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REVIEW ARTICLE

Surface-functionalized design of blood-contacting biomaterials for preventing coagulation and promoting hemostasis

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Abstract: The anticoagulation and hemostatic properties of blood-contacting materials are opposite lines of research, but their realization mechanisms are inspired by each other. Contact between blood and implantable biomaterials is a classic problem in tribological research, as both antithrombotic and hemostatic materials are closely associated with this problem. Thrombus formation on the surfaces of blood-contacting biomedical devices can detrimentally affect their performance and patient life, so specific surface functionalization is required. Currently, intensive research has focused on the development of super-lubricated or super-hydrophobic coatings, as well as coatings that deliver antithrombotic drugs. In addition, hemostatic biomaterials with porous structures, biochemical substances, and strongly adhesive hydrogels can be used to achieve rapid and effective hemostasis via physical or biochemical mechanisms. This article reviews methods of preparing anticoagulant coatings on material surfaces and the current status of rapid hemostatic materials. It also summarizes fundamental concepts for the design and synthesis of anticoagulant and hemostatic materials by discussing thrombosis and hemostasis mechanisms in biomedical devices and normal organisms. Because there are relatively few reports reviewing the progress in surface-functionalized design for anticoagulation and hemostasis, it is anticipated that this review can provide a useful summary of the applications of both bio-adhesion and bio-lubrication techniques in the field of biomedical engineering.

Keywords: anticoagulation; hemostasis; lubrication; hydrogel; fibrous membrane

1 Introduction

Biotribology is an interdisciplinary subject involving tribology, biology, and biomaterial science [1, 2]. The friction and wear of medical devices in musculoskeletal, dental, and cardiovascular systems not only affect the functional performance of devices but also have a potentially adverse effect on the physiological tissue structure [3]. In human blood, the endothelium maintains a dynamic balance between coagulation and bleeding, thereby ensuring normal blood flow [4]. When its dynamic balance is disturbed, the human body reacts accordingly. If a biomedical device or biomaterial comes into direct contact with blood, blood exposure to its surface can trigger a clotting reaction, rendering the device/material ineffective. Furthermore, when a formed clot is dislodged, it may block organs, such as the brain and lungs, leading to

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various complications [5, 6]. In situations where the human body is severely traumatized and the aorta is damaged, the clotting system is often unable to achieve the desired hemostatic effect. Meanwhile, wounds that bleed continuously, leading to the loss of too much blood, can cause hemorrhagic shock, multiple organ failure, and other life-threatening conditions. Therefore, hemostatic biomaterials are required to assist in inhibiting bleeding [7, 8]. When a hemostatic biomaterial contacts with the blood, a series of coagulation reactions occur to form a stable clot, preventing bleeding [9].

Anticoagulation and hemostasis are regarded as two opposing functions, and they have different clinical requirements in the treatment of diverse diseases. For example, systemic antiplatelet or anticoagulation therapy is usually required to prevent thrombosis when using blood-contacting biomedical devices. However, long-term medication can have side effects and increase the risk of bleeding [10]. Therefore, for the long-term stability of biomedical devices, it is necessary to design a surface with optimized hemocompatibility [11], such as a hydrophilic hydrogel lubricant coating [12] or a coating that can encapsulate and release antithrombotic drugs [13]. Moreover, the effectiveness of conventional hemostatic biomaterials in inhibiting bleeding in special wounds is very limited, and new hemostatic biomaterials with rapid and efficient functions should be developed. Examples of these new biomaterials include hemostatic sponges [14] or powders [15] with high-porosity, hemostatic hydrogels with adhesive performance [16], and hemostatic biomaterials with encapsulated bioactive substances [17–19]. These biomaterials can promote hemostasis through contact with the blood and exert different physical or chemical effects.

There are review articles reporting about antithrombotic and hemostatic biomaterials; however, only a few have covered the design and preparation of these materials. These biomaterials are closely related to their interaction with the blood when performing their respective functions, which may be interoperable in some respects. Consequently, we collected and organized relevant studies that were recently published to summarize the research progress in this area. In this review article, we first introduced the mechanisms of thrombosis and hemostasis in biomedical devices and normal organisms to clarify the design concepts of relevant biomaterials. Next, we elaborated on the synthesis strategy of anticoagulant coatings on the surfaces of biomedical devices and rapid hemostatic biomaterials, mainly focusing on the different effects of these coatings/biomaterials on coagulation or bleeding. We also discussed the link between two research directions of preventing coagulation and promoting hemostasis to provide insights and motivate more in-depth investigations in both areas.

2 Biotribological considerations

2.1 Coagulation-related issues

The vasculature consists of the inner, middle, and outer membranes. The endothelial layer of the inner membrane plays an important role in tribological interactions owing to its direct contact with the surface of an implanted medical device. The endothelium can sense various flow properties (e.g., shear magnitude and directionality) and control vascular tension via converting perceptual information into biochemical responses [20, 21]. The glycocalyx in the endothelium is responsible for shear sensing and regulation of nitric oxide levels, which is in direct contact with medical devices; thus, it has high research significance in vascular bio-friction at the microscopic level [22, 23].

Typical biotribological issues exist in medical devices in contact with the blood. As shown in Fig. 1(a_1), the coronary artery is obstructed by stenosis in percutaneous coronary intervention and therefore requires revascularization. When a stent is delivered to the stenosis position with a catheter, the balloon catheter will be inflated to expand the stent. Subsequently, the balloon catheter will be deflated and removed from the vessel, and the stent remains in the dilated vessel to restore blood flow; hence, hemodynamic, normal, and frictional forces will be applied to the stent. Typically, the stent may migrate in vivo owing to a stronger hemodynamic force than the frictional force. To obtain higher friction, the size and structure of the stent can be adjusted to generate

