation is conducive to vascular reconstruction. M2 macrophages release anti-inflammatory cytokines, such as IL-10, and show high levels of iron output to help tissue remodeling and promote vascularization [13].

The balance between M1 and M2 plays a key role in the elimination of apoptotic cells and the healing and remodeling of damaged tissues [24], and according to its division between subgroups, it can allow the use of regeneration functions to control inflammation of myeloid cells function to promote tissue repair [25].

Anti-Thrombotic Strategies in Cardiovascular Grafts

Surface compound modification

The ideal cardiovascular graft should have a bionic structure, and can regulate cell behavior to achieve the aim of anti thrombosis and

promote vascular endothelialization, ensuring long-term patency and stable function in vivo [26,27]. Surface complex modification can maintain the stable structure of tissue engineered blood vessels by changing the surface structure and properties of blood vessels, and can promote the adhesion and differentiation of endothelial progenitor cells. Physical immobilization, surface adsorption [28], chemical immobilization [29,30] and other methods can be used to achieve it.

Layer-by-layer self-assembly (LBL)

LBL is a efficacious method that can separate the substrates, can solve the problem of sustained release of factors, and it is an effective method for the surface modification of cardiovascular grafts [31]. The main advantage of LBL technology is the ability to create well-structured, tunable and stable deposited films at different levels [32]. It has been reported that assembled multilayer components are stable for at least one week or even several weeks under physiological conditions [33,34]. The segments of the polyelectrolyte layer adsorbed first will permeate from the outermost surface [35], and the extensive interpenetration between layers effectively promotes the synergy between different functional molecules [36-38], and functional components. There will not be negative interference between each other. The combination of assembly components can be controlled by changing the assembly conditions. By cross-linking anticoagulant substances such as heparin, they can play different functions [36], such as promoting endothelialization, promoting nerve reconstruction, and anti-thrombotic.

Gelatin-polylysine complex

Negatively charged gelatin (Gel) is a highly bioactive polymer composed of peptides, which can promote endothelial progenitor cell attachment, migration and proliferation [37-39]. Positively-charged Polylysine (PLL) has good biocompatibility and can promote cell adhesion. Based on the interaction between positive and negative charges, the gelatin-polylysine complex can be carried on the surface of the blood vessel by layer-by-layer self-assembly, at the same time, heparin can be cross linked and slow-released, and the surface roughness and hydrophobic properties can be modified to reduce platelets adhesion, and can simultaneously achieve the purpose of anti-coagulation and promote endothelialization.

Au-LBL / CD-L / chitosan complex

Positively charged chitosan has good biocompatibility and antibacterial properties. Sodium 4-vinylbenzenesulfonate (SS) and "1-adamantane-1-ylmethyl methacrylate monomer" P (SS-co-Ada) constitutes a negatively charged copolymer with surface heparin-like activity and effective anti-coagulation. B-cyclodextrin derivative with lysine ligand (CD-L) can be dissolved and grafted New blood clots on the surface of materials. Studies show that using LbL technology to build modified Au-LBL / CD-L / chitosan blood vessels has versatility, it can effectively dissolve new blood clots and prevent internal enlargement, can promote the endothelialization progression of the blood vessels to prevent the occurrence of the infection after vascular transplantation [40].

Surface patterned topology

After tissue engineered blood vessel implantation, homing of endothelial progenitor cells and platelet adhesion are two major factors affecting thrombosis. The adhesion and growth of cells and proteins can be affected by Changes in surface patterning topology directly and selectively [41]. Due to its excellent stress distribution function, the surface patterned topological structure can achieve mechanical stability of complex shapes. Meanwhile, cell migration can be guided by the linear pattern of biological activity, which is beneficial to the homing and distribution of endothelial progenitor cells and prepare for rapid endothelialization [42-45]. Experiments have shown that cell-imprinted polyacrylamide hydrogels can be manufactured without photolithography or other techniques, and do not require biopolymer affinity reagents. Cell imprinting can be used to program cell patterns on hydrogel surfaces and obtain better endothelialization indicators [41]. In addition, experiments have shown that Hydroxyapatite (HA) has high biological activity, which can quickly endothelize by making cell adhesion proteins adsorb on the surface [43-49]. A linear HA pattern was made on a silicon wafer, and then the It was transferred to a Polylactic Acid (PLLA) membrane as an engineered blood vessel. The results showed that the experimental group with HA pattern showed faster endothelialization and anti-platelet adhesion, and also showed better blood compatibility [50].

