

Steps Toward Recapitulating Endothelium: A Perspective on the Next Generation of Hemocompatible Coatings

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Endothelium, the lining in this blood vessel, orchestrates three main critical functions such as protecting blood components, modulating of hemostasis by secreting various inhibitors, and directing clot digestion (fibrinolysis) by activating tissue plasminogen activator. No other surface can perform these tasks; thus, the contact of blood and blood-contacting medical devices inevitably leads to the activation of coagulation, often causing device failure, and thromboembolic complications. This perspective, first, discusses the biological mechanisms of activation of coagulation and highlights the efforts of advanced coatings to recapitulate one characteristic of endothelium, hereafter single functions of endothelium and noting necessity of the synergistic integration of its three main functions. Subsequently, it is emphasized that to overcome the challenges of blood compatibility an endothelium-mimicking system is needed, proposing a synergy of bottom-up synthetic biology, particularly synthetic cells, with passive- and bioactive surface coatings. Such integration holds promise for developing advanced biomaterials capable of recapitulating endothelial functions, thereby enhancing the hemocompatibility and performance of blood-contacting medical devices.

to sustain cells as well as the removal of waste products like carbon dioxide. Additionally, blood cells and enzymatic systems contribute to the body's defense against foreign materials and organisms.^[2,3] To uphold these functions, blood must continuously circulate within the vascular system. By the pumping action of the heart and peristaltic motion blood flows along vessels to reach the most intricate places solely in contact with endothelium, the lining of these vessels. The endothelium provides a very special surface since its interface with blood is the only truly hemocompatible one.^[4,5] It is an active regulator of the complex system that maintains the delicate balance between bleeding and thrombosis.^[5,6] When a vessel is injured, a series of reactions starts to halt unrestricted bleeding. First, platelets rapidly adhere to the damaged tissue, activate more platelets, and form a platelet plug,^[7,8] before subsequently releasing several components and microvesicles that activate the enzymes of the coagulation system (factors). This culminates in the formation

of fibrin supramolecular fibers, which intertwine to hold together the platelet plug preventing any hemorrhage.^[1,9,10] The coagulation cascade is a complex enzymatic pathway involving the conversion of zymogens into enzymes and various amplification events (Figure 1).^[1,11] Due to the injured vessel, tissue factor (TF) is accessible to the coagulation factor VII (FVII). TF binds to FVII (TF-FVII) and activated FVII (FVIIa), present in blood at low concentrations, generating a TF-FVIIa complex

1. Protein Adsorption: The Often Forgotten Evil in Hemocompatibility

Blood is the most complex biological fluid and plays a crucial role in human physiology. It consists of a buffered solution of functional proteins –transporters, coagulation factors, hormones, osmolytes, biomarkers, etc.– DNA, vesicles, and cells.^[1] These components are tasked with a myriad of functions, including the transport of oxygen, nutrients, and signaling molecules