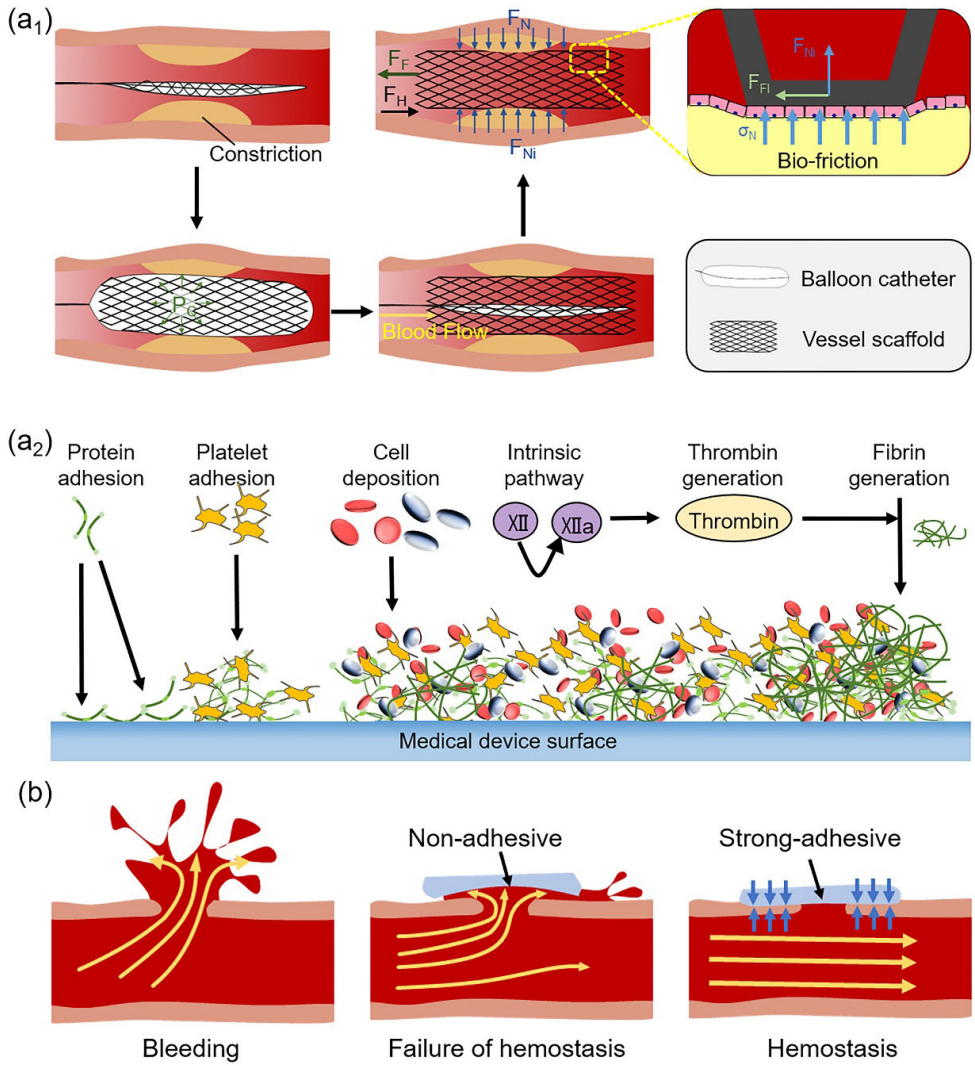

Fig. 1 (a_1) Biotribological considerations during stent implantation. After the balloon and stent are delivered to the stenosis site, the balloon is inflated to expand the stent in position. The stent is subjected to the hemodynamic force F_H, normal force F_{Ni}, and friction force F_F. (a_2) Mechanisms of thrombus formation in blood-contacting biomedical devices. Platelets, white blood cells, and red blood cells can adhere to fibrinogen following fibrinogen deposition on the device surface. Meanwhile, thrombin is produced in response to endogenous coagulation pathways and inflammation, which converts fibrinogen into fibrin, causing thrombus formation [24–30]. Reproduced with permission from Ref. [24], © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, 2015; Reproduced with permission from Ref. [25], © Elsevier, 2020; Reproduced with permission from Ref. [26], © Georg Thieme Verlag KG, 2016; Reproduced with permission from Ref. [27], © Elsevier, 2019; Reproduced with permission from Ref. [28], © The Royal Society of Chemistry, 2015; Reproduced with permission from Ref. [29], © Elsevier Ltd., 2014. Reproduced with permission from [30], © Elsevier B.V., 2022. (b) After severe bleeding, relatively poor or non-adhesive hemostatic materials cannot effectively stop bleeding as they are easily dislodged. However, strong adhesive hemostatic materials can adhere to the wound tissues and rapidly stop bleeding.

a higher pressure or an increased contact area with the blood vessel. However, increasing the stent size may overstretch the vessel wall and potentially cause damage. Therefore, frictional damage to the endothelium is a classic biotribological issue. Additionally, a medical catheter can also cause damage to the endothelium when it comes in contact with the vessel wall. Its lubrication can reduce friction between the catheter and vessel wall, decreasing the risk of complications. Consequently, the mechanisms involved can be more deeply understood by examining the complications caused by implanted vascular devices during friction, lubrication, and wear. This information is useful for the design and optimization

of implanted vascular devices to reduce the occurrence of clinical complications.

The underlying mechanism of thrombus generation when blood comes in contact with the surface of biomedical device or biomaterial is shown in Fig. 1(a_2). Initially, fibrinogen adheres to the material surface, resulting in the adhesion and activation of platelets [24]. Surface modification methods can physically prevent protein adhesion in various materials [25]. Subsequently, several biologically active substances are released, leading to further platelet activation and aggregation to generate thrombi. Platelets can successively bind to factors such as *Va* and *Xa* to form prothrombinase complexes and promote thrombin generation [26]. Accordingly, the antithrombotic property of a biomaterial can be enhanced by adding an antiplatelet substance to its surface [27]. Additionally, leukocytes and factor *XII* can also adhere to fibrinogen (and thus the material surface) to promote thrombosis [28]. Eventually, thrombin facilitates the conversion of fibrinogen into fibrin, which forms a stable blood clot with platelets [29]. Biomaterials containing special functional biomolecules on their surface can inhibit thrombin activity and have an antithrombotic effect [30].

2.2 Hemostasis-related issues

Generally, wound hemostasis is accomplished via blood clot formation [9], which typically involves two stages. The first stage is the primary hemostasis process. In this stage, blood vessels can contract reactively when damaged or irritated. Platelets then rapidly bind to collagen (COL) and the von Willebrand factor via glycoproteins (GPs) in the subendothelium of the damaged site. Subsequently, platelets are activated and aggregated through GPs IIb-IIIa receptors to bind to fibrinogen and form platelet clots. The second stage is a secondary hemostasis process, which involves a coagulation mechanism centered on thrombin production. In the presence of activated platelets, coagulation factors undergo a coagulation cascade to form prothrombinase complexes, which activate the conversion of prothrombin to thrombin. Thrombin then breaks down fibrinogen into fibrin monomers, which successively polymerize to form cross-linked fibrin. Finally, the platelets, blood cells, and fibrin become entangled, forming a solid clot, plugging the wound, and stopping bleeding [31–33].

Materials with excellent hemostatic performance are required under severe bleeding conditions; otherwise, massive blood loss can occur. The adhesion properties of the hemostatic materials affect their hemostatic performance. As shown in Fig. 1(b), relatively poor or non-adhesive hemostatic materials may fall off from the surface of bleeding wound and therefore fail to seal the wound, while strong adhesive hemostatic materials can quickly seal the wound and achieve rapid hemostasis. Current hemostatic materials are mostly composed of biocompatible polymers, so the adhesion properties of polymers are typical tribological issues that need to be carefully investigated.

2.3 Tribological characterization methods

As previously mentioned, the surface tribological properties of blood-contacting biomedical devices are critical for their efficiency. Therefore, quantitative analysis of the tribological behavior of these devices is considered useful for investigating the relationship and mechanism between the tribological property and biological functionality.

Typically, the universal multifunctional tribo-tester has been used to characterize the tribological behavior of various biomaterials at the macroscopic level, obtaining useful information such as the friction coefficient versus time curve. The advantage of using this instrument is that the applied load can be regulated close to the physiological conditions in the human body and it can be personalized with various test parameters, such as the upper/lower specimens, test mode, and test speed. It has been previously reported that the tribological performance of lubrication-enhanced electrospun nanofibrous membranes can be effectively examined using this instrument [34, 35]. Specifically, the friction coefficient was tested at different temperatures (20 and 37 °C), applied loads (0.5, 1, 2, and 3 N), rotational speeds (15, 30, 60, and 120 mm/min), rotational radii (2, 4, 6, and 8 mm), and media (air and water). The applied load and medium had the greatest effect on the friction coefficient. Additionally, it was also demonstrated that consistent results could be obtained with metal (GCr15 steel) or ceramic (SiN) balls for upper

specimens, whereas the results fluctuated slightly and were unstable when using Teflon balls. The in vivo functional verification data were highly correlated with the tribological properties of the materials. Biotribo-corrosion is also an important concern in biotribological research, as biomedical prostheses, such as artificial joints and dental implants, can experience severe biotribo-corrosion in the biological environment of the human body. The biotribo-corrosion behavior of materials can be tested using the universal multifunctional tribo-tester associated with a three-electrode system [36, 37].

Atomic force microscopy (AFM) in contact mode can be used to examine the tribological behavior of various biomaterials at the microscopic level [38, 39]. Generally, a colloidal polystyrene microsphere with a diameter of 5.0 μm is attached to the tip of the cantilever via UV curing to avoid damaging the test samples. Before measurements, the spring constants and lateral sensitivities of the probe should be determined using the frequency method and the improved wedge calibration method. Additionally, the surface roughness values of the test samples should be extremely low to produce plausible results. Likewise, various parameters, such as the applied load, test speed, and test medium, can also be varied to investigate the tribological behavior of biomaterials. Furthermore, the interaction forces between the probe and the surface of biomaterials can be obtained when the AFM works in the force curve mode. Using this technique, the supramolecular interactions between adamantane and β-cyclodextrin, as well as the hydration interactions between bacteria and zwitterionic polymer coatings, have been successfully measured [40, 41].

3 Antithrombotic activity

3.1 Surface coatings

Biomedical devices or biomaterials with lubricating hydrophilic or super-hydrophobic surfaces can become antithrombotic by resisting protein adhesion.

Current research indicates that water-based lubrication is an eco-friendly and clean form of lubrication [42]. Moreover, hydrophilic hydrogel materials can effectively prevent protein adhesion owing to their high water content and lubrication properties of their surfaces [43, 44]. For example, Parada et al. [45] first activated a polyvinyl chloride (PVC) catheter in an ethanol solution of benzophenone, and then added a hydrogel precursor solution of N,N-dimethylacrylamide and Irgacure 2595, followed by curing under UV irradiation to obtain an ultra-thin hydrogel coating on the catheter surface (Fig. 2(a)). This hydrogel coating reduced blood clotting on the catheter wall by 90% and showed an excellent antibacterial effect. The lubrication performance of the hydrogel coating was also tested using a rheometer with a steel parallel plate geometry. It was found that the friction coefficient of the coated surface was much lower than that of the pristine surface. Cheng et al. [46] prepared a hydrophilic polyacrylamide hydrogel network on the surface of decellularized porcine pericardium to enhance the antithrombotic performance of a bioprosthetic heart valve. Park et al. [47] developed a hydrogel coating based on a polysaccharide called O-carboxymethyl chitosan (CMC). First, they grafted CMC onto the surface of an intravascular catheter via electron-beam induction. Subsequently, the coating was modified into a porous structure to increase its swelling rate, enable rapid water absorption, and enhance the antifouling effect on the catheter surface (Fig. 2(b)). When investigated using a force gauge test system, the coating exhibited high lubrication property and durability under continuous wet friction conditions [47]. In a study performed by Li et al. [25], dopamine and Ag^+ were rapidly oxidized in the presence of sodium periodate to form polydopamine (PDA)/silver composite nanoparticles, which were then deposited onto the surface of PVC tubes. This coating contains many hydrophilic groups, such as carboxyl, amino, and phenolic hydroxyl groups, making the PVC tube surface super-hydrophilic with synergistic antibacterial and antithrombotic properties.