Plasma immersion implantation technology

Stromal Cell-Derived Factor 1α (SDF-1α) recruits endothelial progenitor cells and promotes endothelialization of engineered blood vessels [51,52]. The transmembrane protein CD47 can reduce intimal hyperplasia and promote inflammation subsidence after vascular implantation [53,54]. Plasma Immersion Implantation (PIII) is a simple and effective technique that can change the chemical and morphological characteristics of vascular surface materials. By promoting the formation of free radicals, the vascular wall and biomolecules are covalently bonded without a joint [55,56]. Covalently bound heparin, SDF-1α, and CD47 to the surface of engineered blood vessels after PIII treatment, it was found to have anti-thrombotic, EPC recruitment, rapid endothelialization, and anti-inflammatory effects [57].

Controlled release of drugs at different stages of platelets

Nanoparticle-embedded drugs act on different stages of platelet adhesion, activation, and aggregation, respectively, and block or activate corresponding pathways by binding to specific proteins on platelets, thereby achieving the goal of controlling thrombosis.

Inhibiting platelet adhesion

The exposure of collagen fibers stimulates GP IIb / IIa, making platelets easy to adhere. For collagen fibers, drugs such as abciximab and etipeptide can spatially block the binding of blocking ligands to GP IIb / IIa and inhibit platelet adhesion and activation [58]. However, due to strong side effects, it is currently less used. Tirofiban can also inhibit platelet adhesion by interfering with the binding of GPIIb / IIa complex to fibrinogen [58].

Inhibition of platelet activation

Drugs such as aspirin and sulfopyridine can inhibit cyclooxygenase competition, block TXA2 synthesis, reduce intracellular calcium content, and inhibit platelet activation. At the same time, research shows that Ginkgolide B and EGb761 extracted from Ginkgo biloba can inhibit cyclooxygenase-1 activity, block TXA2 synthesis, reduce platelet activation, and inhibit thrombosis to varying degrees [59-61]. In addition, platelet activating factors (PAF) produced by mast cells, monocytes, macrophages, platelets, eosinophils, endothelial cells and

neutrophils promote the aggregation and activation of platelets [62]. PAF structural analogs CV3988, CV6209, synthetic compounds MK-287, TCV309, etc. can be used as PAF antagonists, which block platelet activation pathways and inhibiting thrombosis [63].

Inhibition of platelet aggregation

Platelets contain three ADP receptors, P2Y1, P2Y12, and P2X1. Cangrelor and ticagrelor can block platelet aggregation by inhibiting ADP receptors. Among them, P2Y1 has two different molecular action points, and drugs can exert their effects through different molecular action points [64].

Genetic modification and reprogramming inhibit thrombosis

The expression of genes involved in platelets, endothelial progenitor cells, fibroblasts, and various inflammatory cells after tissue engineered blood vessel implantation has an significant effect on thrombosis. Gene transfer technology can be used to enhance the expression of certain gene products (such as thrombin, vascular endothelial growth factor, zinc finger transcription factor, etc.) to inhibit platelet adhesion, activation, and aggregation processes, while promoting endothelialization, such as lipoplex, viral vectors, plasmid et al. [65]. At the same time, gene reprogramming technology can be used to introduce or up-regulate gene expression of factors that have significant effects on cell phenotype and function. A typical cell reprogramming first transforms cells into an induced Pluripotent Stem Cell (iPSC) state and then differentiates into the desired cell phenotype [66]. In addition, the CRISPR / Cas9 and dCas9 systems can specifically silence or up-regulate the expression of certain key endogenous genes [67,68]. At the same time, using drugs to target the cellular immune response [69], triggering the cascade response to remodel epigenetics can also directly change the epigenetic environment [70,71], thereby inhibiting thrombosis.