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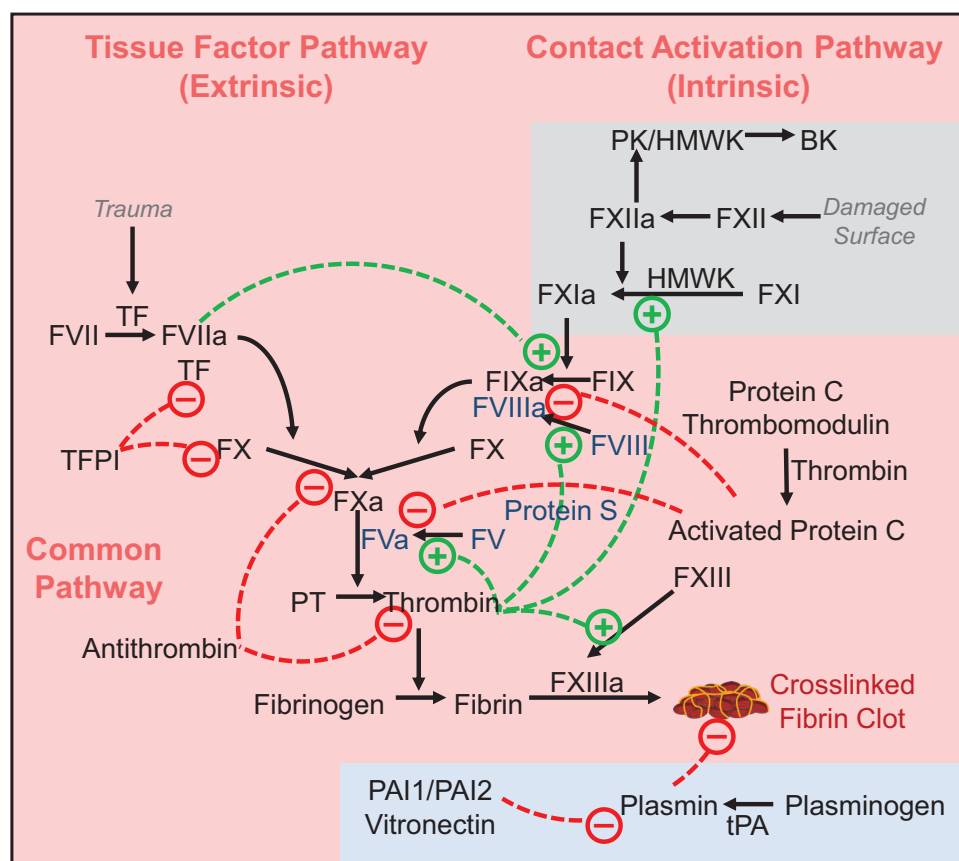


Figure 1. Overview of the coagulation cascade (intrinsic and extrinsic pathways) including the feedback loops. Adapted from.^[11,15]

that activates TF-FVII into more TF-FVIIa. This complex activates FX into FXa, which together with FVa cleaves prothrombin into thrombin.^[11,12] This is the key protease that cleaves fibrinogen into fibrinopeptides, which polymerize to form fibrin, the main component of the clot. Moreover, the generation of thrombin is responsible for several positive feedback loops, e.g. activation of factor XIII (FXIII) that crosslink fibrin stabilizing the clot.^[11] But this physiological and life-saving process cannot run unchecked. Coagulation must be restricted to the exact place where injury occurs to avoid potentially occluding vessels or leading to the release and formation of thrombi, posing a significant risk to life. Here, the endothelium acts also as a regulator by mediating different inhibitors to tightly modulate coagulation. The three main inhibitors are: tissue factor pathway inhibitor (TFPI), thrombomodulin (TM), and antithrombin III (ATIII) (Figure 1).^[11] TFPI is secreted by activated platelets and the vascular lumen to inhibit the TF-FVIIa complex.^[1] TM and ATIII are inhibitors of thrombin.^[1] Thrombin binds to TM generating the thrombin-TM complex altering its substrate specificity and halting the cleavage of fibrinogen. Moreover, the thrombin-TM complex activates protein C resulting in degradation of FVa and FVIIIa, and cofactors of FIXa and FXa.^[1] These cofactors are also inhibited by ATIII leading to a reduction of thrombin production.^[1] The endothelium not only controls the extent to which the clot grows but also has the capacity to “decide” when a clot is no longer needed. Concurrently with the heal-

ing of the vessel, the clot is digested by plasmin, which is generated when tissue plasminogen activator (tPA) or urokinase-type plasminogen activator (uPA) activate plasminogen.^[13,14] These enzymes are produced by the endothelium. This tight and incredible intertwined balance between blood activation – inactivation – fibrinolysis is called hemostasis.^[8] Thus, the endothelium is much more than a simple stealth-inert lining but offers an interface that can communicate with blood and modulate its functions. The endothelium-blood tandem is what sustains the hemostatic balance which is fundamental for life.