Surface modification with amphoteric ions can provide a strong hydration effect and has been widely used to enhance the lubrication properties of biomedical materials [48]. Theoretically, the residual charges on the H and O atoms endow a water molecule with a large electric dipole, forming a strong hydration shell surrounding the zwitterionic charges due to the interactions between the water dipole and enclosed

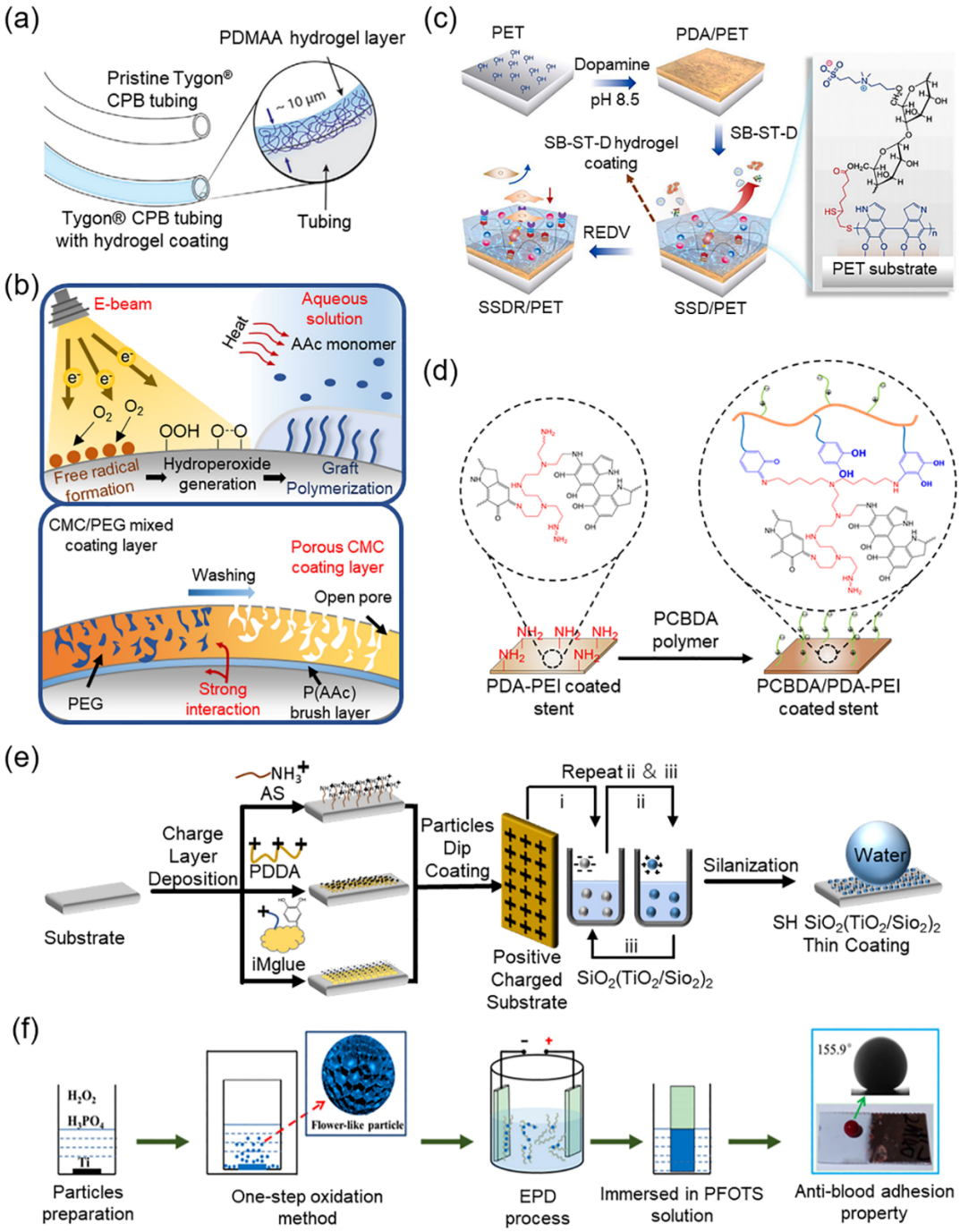

Fig. 2 Various anticoagulation strategies for the surface modification of blood-contacting biomedical devices. (a) N,N-dimethylacrylamide was applied onto the catheter surface via UV irradiation to form an ultra-thin hydrogel coating [45]. Reproduced with permission from Ref. [45], © John Wiley and Sons, 2020. (b) Hydrogel coatings prepared from the polysaccharide of O-carboxymethyl chitosan [47]. Reproduced with permission from Ref. [47], © Elsevier, 2022. (c) Amphoteric hydrogel coatings developed from dihydrolipoic acid-modified sulfobetaine starch (SB-ST-D) on the catheter surface [52]. Reproduced with permission from Ref. [52], © Elsevier, 2021. (d) Amphoteric poly(carboxyl betaine acrylate-co-dopamine methacrylate) copolymer (PCBDA) grafted onto the surface of a poly(lactic acid) scaffold [53]. Reproduced with permission from Ref. [53], © Elsevier, 2019. (e) Super-hydrophobic coating developed based on a layer-by-layer self-assembly technique through the deposition of positively charged SiO_2 and negatively charged TiO_2 nanoparticles [54]. Reproduced with permission from Ref. [54], © American Chemical Society, 2019. (f) Super-hydrophobic biomimetic coating prepared using flower-like micro-nanoparticles based on an electrophoretic deposition technique [55]. Reproduced with permission from Ref. [55], © Elsevier B.V. 2020.

charges. It is difficult for the hydration shells to overlap with each other owing to the steric effect. The water molecules in the hydration shells with a lower Gibbs free energy are difficult to deform; therefore, the hydration shells could bear a large normal load without deformation. On the other hand, the rapid exchange of the water molecules in the hydration shells with nearby "free" water molecules results in a fluidlike manner of the hydration shell when sheared and correspondingly a significantly reduced friction coefficient at the sliding interface [49]. This hydration mechanism is effective in achieving protein adhesion [50]. Dopamine can be employed to graft amphoteric monomers onto the surfaces of blood-contacting biomedical devices. For instance, Zhu et al. [51] constructed a stable amphoteric coating on the surface of polyurethane catheters using a co-deposition method. In this case, dopamine acted as an initiator to polymerize the amphoteric sulfobetaine methacrylate monomer (SBMA) and adhere the polySBMA formed to the catheter surface. Meanwhile, the presence of Cu^{2+} ions in a $CuSO_4/H_2O_2$ solution catalyzed the generation of free radicals by H_2O_2, promoting dopamine polymerization and improving PDA deposition efficiency. Yao et al. [52] successfully synthesized dihydrolipoic acid-modified sulfobetaine-derived starch (SB-ST-D). After depositing PDA on a polyethylene terephthalate (PET) surface to form a viscous PDA/PET composite material, SB-ST-D was immobilized onto the PDA/PET surface via the Michael addition reaction, forming disulfide bonds to produce an amphoteric hydrogel coating (Fig. 2(c)). Yang et al. [53] deposited PDA and polyethyleneimine on a polylactic acid (PLA) scaffold to modify the surface with amino groups. Subsequently, they synthesized an amphoteric poly(carboxybetaine acrylate-co-dopamine methacrylate) copolymer that was grafted onto the PLA scaffold surface due to multiple interactions between the catechol groups of the copolymer and the amino groups of the scaffold (Fig. 2(d)) [53].

Similarly, super-hydrophobic surfaces can be used to prevent protein adhesion. Han et al. [54] initially functionalized the substrate surface with three types of modifiers: amino-silane, poly(diallyldimethyl ammonium chloride) (PDDA), and mussel adhesive protein (iMglue). They also developed a super-hydrophobic coating through the solution-based electrical charge-controlled layer-by-layer self-assembly of positively charged SiO_2 and negatively charged TiO_2 nanoparticles (Fig. 2(e)). Zeng et al. [55] prepared biomimetic flower-like micro-nanoparticles by directly oxidizing titanium in a hydrogen peroxide solution with a small amount of phosphoric acid at 80 °C. The particles were then deposited onto a substrate with electropositive chitosan using the electrophoretic deposition technique, developing a super-hydrophobic coating on the surface of the substrate (Fig. 2(f)). Li et al. [56] cross-linked porcine pericardium with glycidyl methacrylate to introduce a carbon-carbon double bond on the pericardial surface. The pericardial surface was successively converted from being hydrophilic to hydrophobic by adding fluoride monomers. The design of a hydrophobic surface coating greatly enhanced the thrombotic resistance of artificial bioprosthetic valves prepared from porcine pericardium.