Regulating immune response and inhibiting thrombosis

Promoting inflammation regression and inhibiting thrombosis

Netrin-1 plays an anti-inflammatory role and maintains the small diameter TEBVs unobstructed. The neural protective orientation factor 1 (Netrin-1) in ECls was found to have anti-inflammatory effect. Li et al., Showed that Netrin-1 could recombine MΦ to CD163, a scavenger receptor involved in endocytosis of hemoglobin/haptoglobin through A2b receptor, making it express an anti-inflammatory phenotype. With the passage of time, it can promote the infiltration and outflow of MΦ from the inflamed site, and improve the local microenvironment and function of early homing EPCs [72]. Changing the balance of M1 / m2 phenotype of macrophages may dissolve thrombus. The phenotype of macrophages is usually determined by expression of specific surface markers and gene expression. M1-like expresses the proinflammatory mediators (interleukin [IL] - 1B, IL-6, IL-12). M2-like expresses anti-inflammatory mediators (IL-10, Arginase 1 [Arg-1], CD206). Katherine A et al. suggested that changing the balance of macrophages might accelerate thrombolysis [73].

Regulating thrombosis through acting on MKs

Under normal conditions, the cytoplasm of bone marrow megakaryocytes (MKs) in the blood protrudes, forming pre-platelets, and shedding to form platelets. Satoshi Nishimura et al., found another way to produce platelets, which is MK rupture. MK rupture causes the cytoplasm to disintegrate rapidly, and a large number of platelets are released into the blood vessels. After platelet loss or inflammatory stimulation, the level of serum IL-1α increases sharply. IL-1α can rapidly induce MK rupture-dependent platelet formation and increase platelet counts [74]. In addition, TNF-α plays a decisive role in aging individuals' thrombosis. Functional platelet studies of elderly and aging mice have shown that their platelets are overreacting and are prone to form large blood clots. Pavel et al. found that tumor necrosis factor α (TNF-α) is the main aging-related pro-inflammatory cytokine that causes platelet hyper responsiveness. They demonstrated that TNF-α severely regulates hyper responsiveness of MKs living in the bone marrow niche and aging-related platelets. Consequently TNF-α plays a decisive role in aging individuals' thrombosis [75]. Clinically, making several methods to inhibit TNF-α function may play an anti-thrombotic effect.

Promoting endothelialization of cardiovascular grafts to overcome thrombosis

Small diameter TEBVs grafts may cause thrombosis and restenosis due to the lack of a complete endothelial layer [76]. ECs play a central role in TEBVs and are involved in the regulation of coagulation mechanisms, the occurrence of inflammation, immune responses, secretion of multiple hormones and regulation of vascular wall growth. In addition, ECs are also a barrier between blood and smooth muscle of the blood vessel wall, which inhibits intimal hyperplasia. Therefore, the acquisition of ECs is a prerequisite for the construction of TEBVs. SMCs and ECs can be attached to engineering scaffolds to design grafts. Methods to enhance endothelialization are discussed below.

In vitro endothelialization

The method of surface coating is often used in vitro endothelialization. The rate of endothelialization depends to a large extent on the interaction of ECs with Extracellular Matrix (ECM) molecules such as Fibronectin (FN) and Laminin (Ln). Some of these molecules have been studied and applied to surface endothelial modification. Therefore, coating with adhesion proteins on the surface of biomaterials can promote the adhesion, migration and proliferation of ECs in vitro, thereby shortening the culture period. One of the most popular methods is to fix the optimal FN-derived peptide sequence RGD (Arg-Gly-Asp). Numerous studies have shown that RGD peptides can enhance ECs adhesion, growth and proliferation. Another method is to use Arg-Glu-Asp-Val (REDV). REDV is a fibronectin-derived peptide that has high activity on ECs and low activity on SMCs. Wei et al. immobilized the REDV peptide on the surface, and the surface coating had good blood compatibility, and could promote the adhesion, proliferation, and growth of ECs. Coating with YIGSR is also a common method [77].

In vivo endothelialization

The key to endothelialization in vivo is Endothelial Progenitor Cells (EPCS). EPCs can secrete cytokines to support other EPCs and ECs. Among these cytokines, VEGF is the most widely used in microenvironment engineering. VEGF can promote cell proliferation, migration, and endothelial capillary formation. The most widely studied genetic modifier in gene therapy in the past few years is the VEGF gene [77]. EPCs can be obtained from bone marrow, peripheral blood, and umbilical cord blood; however these populations are not exactly

the same. EPCs obtained from umbilical Cord Blood-Endothelial Progenitor Cells (CB-EPCs) shows high proliferation potential and adhesion to Peripheral Blood (PB-EPCs) or aortic endothelial cells [78]. During angiogenesis, CB-EPCs can form a stable vascular network, while BM-EPC cannot. CB-EPCs are 7 times more than PB-EPCs; however PB-EPCs can use various growth factors, cytokines, drugs and hormones to mobilize into the circulation from the bone marrow. A report showed that seeding EPCs on the surface of biological materials can prevent thrombosis and accelerate endothelialization of blood vessels [79].