But blood may also come into contact with surfaces –natural or synthetic– different than endothelium as in blood-contacting medical devices. In this case the intrinsic pathway of the coagulation system is initiated through the activation of coagulation factor XII (FXII), plasma kallikrein (PK) and its co-factor High-Molecular-Weight Kininogen (HMWK) – the key components of the contact activation (Figure 1). Thus, these surfaces, even if designed to be “stealth”, all inevitably cause the activation of hemostasis but contrary to endothelium are not capable of modulating and stopping coagulation after it has begun.^[16] This leads to the formation of clots which cause malfunction of the device, e.g. clogging of pumps and catheters, false results in biosensors, reduction of performance of membranes for hemodialysis or oxygenation, and occlusion of stents, just to mention a few (Figure 2).^[17]

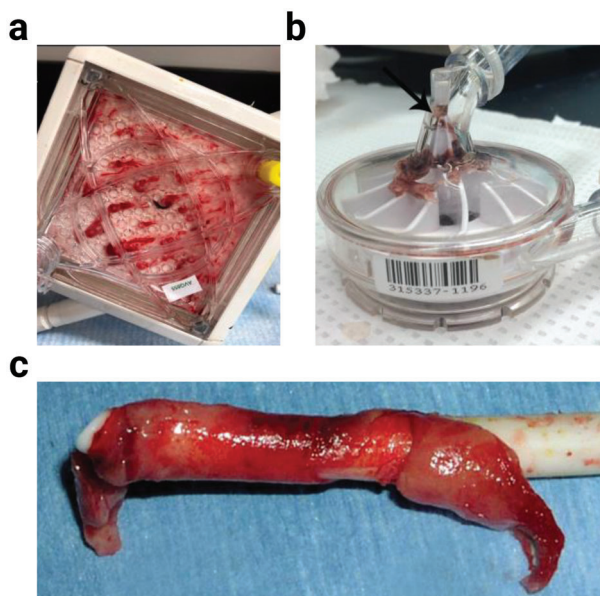


Figure 2. Selected examples of clot formation in blood-contacting medical devices. a) Thrombus burden in an extracorporeal membrane oxygenator. A large number of clots can be observed on the surface of the hollow fiber membrane. Reprinted with permission from.^[18] Copyright 2020, M. Chlebowski et al, published by SpringerNature. b) Thrombus formation in a centrifugal pump of a clinical circuit. Reprinted with permission from.^[19] Copyright 2016, SAGE Publications. c) Fibrin sheath formation on a venous catheter. The fibrin sheath poses risks during withdrawal of the catheter, particularly in thin catheters for neonates, where the vessel can be damaged, or the catheter broken inside. Reprinted with permission from.^[20] Copyright 2016, SAGE Publications.

Furthermore, in those devices that are indwelling, directly connected to the circulatory system, there is an activation of inflammatory reactions and an overactivation of coagulation that disseminates, leading to a more procoagulant condition.^[11,16,17] On top of that, the flow can dislodge formed clots, which can obstruct vessels with the concomitant risk of embolism and stroke. These complications combined with the poor health conditions of the patient can lead to elevated mortality rates, as well as increased healthcare costs associated with additional interventions and treatments.^[21] The mortality rate for patients requiring extracorporeal membrane oxygenation (ECMOs), for example, is 31%,^[22] while patients on hemodialysis have a mortality rate of 15%–20% after one year and $\approx 50\%$ after five years.^[23] Those patients with stents additionally face a mortality rate of 15% after the first year, rising up to 34% at 10 years.^[24] Such risks have become particularly critical owing to the use of blood-contacting medical devices skyrocketing compared to a few decades ago.^[25] Their global impact is significant, with several million cardiac stent implantations,^[26] 2.7 million patients requiring hemodialysis,^[27] 250 000 with heart valves,^[28] 18 000 undergoing ECMO,^[22] and 8000 with ventricular assist devices (VAD)^[29] annually. Therefore, the need to introduce new concepts that advance the hemocompatibility of surfaces and coatings beyond the present standard is of increasing importance.