3.2 Functional biomolecules

Thrombosis can be reduced by inhibiting platelet activation and aggregation. This can be achieved through the generation of nitric oxide (NO) by endothelial cells to elevate the levels of cyclic guanosine monophosphate [57]. NO generation via the introduction of an exogenous donor on a material surface can have an antithrombotic effect. For instance, Griffin et al. [58] impregnated a PVC tubing with S-nitroso glutathione (GSNO) through solvent swelling, and the resulting GSNO–PVC material encapsulated sufficient GSNO to achieve physiological endothelial NO flux values within 4 h. Endogenous S-nitrosothiols (RSNO) can decompose to NO via catalysis by copper ions (Fig. 3(a)); thus, encapsulating copper ions on a material surface can impart antithrombotic properties to biomedical devices [59, 60]. Jiang et al. [61] prepared a multifunctional nano-membrane for NO generation by combining CuO/Cu_2O with TiO_2. Cu^{2+} can not only catalyze the release of NO but also enhance the photocatalytic activity of the TiO_2 nano-membrane and the formation of more pores to produce a super-hydrophilic surface, which can be used to inhibit protein adhesion (Fig. 3(b)). Yu et al. [62]

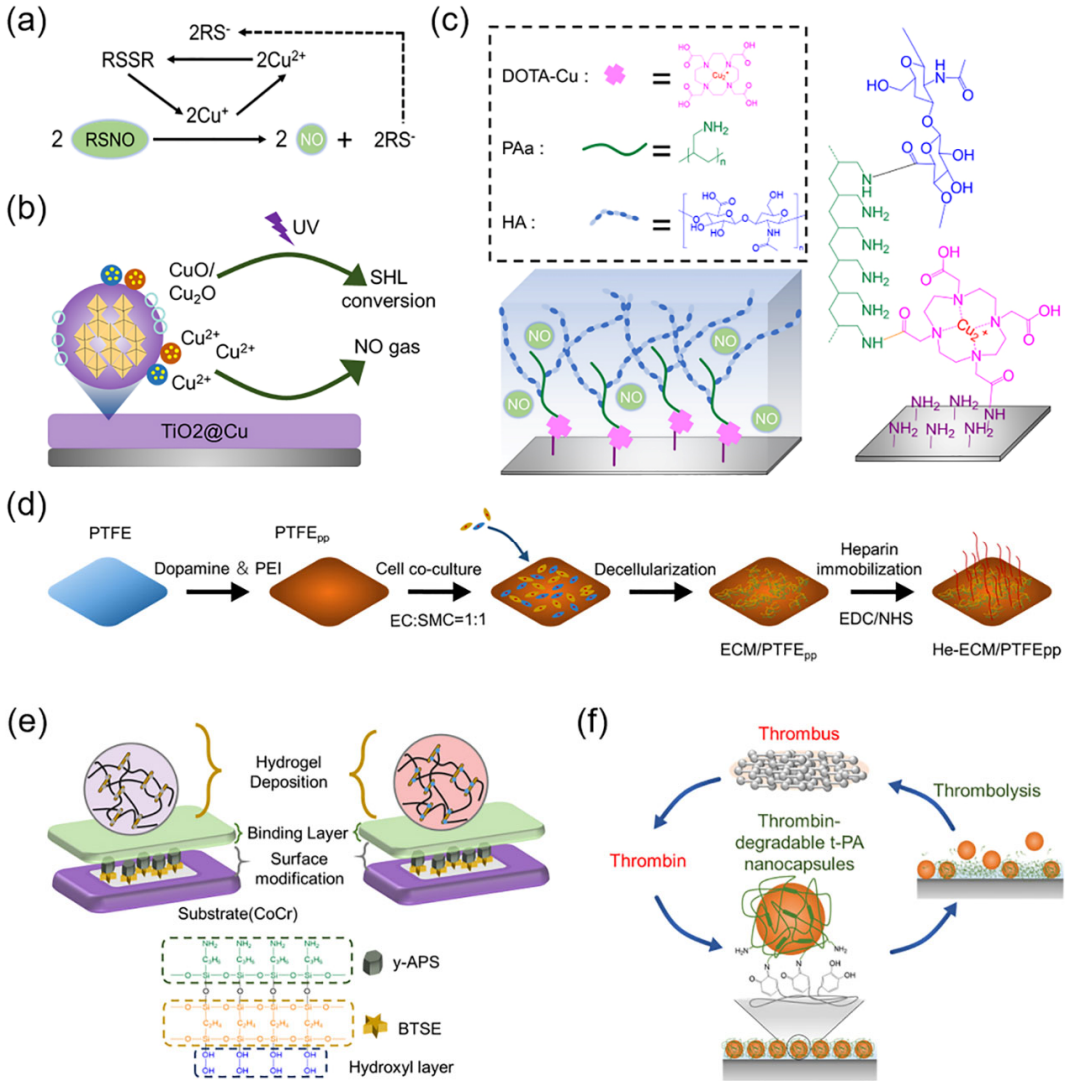

Fig. 3 Chemical strategies in materials to prevent thrombosis. (a) Decomposition of S-nitrosothiol (RSNO) to NO catalyzed by copper ions [59, 60]. Reproduced with permission from Ref. [59], © John Wiley & Sons, Inc., 2016; and Ref. [60], © American Chemical Society, 2019. (b) A nano-membrane was prepared by combining CuO/Cu_2O with TiO_2, where Cu^{2+} not only catalyzed the generation of NO but was also used for preparing a super-hydrophilic surface [61]. Reproduced with permission from Ref. [61], © Elsevier, 2020. (c) A bifunctional coating mimicking the endothelial glycocalyx prepared via layer-by-layer grafting [63]. Reproduced with permission from Ref. [63], © John Wiley and Sons, 2021. (d) An artificial blood vessel prepared through the combination of heparin with a simulated extracellular matrix layer based on 1-ethyl-3-[3-dimethylaminopropyl] carbodiimide hydrochloride (EDC)/N-hydroxysuccinimide (NHS) coupling [66]. Reproduced with permission from Ref. [66], © Elsevier, 2021. (e) A cobalt-chromium vascular scaffold containing a heparin hydrogel coating prepared using a spray technique [67]. Reproduced with permission from Ref. [67], © Elsevier, 2021. (f) A thrombin-responsive fibrinogen activator (t-PA)-containing nanocapsule (NC) coating that can be used for treating blood-contacting materials [70]. Reproduced with permission from Ref. [70], © John Wiley and Sons, 2017.

first treated the PVC catheter with PDA and then grafted polyallylamine molecules onto PDA based on the Schiff-base and Michael addition reactions to successfully produce an amino-rich surface coating (PADA). Meanwhile, by chelating Cu^{2+} with macrocyclic polyamines (DOTA), a DOTA–Cu^{2+} complex was prepared, which could catalyze NO generation from endogenous RSNO. The produced DOTA–Cu^{2+} complex was finally grafted onto the PADA coating through amide condensation, and an antimicrobial peptide was also modified onto this coating via click chemistry. Lyu et al. [63] synthesized a bifunctional coating by mimicking the endothelial glycocalyx. The carboxyl group of DOTA was unilaterally coupled

with the amino group of plasma polymeric allylamine on the scaffold surface. Subsequently, the remaining carboxyl group of DOTA was reacted with the amino groups of polypropylene amine (POPAM) to generate more amino grafting sites. Finally, hyaluronic acid (HA) was grafted onto POPAM to produce a biomimetic coating on the vascular stent surface (Fig. 3(c)). The layer-by-layer approach allows independent control of the density and content of each grafted layer, achieving NO-releasing and endothelial glycocalyx functions.

Heparin has been widely used to prevent blood coagulation in clinical applications as it can inhibit the activity of prothrombin in the coagulation cascade by enhancing the physiological effects of antithrombin [64, 65]. Yu et al. [66] prepared a small-diameter artificial blood vessel containing heparin. Here, they modified a polytetrafluoroethylene substrate via PDA/polyethyleneimine co-deposition and co-cultured it with endothelial and smooth muscle cells. Next, an extracellular matrix (ECM) layer was obtained through decellularization, and heparin was introduced into the artificial blood vessel via EDC/NHS coupling (Fig. 3(d)). Since heparin was chemically grafted onto the substrate at different concentrations, the optimal concentration could be determined to promote the proliferation of endothelial cells and inhibit the growth of smooth muscle cells. Johnbosco et al. [67] designed and prepared a four-armed polyethylene glycol (starPEG)/heparin hydrogel-coated vascular scaffold. To do this, they first subjected a cobalt-chromium metal substrate to two-step sialylation, which was followed by immersion in a poly (ethylene/maleic anhydride) (PEMA) tetrahydrofuran solution to form a PEMA film. Then, a thrombin-cleavable starPEG/heparin hydrogel coating was prepared by spraying the hydrogel precursor solution onto the stent surface via EDC/NHS coupling with a commercial air-brush device (Fig. 3(e)). In addition, the anticoagulant effect of blood-contacting devices can be enhanced by the synergistic effects of heparin and NO. Qiu et al. [68] constructed a plasma polyallylamine film on stainless steel 316L vascular scaffold through chemical vapor deposition to enrich the scaffold with amino groups and then grafted active heparin and selenocystamine via amide condensation.