Inducting neuroimmunity homeostasis and inhibiting thrombosis

Current researches of organ transplantation mainly focus on drug suppression of immune rejection, but little attention has been paid to neural network reconstruction. Nerves, especially sympathetic nerves, play a vital effect in the maintenance of immune homeostasis. Based on the vascular-nerve companionship, the growth of blood vessels is always accompanied by the distrihoweverion of the sympathetic postganglionic fiber network, and nerves are significant related factors of the microenvironment after vascular implantation. The activation of the Sympathetic Nervous System (SNS) and the release of catecholamine, neuropeptide Y and endogenous opioids as well as ATP affect immune cells [80,81]. However, nerve regeneration is difficult and it is difficult to grow into TEBVs. TET (ten-eleven translocation) protein is an α-Ketoglutarate (α-KG) and Fe-dependent dioxygenase, which can catalyze the conversion of 5-methylcytosine (5-mC) to 5-hydroxymethyl Cytosine (5-hmC), demethylating DNA [82,83]. Among them, TET2 can significantly promote T-reg cells to secrete cytokines and increase the secretion of IL-6 [82,84]. With the new nanomaterial Entranster TM transfection reagent [85] containing the crisper / cas9 system [86] and the TET2 overexpression promoter vector, the TET2 overexpression promoter can be transfected into T-reg cells to activate them and release more cytokines, thus preventing thrombosis.

Conclusion

In this review, we have summarized the types and mechanisms of thrombosis induced by cardiovascular grafts, and also summarized the anti-thrombotic methods based on the mechanism of thrombosis, which provide references for long-term maintenance of the function after cardiovascular implantation, and Laying the foundation for future research in tissue engineering.

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References

1. Huo D, Liu G, Li Y, Wang Y, Guan G, et al. (2017) Construction of Anti-thrombotic Tissue-Engineered Blood Vessel via Reduced Graphene Oxide Based Dual-Enzyme Biomimetic Cascade. ACS Nano 11: 10964-10973.

2. Kanitakis J, Petruzzo P, Gazarian A, Karayannopoulou G, Buron F, et al. (2016) Capillary Thrombosis in the Skin: A Pathologic Hallmark of Severe/Chronic Rejection of Human Vascularized Composite Tissue Allografts? Transplantation 100: 954-957.

3. Casa LD, Deaton DH, Ku DN (2015) Role of high shear rate in thrombosis. J Vasc Surg 61: 1068-1080.

4. Geelhoed WJ, Moroni L, Rotmans JI (2017) Utilizing the Foreign Body Response to Grow Tissue Engineered Blood Vessels in Vivo. J Cardiovasc Transl Res 10: 167-179.

5. Scharf RE (2018) Platelet Signaling in Primary Haemostasis and Arterial Thrombus Formation: Part 1. Hamostaseologie 38: 203-210.

6. Tesfamariam B (2008) Platelet function in intravascular device implant-induced intimal injury. Cardiovasc Revasc Med 9: 78-87.

7. Cui Y, Liu Y, Zhao F, Shi D, Chen K (2016) Neoatherosclerosis after Drug-Eluting Stent implantation: Roles and Mechanisms. Oxid Med Cell Longev 2016: 5924234.

8. Lisman T (2018) Platelet-neutrophil interactions as drivers of inflammatory and thrombotic disease. Cell Tissue Res 371: 567-576.

9. Jaffer IH, Fredenburgh JC, Hirsh J, Weitz JI (2015) Medical device-induced thrombosis: what causes it and how can we prevent it? J Thromb Haemost 1: 72-81.

10. Gremmel T, Ay C, Riedl J, Kopp CW, Eichelberger B, et al. (2016) Platelet-specific markers are associated with monocyte-platelet aggregate formation and thrombin generation potential in advanced atherosclerosis. Thromb Haemost 115: 615-621.

11. Hui H, Fuller K, Erber WN, Linden MD (2015) Measurement of monocyte-platelet aggregates by imaging flow cytometry. Cytometry A 87: 273-278.

12. Marin Oyarzún CP, Heller PG (2019) Platelets as Mediators of Thromboinflammation in Chronic Myeloproliferative Neoplasms. Front Immunol 10: 1373.