Research into surface hemocompatibility has traditionally placed the focus on platelets as the main culprit of coagulation because they initiate coagulation inside the vessels (*vide supra*).

However, the activation of hemostasis due to foreign surfaces involves protein adsorption, activation of platelets, leukocytes, the activation of kinin-kallikrein, complement system, etc., all of which are highly intertwined (**Figure 3a**). Coagulation begins at the molecular level, when proteins adsorb at the surface. The presence of an artificial surface manifests as a new thermodynamic phase in contact with blood. This contact results in an interfacial energy cost. The interfacial energy can be interpreted as the discomfort of blood being contacted with the surface, resulting in a driving force for molecules to adsorb and reduce it. The pioneering work of Andrade, Anderson, Vroman, Vogler and others elucidate the importance of surface proteins in the extent, type, dynamics and non-equilibrium effects.^[2,30–40] Subsequent work from Weitz, Maas, Siedlecki, Latour and others highlighted that there was more than just the adsorption but the way proteins were presented after adhering, including exposing different epitopes or mechanocleavage of bonds.^[17,25,41–52] Proteins, present at very high concentration in blood (70 g L^{-1}),^[53] are polymerized amino acids soluble in water owing to their given sequence, which allows folding into secondary and tertiary structures. Their structures and folding make proteins the most promiscuous of macromolecules, capable of adsorbing to nearly any surface by changing their conformation and exposing those residues that best interact with a surface.^[16,17,54] Protein adsorption begins at the first second of contact, when the most abundant ones arrive and populate the surface.^[17,32,35–37,55] Subsequently, those with higher affinity for the surface partly replace the initial ones in a competition between kinetics and thermodynamics referred to as the Vroman effect.^[32,35–37,55,56] The process of seemingly reversible protein adsorption is almost impossible to completely revert because the increasing force of adhesion changes the protein's conformation, disrupting its secondary structure^[44,51,52,57] and even in some cases cleaving covalent bonds.^[44,58,59] The latter is a strategy used by some zymogens to become active proteases.^[44,58,59] From a kinetic point of view, these changes in conformation and secondary structure almost completely stall desorption turning the process into quasi-irreversible.^[60–63] Thus, protein adsorption, usually considered unimportant, is the key event where the adsorbed proteins act as biological transducers to inform the living counterpart of the presence and nature of a surface. This, in itself, can trigger several events, such as platelet activation, thrombin generation, complement activation and leukocyte activation (**Figure 3a**).^[64]

At the very beginning the most abundant plasma proteins –albumin and fibrinogen– adsorb on the surface.^[17] Unfortunately, such adsorption is often regarded as benign, even sought after as a means to passivate surfaces with the argument that these proteins are present in blood and therefore must be innocuous to it.^[74] However, this is far from reality as the adsorption process changes their conformation turning them into strong activators of coagulation.^[60] For example, albumin –a protein merely associated with maintaining the osmotic balance– once adsorbed exposes regions that facilitate specific platelet adhesion and activation through GPIIb/IIIa receptors.^[52] Thus, the amount of platelet activation correlates with the loss of secondary structure.^[75–77] Similarly, the adsorption of fibrinogen increases its affinity for the $\alpha\text{IIb}\beta_3$ integrins at the surface of platelets.^[78] In this way, adsorbed fibrinogen serves as an activator for platelet adhesion, where even few ng cm^{-2} of adsorbed fibrinogen are suffi-