Tissue fibrinogen activator (t-PA) can degrade fibrin by activating the conversion of plasminogen to plasmin, resulting in anti-thrombosis. However, the direct release of tPA into the blood may lead to hemorrhagic complications [69]. Li et al. [70] prepared tPA-containing nanocapsules (NCs) using a thrombin substrate peptide as a cross-linking agent. A NC/glutathione (GSH) coating was obtained by treating the blood-contacting material with GSH after attaching the NCs to its surface through covalent bonds using PDA. This coating rapidly released tPA in the presence of thrombin to activate the fibrinolytic system (Fig. 3(f)). In addition, a study by Cihova et al. [71] showed that a palladium-based metallic glass altered the conformation of fibrinogen and reduced the expression levels of CD62P and CD41/CD61 in platelets. The resulting blood-contacting material can greatly reduce platelet activation and retard fibrin formation. Rivaroxaban, a factor *Xa* inhibitor, blocks the coagulation cascade and acts as an anticoagulant. In a study performed by Wang et al. [72], rivaroxaban was loaded into a thrombin-responsive nanogel, which consisted of oxidized HA and a thrombin cleavage peptide cross-linker that rapidly released rivaroxaban in a thrombin environment. The nanogel was coated onto a biological valve or vascular scaffold. Bivalirudin (BV), a direct thrombin inhibitor, is an effective anticoagulant. Sun et al. [73] prepared artificial polycaprolactone vascular grafts by electrospinning and loaded BV to improve their patency. Furthermore, antithrombotic peptides can inhibit platelet aggregation and exert anticoagulant effects. Zhao et al. [74] first aminated a gold surface with 2-aminoethanethiol and then reacted it with PEG-antithrombotic ACH_{11} to obtain a multifunctional Au–PEG–ACH_{11} surface.

4 Haemostatic strategy

4.1 Physical method

4.1.1 Porous hemostatic biomaterials

Highly porous hemostatic materials (such as gauzes and sponges) and hemostatic powders can concentrate blood cells, platelets, and clotting factors because of their strong water absorption, facilitating the clotting process [75, 76].

Hemostatic gauze is a commonly used material that can be prepared via either traditional methods or electrospinning. For example, nanoclay electrospun membranes developed by Cui et al. [77] are highly hydrophilic and can rapidly concentrate blood components. However, although the absorbency of gauze promotes hemostasis, the excessively rapid diffusion of blood within it causes significant blood loss. He et al. [78] suggested that controlling the movement of blood fluid at the gauze/tissue interface could reduce gauze absorbency. For example, after grafting a few catechol compounds containing long chains of alkyl groups onto a gauze surface, the gauze retained its absorbency properties while achieving hydrophobicity and tissue adhesion. The hydrophobicity of this newly modified gauze impedes blood movement, reducing tissue adhesion-induced blood leakage from the tissue to the gauze (Fig. 4(a)). In addition, Zhu et al. [79] applied a paraffin/hexane solution to a conventional hydrophilic gauze to achieve super-hydrophobicity. Then, the super-hydrophobic gauze was laminated with hydrophilic gauze. In this setup, the lower layer of the hydrophilic gauze could increase blood concentration, whereas the upper layer prevented blood penetration, attained hemostasis, and reduced bleeding volume.

Hemostatic sponges are highly porous materials that can rapidly concentrate blood. Various polymers, including chitosan (CS) that contains positively charged amino groups in its molecular backbone, have been used to prepare hemostatic sponges. Amino groups can attract negatively charged red blood cells and induce aggregation [80]. Deacetylated CS can improve the water absorption of CS sponges and enhance their ability to adsorb blood cells [81]. COL is the main component of the ECM, and the network structure inside hemostatic COL sponges with a three-dimensional mesh has a large contact area with blood [82]. In addition, PEG and polyvinyl alcohol, which have good water absorption performance, have also been used to prepare hemostatic sponges [83, 84].

Hemostatic sponges can be prepared using various methods, of which freeze drying is a simple and commonly used method. For example, Yuan et al. [85] added a CS acetate solution dropwise to a mixture of oxidized bacterial cellulose (OBC) and COL, which was followed by freeze-drying to prepare hemostatic OBC/COL/CS sponges. Because of the electrostatic interactions between OBC and CS, the two solutions self-assembled quickly after mixing. Therefore, using toxic cross-linking agents could be avoided. Cryogels prepared in a subzero environment have high porosity and can improve the connectivity of pores in hemostatic sponges. Liang et al. [86] modified CS via quaternization and double bonding, modified HA with dopamine, and prepared zeolite nanoparticles. The mixed solution of these three materials was subsequently subjected to redox reactions employing ammonium sulfate and tetramethylenediamine at −20 °C to form a double cross-linked network cryogel containing covalent bonds with electrostatic forces. This cryogel was endowed with a penetrating porous structure, allowing rapid hemostasis (Fig. 4(b)). Hemostatic sponges can also be prepared through foaming reactions. Zhao et al. [87] condensed CS with PEG and formaldehyde in a slightly acidic environment, where the foaming reaction caused the polymer to expand. This reaction formed a new polymer containing O–C–O bonds that was successively compressed to obtain an injectable poly(vinyl alcohol)/CS sponge. Additionally, electrospinning can be used to fabricate sponges. Xie et al. [76] prepared a lightweight three-dimensional gelatin sponge based on electrospinning. The positively and negatively charged nanofibers, which were ejected from the gelatin solution under both positive and negative high-voltage electric fields, were entangled with each other. Subsequently, they were deposited using a conductive metal funnel. These nanofibers were successively cross-linked by heating at 190 °C to form a gelatin nanofiber sponge with a porous structure, high surface area, and good compressibility, which could control many forms of bleeding (Fig. 4(c)). Zhang et al. [88] prepared nanofibers containing anticancer drugs using electrospinning to develop a hemostatic material for chemotherapeutic applications. The nanofibers were placed in gelatin/CS gel solutions, which were then lyophilized to obtain a sandwich-structured fiber/sponge complex (Fig. 4(d)). This hemostatic material was easy to fold and can be used in hard-to-reach bleeding sites. The nanofibers