13. Sridharan R, Cameron AR, Kelly DJ, Kearney CJ, O'Brien FJ (2015) Biomaterial based modulation of macrophage polarization: a review and suggested design principles. Materials Today 18: 313-325.

14. Kounis NG, Koniari I, Roumeliotis A, Tsigkas G, Soufras G, et al. (2017) Thrombotic responses to coronary stents, bioresorbable scaffolds and the Kounis hypersensitivity-associated acute thrombotic syndrome. J Thorac Dis 9: 1155-1164.

15. Niccoli G, Montone RA, Sabato V, Crea F (2018) Role of Allergic Inflammatory Cells in Coronary Artery Disease. Circulation 138: 1736-1748.

16. Yahagi K, Kolodgie FD, Otsuka F, Finn AV, Davis HR, et al. (2016) Pathophysiology of native coronary, vein graft, and in-stent atherosclerosis. Nat Rev Cardiol 13: 79-98.

17. Bot I, Shi GP, Kovanen PT (2015) Mast cells as effectors in atherosclerosis. Arterioscler Thromb Vasc Biol 35: 265-271.

18. Eppensteiner J, Davis RP, Barbas AS, Kwun J, Lee J (2018) Immunothrombotic Activity of Damage-Associated Molecular Patterns and Extracellular Vesicles in Secondary Organ Failure Induced by Trauma and Sterile Insults. Front Immunol 9: 190.

19. Andreou I, Stone PH (2016) In-Stent Atherosclerosis at a Crossroads: Neoatherosclerosis … or Paleoatherosclerosis? Circulation 134: 1413-1415.

20. Wu B, Mottola G, Schaller M, Upchurch GR Jr, Conte MS (2017) Resolution of vascular injury: Specialized lipid mediators and their evolving therapeutic implications. Mol Aspects Med 58: 72-82.

21. Hibino N, Villalona G, Pietris N, Duncan DR, Schoffner A, et al. (2011) Tissue-engineered vascular grafts form neovessels that arise from regeneration of the adjacent blood vessel. FASEB J 25: 2731-2739.

22. Sapienza P, Mingoli A, Borrelli V, Grande R, Sterpetti AV, et al. (2019) Different inflammatory cytokines release after open and endovascular reconstructions influences wound healing. Int Wound J 16: 1034-1044.

23. Ma J, Zhao N, Betts L, Zhu D (2016) Bio-Adaption between Magnesium Alloy Stent and the Blood Vessel: A Review. J Mater Sci Technol 32: 815-826.

24. Boersema GS, Grotenhuis N, Bayon Y, Lange JF, Bastiaansen-Jenniskens YM (2016) The Effect of Biomaterials Used for Tissue Regeneration Purposes on Polarization of Macrophages. Biores Open Access 5: 6-14.

25. Ogle ME, Segar CE, Sridhar S, Botchwey EA (2016) Monocytes and macrophages in tissue repair: Implications for immunoregenerative biomaterial design. Exp Biol Med (Maywood) 241: 1084-1097.

26. Theocharis AD, Skandalis SS, Gialeli C, Karamanos NK (2016) Extracellular matrix structure. Adv Drug Deliv Rev 97: 4-27.

27. Rosales AM, Anseth KS (2016) The design of reversible hydrogels to capture extracellular matrix dynamics. Nat Rev Mater 1: 1-15.

28. Guo X, Liu Y, Bai J, Yu B, Xu M, et al. (2019) Efficient Inhibition of Wear-Debris-Induced Osteolysis by Surface Biomimetic Engineering of Titanium Implant with a Mussel-Derived Integrin-Targeting Peptide. Adv Biosyst 3: 1800253.

29. Li Y, An Q, Hu Y, Luan X, Zhang Q, et al. (2015) A facile method for the construction of covalently cross-linked layered double hydroxides layer-by-layer films: enhanced stability and delayed release of guests. Chem Phys Lett 632: 118-123.

30. Jin S, Gu H, Chen X, Liu X, Zhan W, et al. (2018) A facile method to prepare a versatile surface coating with fibrinolytic activity, vascular cell selectivity and antibacterial properties. Colloids Surf B Biointerfaces 167: 28-35.

31. Richardson JJ, Bjornmalm M, Caruso F (2015) Technology-driven layer-by-layer assembly of nanofilms. Science 348: 2491.