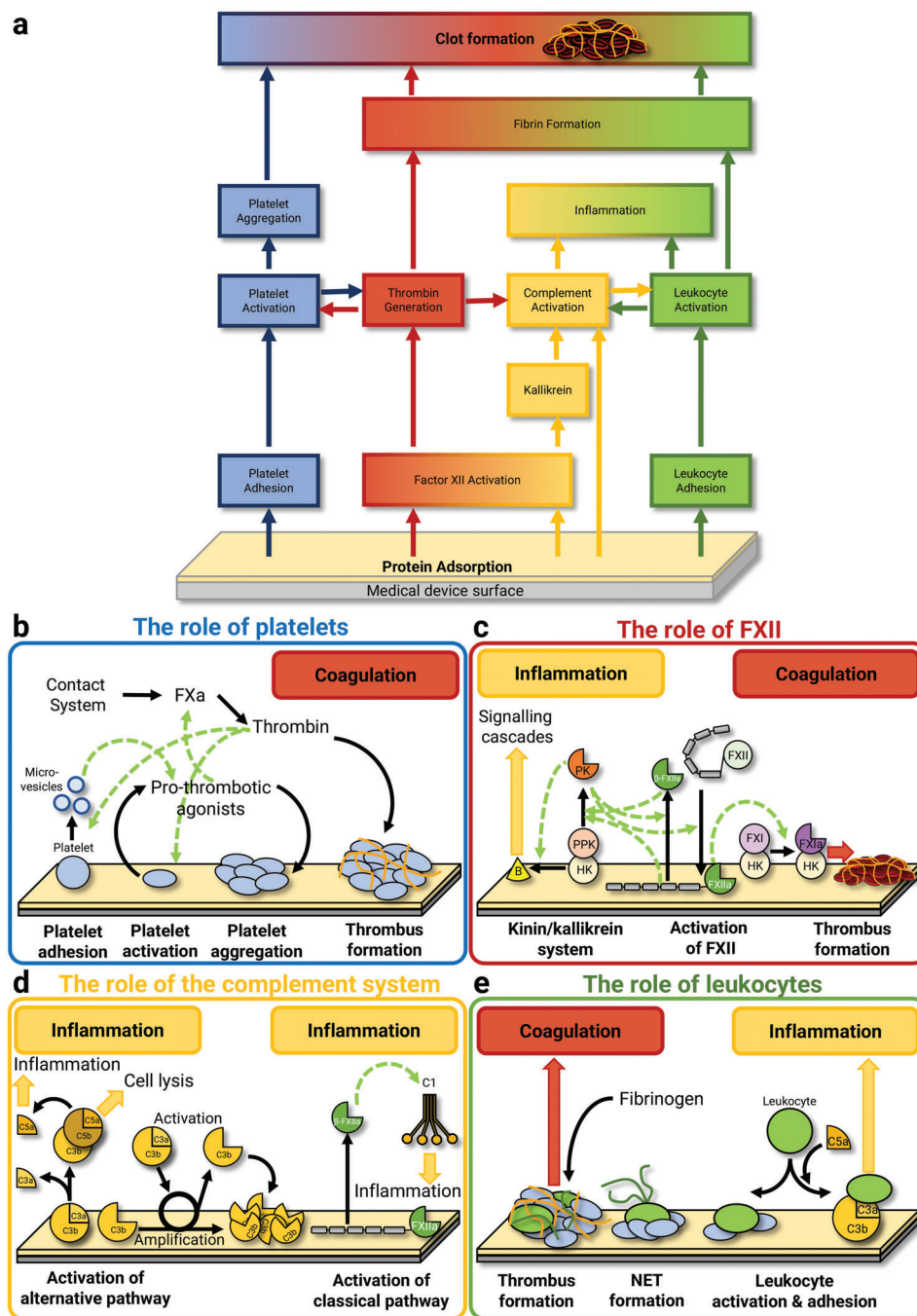


Figure 3. Scheme of the procoagulant events present on the surface of blood-contacting medical devices. a) Protein adsorption is the key event being the biological transducer of the presence of a surface. It triggers several events, such as platelet activation, thrombin generation, complement activation, and leukocyte activation. All these procoagulant events occur simultaneously and are highly interconnected resulting in failure of the hemostatic system and uncontrolled clot formation directly grown from the surface of blood-contacting medical devices. b) Protein adsorption initiates platelet adhesion triggering platelet activation and aggregation, pivotal steps in the formation of a clot.^[17,65] Activated platelets catalyze thrombin production, solidifying the clot formation process while continuing to activate more platelets. c) The adsorption of FXII through its heavy chain result in its unfolding and mechanical activation into α -FXIIa,^[44] which cleaves surface-bound PPK into PK and surface-bound FXI into FXIa. Activation of FXI leads to a cascade of coagulation reactions (intrinsic pathway) at the surface.^[41,43,44,66,67] Generated PK on the other hand cleaves FXII into more α -FXIIa and simultaneously releases β -FXIIa.^[44,68] Its release from the surface is responsible for the generation of more PK and the dissemination of coagulation. Moreover, the activation of the kallikrein/kinin system induces further activation of the complement system and an inflammatory response.^[69] d) The complement system can be activated by both the kallikrein/kinin system as well as via the adsorption and activation of complement factors.^[70] Once adsorbed complement component C3b leads to an amplification of complement activation.^[71] e) Leukocytes play a crucial role in clot formation; their adhesion to adsorbed proteins via their NETs on the surface results in activation further facilitating clot formation.^[72,73] On the other hand, activated leukocytes interact with the complement system, thus signaling to the body's defense mechanisms.

cient to mediate platelet adhesion.^[17,65] Those adherent platelets become activated and release adenosine diphosphate (ADP) and thromboxane A₂, among many other bioactive substances.^[17] This results in an amplification mechanism of adhesion, activation, and aggregation of platelets on the surface turning it thrombogenic (Figure 3b). Besides albumin and fibrinogen, other proteins, such as fibronectin, von Willebrand factor (vWF), and vitronectin also undergo adsorption-induced conformational changes.