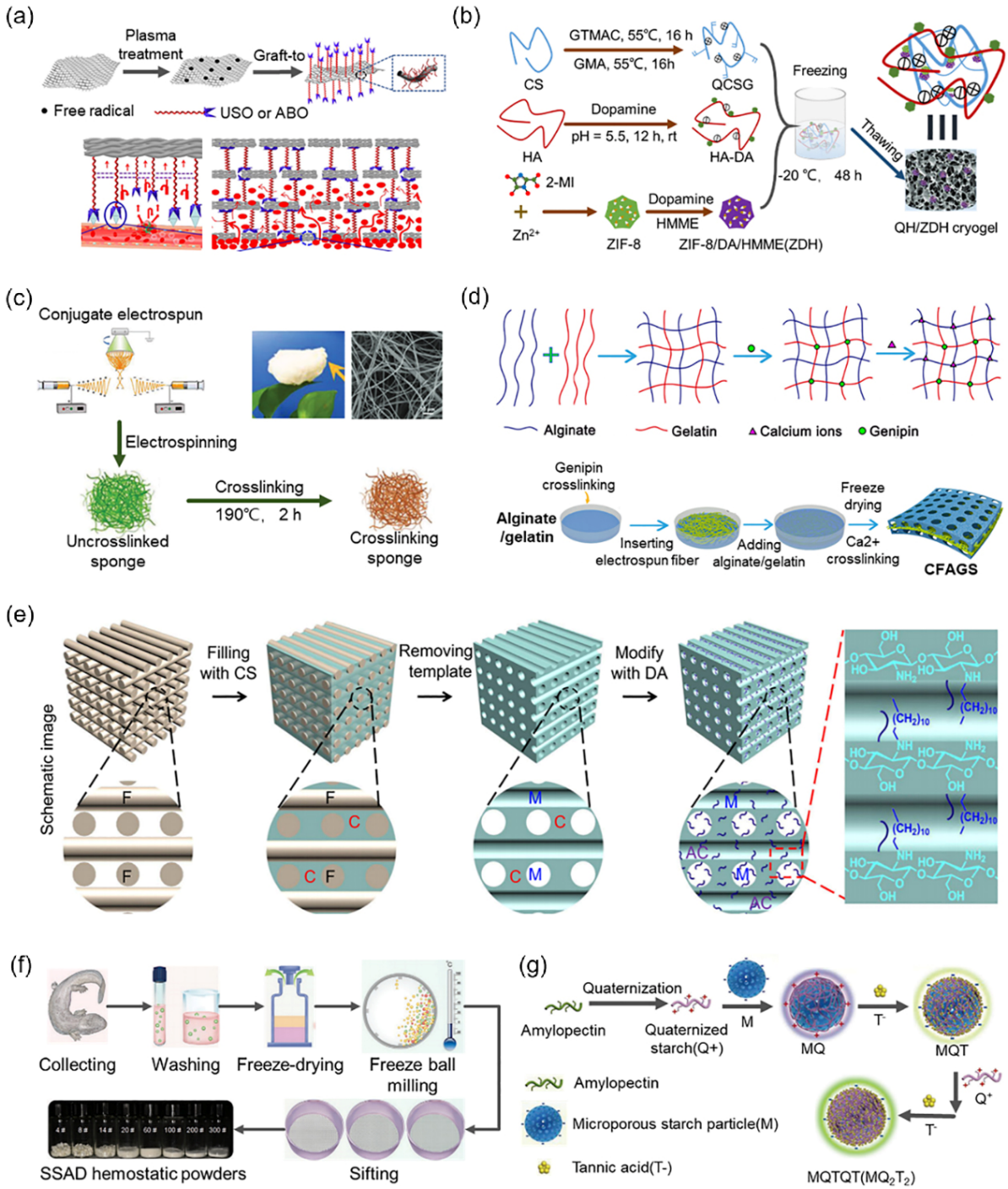

Fig. 4 Hemostatic materials that can increase blood concentration. (a) Reduction of excessive blood absorption by reducing the movement of blood fluid within the gauze and at the gauze/tissue interface [78]. Reproduced with permission from Ref. [78], © Springer Nature, 2022. (b) A double cross-linked network cryogel manufactured via freeze-drying [86]. Reproduced with permission from Ref. [86], © John Wiley and Sons, 2021. (c) A three-dimensional gelatin sponge prepared through electrospinning [76]. Reproduced with permission from Ref. [76], © John Wiley and Sons, 2021. (d) A fiber/sponge complex fabricated via electrospinning and lyophilization for tumor resection hemostasis and prevention of tumor recurrence post-operatively [88]. Reproduced with permission from Ref. [88], © John Wiley and Sons, 2018. (e) A chitosan-based hemostatic sponge prepared using 3D printing technology [89]. Reproduced with permission from Ref. [89], © Springer Nature, 2021. (f) A natural hemostatic powder prepared using salamander skin secretions [91]. Reproduced with permission from Ref. [91]. © John Wiley and Sons, 2022. (g) Multi-layered starch hemostatic microspheres prepared through a layer-by-layer assembly method [92]. Reproduced with permission from Ref. [92], © John Wiley and Sons, 2020.

in the inner layer can release anticancer drugs to prevent recurrence and metastasis after tumor resection. To develop a shape-memory hemostatic material, Du et al. [89] prepared a microfiber template based on 3D printing technology, which was then filled with a CS acetate solution, lyophilized, and finally modified with hydrophobic dichloromethane to produce an alkylated chitosan hemostatic sponge (Fig. 4(e)). This hemostatic sponge can rapidly recover its shape by absorbing water or blood.

Hemostatic powders can be used for various types of wounds. Some compounds with large porosity, such as silica nanoparticles (NPs), not only have an ultrahigh surface area but also can release calcium ions to directly participate in the coagulation cascade. Porous starch microspheres made from corn starch via enzymatic digestion also have a high surface area. Starch-based porous NPs made by cross-linking Si NPs with starch microspheres as a substrate via electrostatic adsorption can rapidly control bleeding [90]. Some biological materials can also be used to prepare hemostatic powders. For instance, Zhang et al. [91] developed hemostatic powders with different particle sizes by grinding a solution of salamander skin secretions after lyophilization (Fig. 4(f)). Hemostatic powders prepared from natural materials can quickly absorb blood and promote wound healing. Liu et al. [92] constructed multi-layered hemostatic microspheres by modifying quaternized branched-chain starch and tannic acid (TA) on the surface of electronegative porous starch using a layer-by-layer assembly method (Fig. 4(g)). These hemostatic microspheres demonstrated excellent hemostatic performance in the treatment of cancellous bone defects. In addition, hemostatic powders prepared from hydrogels can also promote hemostasis owing to their high hydrophilicity. For example, Cheng et al. [93] cross-linked carboxymethyl CS and sodium alginate in an alkaline solution to prepare a hydrogel, which was immersed in an aqueous solution containing calcium ions for cross-linking, lyophilized, and ground to obtain a gel powder.

4.1.2 *Hemostatic hydrogels*

Hydrogels are polymer-based materials with three-dimensional networks that have attracted widespread interest in many fields [94]. Hemostatic hydrogel materials not only promote hemostasis by rapidly sealing wounds but also enhance wound healing by keeping wounds moist [95]. The special structure of a polymer produces complex mechanical behavior, in which the friction of the polymer is mainly affected by two types of interactions, i.e., adhesion and deformation [96]. Generally, the frictional adhesion component of a polymer is considered to be larger than its deformation [97]. Van der Waals forces, electrostatic forces, hydrogen bonds, and molecular bonds are present at the contact interface of polymers, and chemical bonds are much stronger than intermolecular bonds [98]. Hemostatic hydrogels can adhere to soft tissues via various forces, including physical forces such as hydrogen bonding and electrostatic force, and chemical forces such as amide bonding and Schiff-base bonding [99].

The reaction of aldehyde groups with amino groups via Schiff-base bonding can produce injectable hydrogel materials. The remaining aldehyde groups in the obtained hydrogels can react with amino groups in tissues to provide the material with tissue adhesion behavior (Fig. 5(a)). Various polymers, such as HA [100], sodium alginate [101], and dextrose [102], can be oxidized by $NaIO_4$ to form aldehyde groups (Fig. 5(b)). For example, Li et al. [103] fabricated a hydrogel from oxidized HA, glycol CS, and the conditioned medium of menstrual blood-derived stem cells. The Schiff-base bonding generated between oxidized HA and glycol CS provides the hydrogel with injectability and self-healing properties. In addition to the generation of aldehyde groups via polymer oxidation, Hong et al. [104] prepared N-(2-aminoethyl)-4-(4-(hydroxymethyl)-2-methoxy-5-nitrosophenoxy) butanamide (NB)-modified HA, which could produce aldehyde groups via photoreactions. The material was blended with gelatin methacrylate (GelMA) to form a double cross-linked network hydrogel with covalent bonding and Schiff-base bonding under UV irradiation (Fig. 5(c)). This hydrogel could rapidly adhere to the surface of wet tissues and exhibited high mechanical strength to withstand pressures of up to 290 mmHg, enabling hemostasis after arterial and cardiac injury.

The strong adhesion of mussel adhesive proteins due to their high content of catechol groups has inspired the study of hemostatic hydrogel materials