32. Raoufi N, Surre F, Rajarajan M, Sun T, Grattan KTV (2014) Optical sensor for pH monitoring using a layer-by-layer deposition technique emphasizing enhanced stability and re-usability. Sens Actuators B 195: 692-701.

33. He W, Bellamkonda RV (2005) Nanoscale neuro-integrative coatings for neural implants. Biomaterials 26: 2983-2990.

34. Gattás-Asfura K, Valdes M, Celik E, Stabler C (2014) Covalent layer-by-layer assembly of hyperbranched polymers on alginate microcapsulesto impart stability and permselectivity. J Mater Chem B 2: 8208-8219.

35. Shiratori S, Rubner MF (2000) pH-Dependent thickness behavior of sequentially adsorbed layers of weak polyelectrolytes, Macromolecules 33: 4213-4219.

36. Fu J, Ji J, Yuan W, Shen J (2005) Construction of anti-adhesive and antibacterial multilayer films via layer-by-layer assembly of heparin and chitosan. Biomaterials 26: 6684-6692.

37. Lin Q, Yan J, Qiu F, Song X, Fu G, et al. (2011) Heparin/collagen multilayer as a thromboresistant and endothelial favorable coating for intravascular stent. J Biomed Mater Res A 96: 132-141.

38. Deng J, Liu X, Ma L, Cheng C, Shi W, et al. (2014) Heparin-mimicking multilayer coating on polymeric membrane via LbL assembly of cyclodextrin-based supramolecules, ACS Appl Mater Interfaces 6: 21603-21614.

39. Cao L, Qu Y, Hu C, Wei T, Zhan W, et al. (2016) A Universal and Versatile Approach for Surface Biofunctionalization: Layer-by-Layer Assembly Meets Host–Guest Chemistry. Adv Mater Interfaces 3: 16-18.

40. Jin S, Gu H, Chen X, Liu X, Zhan W, et al. (2018) A facile method to prepare a versatile surface coating with fibrinolytic activity, vascular cell selectivity and antibacterial properties. Colloids Surf B Biointerfaces167: 28-35.

41. DePorter SM, Lui I, McNaughton BR (2012) Programmed cell adhesion and growth on cell-imprinted polyacrylamide hydrogels. Soft Matter 8: 10403-10408.

42. Lee JH, Lee KY, Gupta MK, Kim TY, Lee DY, et al. (2013) Highly stretchable piezoelectric-pyroelectric hybrid nanogenerator. Adv Mater 26: 765-769.

43. Tu Q, Zhao Y, Xue X, Wang J, Huang N (2010) Improved endothelialization of titanium vascular grafts by extracellular matrix secreted from endothelial cells. Tissue Eng A 16: 3635-3645.

44. Liu K, Wang N, Wang W, Shi L, Li H, et al. (2017) A bio-inspired high strength three-layer nanofiber vascular graft with structure guided cell growth. J Mater Chem B 5: 3758-3764.

45. Tan Z, Gao X, Liu T, Yang Y, Zhong J, et al. (2017) Electrospun vein grafts with high cell infiltration for vascular tissue engineering. Mater Sci Eng C Mater Biol Appl 81: 407-415.

46. Furuzono T, Masuda M, Okada M, Yasuda S, Kadono H, et al. (2006) Increase in cell adhesiveness on a poly(ethylene terephthalate) fabric by sintered hydroxyapatite nanocrystal coating in the development of an artificial blood vessel. ASAIO J 52: 315-320.

47. Korematsu A, Furuzono T, Yasuda S, Tanaka J, Kishida A (2005) Nano-scaled hydroxyapatite/polymer composite III. Coating of sintered hydroxyapatite particles on poly(4-methacryloyloxyethyl trimellitate anhydride)-grafted silk fibroin fibers. J Mater Sci Mater Med 16: 67-71.

48. Wang K, Wang M, Wang Q, Lu X, Zhang X (2017) Computer simulation of proteins adsorption on hydroxyapatite surfaces with calcium phosphate ions. J Eur Ceram Soc 37: 2509-2520.

49. Iijima K, Iizuka A, Suzuki R, Ueno-Yokohata H, Kiyokawa N, et al. (2017) Effect of protein adsorption layers and solution treatments on hydroxyapatite deposition on polystyrene plate surfaces in simulated body fluids. J Mater Sci: Mater Med 28: 193.

50. Kang I-G, Park C-I, Seong Y-J, Lee H, Kima H-E, et al. (2020) Bioactive and mechanically stable hydroxyapatite patterning for rapid endothelialization of artificial vascular graft. Materials Science & Engineering C 106: 110287.

51. Stellos K, Gawaz M (2007) Platelets and stromal cell-derived factor-1 in progenitor cell recruitment. Semin Thromb Hemost 33: 159-164.

52. Ceradini DJ, Kulkarni AR, Callaghan MJ, Tepper OM, Bastidas N, et al. (2004) Progenitor cell trafficking is regulated by hypoxic gradients through HIF-1 induction of SDF-1. Nat Med 10: 858-864.

53. Kim YK, Chen EY, Liu WF (2016) Biomolecular strategies to modulate themacrophage response to grafted materials. J Mater Chem B 4: 1600-1609.

54. Inoue T, Croce K, Morooka T, Sakuma M, Node K, et al. (2011) Vascular inflammation and repair: implications for re-endothelialization, restenosis, and stent thrombosis. JACC Cardiovasc Interv 4: 1057-1066.

55. Wang H, Kwok DT, Xu M, Shi H, Wu Z, et al. (2012) Tailoring of mesenchymal stem cells behavior on plasma-modified polytetrafluoroethylene, Adv Mater 24: 3315-3324.

56. Wang H, Kwok DT, Wang W, Wu Z, Tong L, et al. (2010) Osteoblast behavior on polytetrafluoroethylene modified by long pulse, high frequency oxygen plasma immersion ion implantation, Biomaterials 31: 413-419.

57. Gao A, Hang R, Li W, Zhang W, Li P, et al. (2017) Linker-free covalent immobilization of heparin, SDF-1α, and CD47 on PTFE surface for antithrombogenicity, endothelialization and anti-inflammation. Biomaterials 140: 201-211.

58. Vergara-Jimenez J, Tricoci P (2010) Safety and efficacy of abciximab as an adjunct to percutaneous coronary intervention. Vasc Health Risk Manag 6: 39-45.

59. Xu LN, Yu WG, Tian JY, Liu QY (1990) Effect of sodium ferulate on arachidonic acid metabolism. Yao Xue Xue Bao 25: 412-416.

60. Jantan I, Raweh SM, Sirat HM, Jamil S, Mohd Yasin YH, et al. (2008) Inhibitory effect of compounds from Zingiberaceae species on human platelet aggregation. Phytomedicine 15: 306-309.

61. Crescente M, Jessen G, Momi S, Höltje HD, Gresele P, et al. (2009) Interactions of gallic acid, resveratrol, quercetin and aspirin at the platelet cycloox-ygenase-1 level. Functional and modelling studies. Thromb Haemost 102: 336-346.

62. Iovino F, Brouwer MC, van de Beek D, Molema G, Bijlsma JJ (2013) Signalling or binding: the role of the platelet-activating factor receptor in invasive pneumococcal disease. Cell Microbiol 15: 870-881.

63. Bao-lei W, Jia W, GUO Chun-yan (2017) Study on anti-thrombotic Mechanism Based on Platelet: 1396-2095.

64. Hechler B, Nonne C, Roh EJ, Cattaneo M, Cazenave JP, et al. (2006) MRS2500 [2-iodo-N6-methyl-(N)-methanocarba-2′-deoxyadenosine-3′, 5′-bisphosphate], a potent, selective, and stable antagonist of the platelet P2Y1 receptor with strong anti-thrombotic activity in mice. J Pharmacol Exp Ther 316: 556-563.

65. Chung E, Ricles LM, Stowers RS, Nam SY, Emelianov SY, et al. (2012) Multifunctional nanoscale strategies for enhancingand monitoring blood vessel regeneration. Nano Today 7: 514-531.

66. Margariti A, Winkler B, Karamariti E, Zampetaki A, Tsai TN, et al. (2012) Direct reprogramming of fibroblasts into endothelial cellscapable of angiogenesis and reendothelialization in tissue-engineered vessels. ProcNatlAcadSci109: 13793-13798.

67. Chen Z, Li S, Subramaniam S, Shyy JY-J, Chien S (2017) Epigenetic Regulation: A newfrontier for biomedical engineers. Annu Rev Biomed Eng19: 195-219.