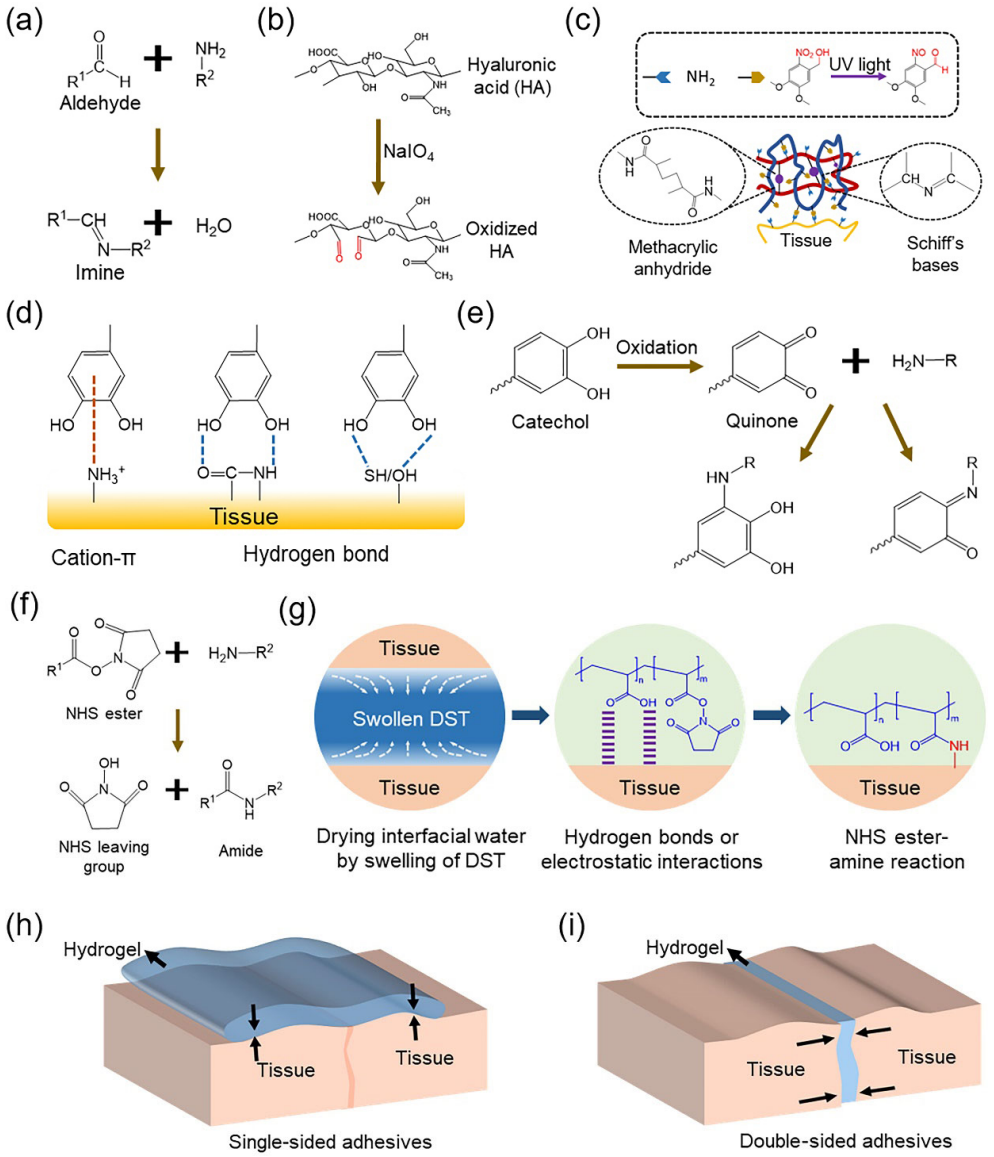

Fig. 5 (a) Schiff-base reaction between aldehyde groups and amino groups. (b) Oxidation of hyaluronic acid by $NaIO_4$ to produce an aldehyde group [100]. Reproduced with permission from Ref. [100], © Elsevier, 2021. (c) Use of *N*-(2-aminoethyl)-4-(4-(hydroxymethyl)-2-methoxy-5-nitrosophenoxy) butanamide for the preparation of functionalized hyaluronic acid (HA-NB), which can generate aldehyde groups via UV irradiation. HA-NB is blended with methacrylate-based gelatin to make a light-responsive hemostatic hydrogel [104]. Reproduced with permission from Ref. [104]. © Springer Nature, 2019. (d) Catechol moieties generate hydrogen bonds and cation-π interactions between catechol groups and wound tissues to produce adhesion. (e) Catechol moieties are oxidized to form quinone groups, which can interact with amino groups via Michael addition or Schiff base reactions [108]. Reproduced with permission from Ref. [108]. © PLOS, 2016. (f) The reaction of an *N*-hydroxy succinimide (NHS) reactive ester with an amino group to form an amide bond [111]. Reproduced with permission from Ref. [111], © John Wiley & Sons, 2019. (g) Hydrogel patches prepared from acrylic acid, acrylic acid NHS esters, and GelMA absorb surface water upon contact with tissues and then form primary adhesion via hydrogen bonding. This is followed by the reaction of active NHS esters with amino groups within tissues to produce firm adhesion [113]. Reproduced with permission from Ref. [113], © Springer Nature, 2019. (h) A hydrogel covering the surface of injured tissue, producing a single-sided adhesion. (i) A hydrogel producing a double-sided adhesion between injured tissues.

containing catechol groups [105]. Catechol groups not only provide the internal force of such materials but also generate strong hydrogen bonds and cation-π interactions between materials and tissues to enhance adhesion (Fig. 5(d)). Dopamine has been widely used to develop mucoadhesive hydrogel

materials because it contains catechol groups [106]. Lu et al. [106] prepared a blue light-activated adhesive hydrogel by employing a cellulose and dopamine cationic copolymer. The resulting mucoadhesive hydrogel was synthesized via copolymerization under blue light, rapidly stopping bleeding by sealing blood vessels. Moreover, quaternary ammonium cationic polymers also exhibited good antibacterial properties [107]. Catechol moieties are prone to be oxidized by peroxidase to form quinone groups, which can then be conjugated with amino groups via Michael addition or Schiff-base reactions (Fig. 5(e)) [108]. For example, Han et al. [105] grafted dopamine onto gelatin (GelDA) via EDC/NHS coupling. Afterwards, GelDA was mixed with 1-4-phenylenebisboronic acid and graphene oxide (GO), and a GelDA/GO hydrogel was obtained after catalysis by H_2O_2/horseradish peroxidase. This hydrogel displayed high viscous strength (16.2 kPa). TA has been utilized to fabricate viscous hydrogels owing to its abundance of catechol groups [109]. Pan et al. [110] extracted L-3,4-dihydroxyphenylalanine from mussel proteins and grafted it onto CS (C-CHI). Next, a composite hydrogel was obtained by mixing C-CHI, TA, and silk fibroin, which achieved reproducible wet tissue adhesion and excellent hemostatic properties.

The reaction between NHS active esters and amino groups within wound tissues can form an amide bond, which is chemically stable (Fig. 5(f)) [111]. Mucoadhesive hydrogel patches prepared from NHS active esters exhibited strong tissue adhesion. For example, Zhang et al. [112] developed a hydrogel patch for the rapid repair of vascular defects and surgical hemostasis by mixing polymers containing NHS and acrylate with PEG diacrylate and biopolymers. This patch attained rapid and strong adhesion to tissues owing to the interfacial drainage mechanism, where adhesion was enhanced by the synergistic effects of hydrogen bonding and chemical cross-linking. Yuk et al. [113] successfully prepared a new double-sided adhesive tape (DST) by dissolving a mixture of acrylic acid, gelatin, acrylic acid NHS ester, and GelMA, which was followed by cross-linking under UV irradiation and complete drying. DST could quickly absorb moisture from the wet tissue surface, while the carboxylic acid groups and NHS active esters generated hydrogen and covalent bonds with the tissues, achieving strong adhesion within 5 s (Fig. 5(g)). Injectable hydrogels prepared from NHS active esters also exhibited strong hemostatic effects. He et al. [114] manufactured pH-responsive and injectable self-healing hydrogels through free radical polymerization of acryloyl-6-aminohexanoic acid (AA) and AA-g-NHS (AA–NHS) monomers. A comparison of hydrogels containing various concentrations of AA–NHS monomers showed that introducing NHS active esters enhanced hydrogel viscosity. Various hydrogels with tissue adhesive properties can either cover the surface of injured tissue to produce a single-sided adhesion (Fig. 5(h)) or a double-sided adhesion between injured tissues, both of which can be very effective in quickly stopping bleeding (Fig. 5(i)).

4.2 Biological methods

Some hemostatic materials can be used to stop bleeding by directly stimulating the clotting response through biochemical strategies, as shown in Table 1.

4.2.1 Bioactive substances

Some hemostatic materials contain bioactive substances directly involved in blood clotting, which can promote coagulation reactions. For example, platelets can release various bioactive substances associated with hemostasis and wound healing [115]. Lee et al. [116] prepared platelet-derived spherical vesicles from thrombin-activated murine platelets with a high expression of active GP IIb/IIIa. Compared with resting platelets, these spherical vesicles can form larger aggregates in the presence of thrombin and $CaCl_2$. Platelet lysates and aldehyde-functionalized cellulose nanocrystals have been employed to develop intrinsically bioactive hemostatic gels [117]. Wang et al. [118] fabricated a platelet-mimetic body by integrating platelet membranes with functionalized synthetic liposomes.

In addition, thrombin promotes the conversion of fibrinogen to fibrin, activating the coagulation pathway. Therefore, it can be used to prepare hemostatic materials. However, since thrombin is less sensitive to the environment and cannot be stored easily compared with other hemostatic materials

Table 1 Biochemical strategies for achieving hemostasis using various materials.

Hemostatic material		Hemostatic mechanism	Material application
Bioactive materials	Platelets	Involved in the formation of blood clots and release of biological factors	Activated platelet vesicles [116], platelet lysates [117], and bionic platelet bodies [118]
	Thrombin	Promotes fibrin production and activates coagulation pathways	Thrombin starch granules [119, 121, 122], thrombin gauze [120], and thrombin nanofiber membrane [123]
Inorganic materials	Mesoporous silica	Activation factor *XII*	Mesoporous silica nanoparticles [126], mesoporous silica foam [127],
	Kaolin	Activation factor *XII*	kaolin hemostatic hydrogel [128], and kaolin hemostatic sponge [125]
	Polyphosphate	Forms fibrin clots and activates clotting pathways	Polyphosphate hemostatic hydrogel [130]
Metal ion materials	Ca	Promotes thrombin generation	Calcium alginate hemostatic sponge [131], calcium chloride hemostatic hydrogel [132], calcium carbonate nanofiber membrane [134], and calcium zeolite hemostatic cotton [135]
	Zn	Activates coagulation factors *XII* and *VII*, promotes platelet activation	Zinc metal-organic framework sponge [138] and zinc oxide nanofiber dressing [139]
	Ag	Promotes platelet aggregation	Silver freezing gel [141]
	Ce	Promotes blood cell aggregation and platelet adhesion	Cerium-containing bioglass sponge [143]

such as inorganic and metal ionic materials, the encapsulation of thrombin into carriers is required to enhance its stability. For example, Li et al. [119] encapsulated thrombin into hemostatic granules prepared from microporous starch, while Shi et al. [120] encapsulated different metal ions with thrombin after hybridization and then combined them with dopamine-treated gauze to achieve rapid hemostatic performance. Leng et al. [121] introduced thrombin into hemostatic microspheres using an aqueous two-phase carboxymethyl chitin/PEG system via covalent grafting. They obtained biodegradable and size-tunable thrombin-functionalized microspheres that could be used to treat endovascular embolization. The composite hemostatic microspheres prepared by Lu et al. [122] were loaded with thrombin and protonated tranexamic acid (TXA–NH^{3+}). The microspheres were stimulated with TXA–NH^{3+} to decompose and release thrombin. Meanwhile, CO_2 bubbles produced during the decomposition process can propel thrombin into the wound site. Mendes et al. [123] loaded active thrombin into poly(ethylene oxide) nanofibers via electrospinning. Upon contact with a wound, the nanofibrous membranes are degraded by water in the skin or blood, resulting in thrombin release.