68. Rubio A, Luoni M, Giannelli SG, Radice I, Iannielli A, et al. (2016) Rapid and efficient CRISPR/Cas9 gene inactivation in humanneurons during human pluripotent stem cell differentiation and direct reprogramming. Sci Rep 6: 37540.

69. Sayed N, Wong WT, Ospino F, Meng S, Lee J, et al. (2015) Transdifferentiation of human fibroblasts to endothelial cellsrole of innate immunity. Circulation 131: 300-309.

70. Kaur K, Yang J, Eisenberg CA, Eisenberg LM (2014) 5-Azacytidine promotes theTransdifferentiation of cardiac cells to skeletal myocytes. Cell Reprogram 16: 324-330.

71. Naeem N, Haneef K, Kabir N, Iqbal H, Jamall S, et al. (2013) DNA methylation inhibitors, 5-azacytidine and zebularinepotentiate the transdifferentiation of rat bone marrow mesenchymal stemcells into cardiomyocytes. CardiovascTher31: 201-209.

72. Li Y, Wan S, Liu G, Cai W, Huo D, et al. (2017) Netrin-1 Promotes Inflammation Resolution to Achieve Endothelialization of Small-Diameter Tissue Engineering Blood Vessels by Improving Endothelial Progenitor Cells Function In Situ. AdvSci (Weinh) 4:1700278.

73. Gallagher KA, Obi AT, Elfline MA, Hogikyan E, Luke CE, et al. (2016) Alterations in macrophage phenotypes in experimental venous thrombosis. J VascSurg Venous LymphatDisord 4: 463-471.

74. Nishimura S, Nagasaki M, Kunishima S, Sawaguchi A, Sakata A, et al. (2015) IL-1α induces thrombopoiesis through megakaryocyte rupture in response to acute platelet needs. J Cell Biol 209: 453-466.

75. Davizon-Castillo P, McMahon B, Aguila S, Bark D, Ashworth K, et al. (2019) TNF-α-driven inflammation and mitochondrial dysfunction define the platelet hyperreactivity of aging. Blood 134: 727-740.

76. Bos GW, Poot AA, Beugeling T, van Aken WG, Feijen J (1998) Small-diameter vascular graft prostheses: Current status. Arch Physiol Biochem 106: 100-115.

77. Adipurnama I, Yang MC, Ciach T, Butruk-Raszeja B (2016) Surface modification and endothelialization of polyurethane for vascular tissue engineering applications: A review. Biomater Sci 5: 22-37.

78. Pacholczyk R, Kraj P, Ignatowicz L (2002) Peptide specificity of thymic selection of CD4+CD25+ T cells. J Immunol168:613-620.

79. Wang Y, Yin P, Bian GL, Huang HY, Shen H, et al. (2017) The combination of stem cells and tissue engineering: An advanced strategy for blood vessels regeneration and vascular disease treatment. Stem Cell Res Ther 8:194.

80. Vizi ES, Orsó E, Osipenko ON, Haskó G, Elenkov IJ (1995) Neurochemical, electrophysiological and immunocytochemical evidence for a noradrenergic link between the sympathetic nervous system and thymocytes. Neuroscience 68:1263-1276.

81. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES (2000) The sympathetic nerve-an integrative interface between two supersystems: The brain and the immune system. Pharmacol Rev 52: 595-638.

82. Ichiyama K, Chen T, Wang X, Yan X, Kim BS, et al. (2015) Themethylcytosinedioxygenase Tet2 promotes DNA demethylation and activation of cytokine gene expression in T cells. Immunity 42:613-626.

83. Qiang GX, Yuejia W, Zhenqing W (2011) TET protein: A new family of DNA modifying enzymes. Chinese Journal of Biochemistry and Molecular Biology 27:1101-1105.

84. Shen Q, Zhang Q, Shi Y, Shi Q, Jiang Y, et al. (2018) Tet2 promotes pathogen infection-induced myelopoiesis through mRNA oxidation. Nature 554: 123-127.

85. Zhang Y, Zhang S, Chen X, Hu S (2015) An experimental study on inhibiting graft rejection following high-risk penetrating keratoplasty by CD25 siRNAnanocarrier in rats. Medical Journal of Chinese Peoples Liberation Army 40:297-302.

86. Xu C, Lu Z, Luo Y, Cao Z, Shen S, et al. (2018) Targeting of NLRP3 inflammasome with gene editing for the amelioration of inflammatory diseases. Nat Commun 9: 4092.

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