4.2.2 *Inorganic non-metallic materials*

Silica and kaolin can activate coagulation factor Ⅻ and endogenous coagulation pathways [124, 125]. In a study performed by Wang et al. [126], TA-loaded mesoporous silica NPs effectively promoted protein adhesion and contact activation pathways of the coagulation cascade. Moreover, an injectable hydrogel sponge prepared using a quaternized hydroxyethyl/cellulose composite hydrogel with mesoporous silica foam can promote hemostasis by activating coagulation factors [127]. Fan et al. [128] prepared a polyacrylamide-tannic acid-kaolin-bonded hemostatic hydrogel, where kaolin not only activated the coagulation pathway but also acted as a physical cross-linking agent to enhance the mechanical properties of the hydrogel. Liang et al. [125] prepared a composite sponge containing kaolin and graphene via a simple hydrothermal reaction, where the role of kaolin in activating coagulation factors was demonstrated. Polyphosphate (polyP) is released by activated platelets, promoting fibrin clot formation and activating coagulation pathways [129]. Cao et al. [130] prepared an antimicrobial hemostatic hydrogel using GelMA, TA, polyP, and Ag NPs. PolyP was released as this hydrogel degraded, thus stimulating coagulation pathways.

4.2.3 *Metal ion release*

Metal ions contained in some materials can be used to activate coagulation reactions. For instance, calcium ions, which are the coagulation factor *IV*, can stimulate the conversion of prothrombin into thrombin. The donors of calcium ions in hemostatic materials include calcium alginate [131], calcium chloride [132, 133], calcium carbonate [134], and calcium zeolite [135]. Dai et al. [131] prepared a porous hemostatic composite material by combining silk protein, gelatin, and calcium alginate. Compared with the material based on silk proteins alone, the developed composite material could adhere to more platelets and showed a relatively shorter clotting time and higher whole blood coagulation capacity.

Zinc is regarded as the second most abundant metal ion in the blood, which can activate coagulation factors Ⅻ and Ⅶ, initiate the coagulation cascade reaction, and promote platelet activation [136, 137]. Xu et al. [138] firmly bound a zinc metal–organic framework (ZIF-8) to a chitin composite sponge via ultrasonic treatment. ZIF-8 can release Zn^{2+}, and its high porosity promotes blood concentration. Wang et al. [139] prepared functional composite dressings using polycaprolactone nanofibers, self-assembled zein coating, and modified ZnO NPs to improve wound management.

Silver NPs have antibacterial effects and can promote platelet aggregation [140]. Zhu et al. [141] prepared a silk-gelatin-methacryloyl/silver cryogel, which could act as an effective hemostatic agent by activating coagulation pathways and promoting platelet adhesion.

Ce-containing mesoporous bioglass can also promote coagulation and platelet adhesion as well as shorten bleeding time [142]. Liu et al. [143] fabricated a composite hemostatic sponge with Ce-containing mesoporous bioactive glass and CS using the freeze-drying method and successfully achieved rapid hemostasis and excellent antibacterial performance.

5 Perspectives and conclusions

Coagulation and bleeding are analogous to the balance between Gossip Yin and Yang in traditional Chinese philosophy. Thrombosis or bleeding can occur if this balance is disturbed. To prevent thrombosis in blood-contacting biomedical devices and achieve rapid and effective hemostasis in the event of vascular damage, the coagulation response of the body to the external environment should be investigated to develop appropriate functional materials. Regarding the design of the surfaces of blood-contacting biomedical devices, hydrogel lubricating coatings can be synthesized using hydrophilic polymers to inhibit protein adhesion on the surface itself [45], where amphiphilic polymers can strongly bind water molecules to form a stable hydration layer and achieve a lubricating effect [48, 52]. Additionally, super-hydrophobic surfaces have been developed to fabricate antithrombotic coatings that can resist protein adhesion [144]. Thrombosis can also be prevented by the production or release of active substances from the coating surface, including nitric oxide [63], heparin [66], and tissue-type fibrinogen activators [70]. The preparation of highly porous hemostatic sponges [88] and powders [91] can be achieved using different techniques so that they can come into full contact with the water in the blood, increasing the concentration of clotting factors and platelets to promote clotting. Hydrogels with enhanced adhesion to the tissue surface can be used to close bleeding wounds quickly [145]. Biologically active substances (such as thrombin [120]), inorganic non-metallic materials (such as kaolin [125]), and metallic substances (such as zinc [138]) can also be employed to prepare different hemostatic materials that biochemically stimulate the coagulation response. Generally, current research on blood-contacting materials focuses on inhibiting or promoting the coagulation response of the body by exerting physical and biochemical effects to achieve the desired biomedical purpose (Fig. 6).

A comparison of various strategies for the development of antithrombotic materials has revealed that drug delivery coatings have non-negligible side effects. Hydrogels with high water content are endowed with excellent lubricating properties and can be applied as a defensive approach to inhibit protein adhesion on the material surface to prevent thrombus formation effectively [146, 147]. Consequently, it is expected that the design of antithrombotic surfaces for biomedical devices will focus more on the study of super-lubricated hydrophilic hydrogel

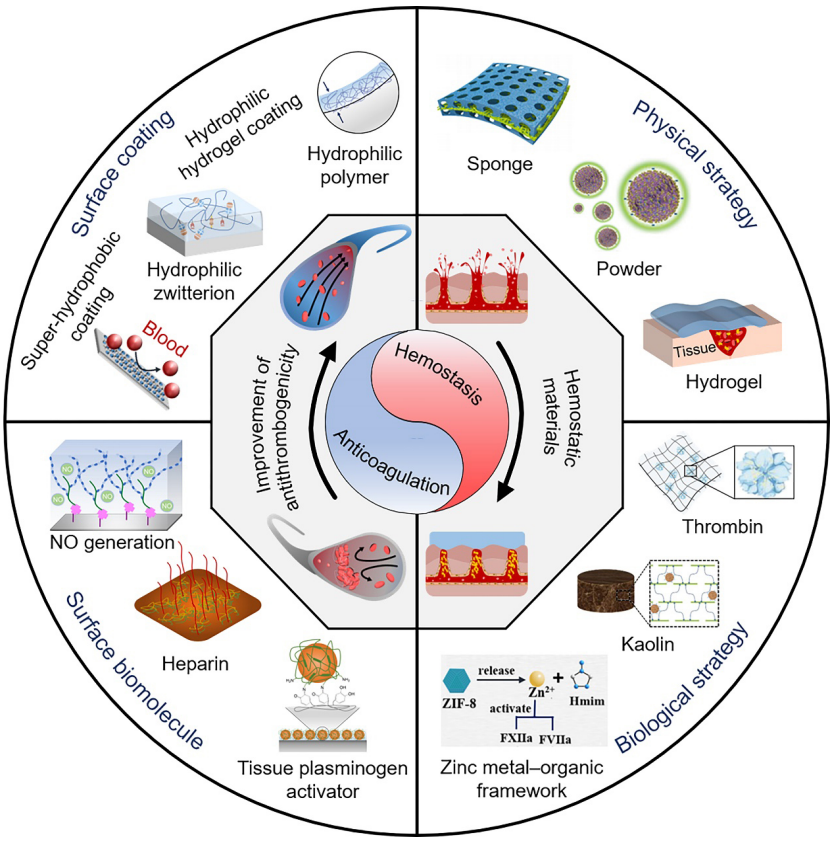

Fig. 6 Diagram showing the design and development of anticoagulant and hemostatic materials [45, 63, 66, 70, 88, 92, 120, 125, 138]. Reproduced with permission from Ref. [45], © John Wiley and Sons, 2020; Ref. [63], © John Wiley and Sons, 2020; Ref. [66], © Elsevier, 2021; Ref. [70], © John Wiley and Sons, 2017; Ref. [88], © John Wiley and Sons, 2018; Ref. [92], © John Wiley and Sons, 2020; Ref. [120], © Royal Society of Chemistry, 2021; Ref. [125], © Elsevier, 2018; Ref. [138], © American Chemical Society, 2020.

coatings. As for hemostatic materials, hydrogels with instantaneous adhesion properties can not only quickly adhere to a tissue surface and close the wound with a rapid and strong hemostatic effect, but may also replace traditional sutures, keeping the wound moist and promoting wound healing [148]. In the future, as research in the directions of preventing coagulation and promoting hemostasis proceeds, the optimized design and development of antithrombotic and hemostatic materials are anticipated to further promote the progress of interfacial science and technologies and achieve clinical benefits.

Acknowledgements

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