^[46,79,80] These proteins play pivotal roles in mediating platelet adhesion and activation.^[46,79,80] Additionally, apolipoproteins – proteins of the lipid metabolism – were found to adsorb on the surface of blood-contacting medical devices.^[81–84] These proteins are associated with the modulation of platelet and coagulation activation,^[85] as well as prothrombotic properties and the risk of venous thromboembolism.^[86] Moreover, the adsorption-induced alterations also influence the activation of factor XII (Hageman factor, FXII), the essential initiator of intrinsic blood coagulation processes.^[87] FXII is the circulating zymogen, which can be activated into α -FXIIa or β -FXIIa. The adsorption of FXII leads to its mechanical activation into α -FXIIa, a disulfide-linked, two-chain active enzyme, that remains adsorbed. This acts as a surface immobilized catalyst to induce the intrinsic coagulation pathway by activating surface-bound FXI, causing thrombin production and clot formation (Figure 3c).^[44] Thrombin also activates platelets, which then release microvesicles that provide the necessary surface for the activation of other coagulatory factors (Figure 3b).^[11] Additionally, α -FXIIa activates surface-bound plasma prekallikrein (PPK) into plasma kallikrein (PK) which leads to further activation of FXII and the simultaneous cleavage of α -FXIIa into its low molecular weight fragment β -FXIIa.^[44,68] The latter is released from the surface because it misses the heavy chain. Soluble β -FXIIa activates more PPK and generates more FXIIa.^[68] Thus, it is responsible for the autocatalytic amplification of FXII activation.^[47] This amplification means that even a minute amount of it can have a profound effect in the activation of coagulation. Thus, FXII activation is considered the root cause of surface-induced coagulation in blood-contacting medical devices.^[17,45,66,88,89] Besides that, PK liberates kinins, such as bradykinin, from high molecular weight kininogen (HMWK) that binds to cells causing systemic inflammation. This process is also known as the kallikrein/kinin system.^[42,43,45,90] Moreover, the presence of an artificial surface can induce the activation of the complement system. Proteins from the complement system, such as C3b and C5b, adsorb on the surface and can be activated in a similar way as FXII. Surface-bound C3b can form a proteolytic complex that activates more C3 resulting in the generation of more C3b that binds to the surface (Figure 3d).^[71] This autocatalytic amplification mechanism accelerates protein adsorption and activates the alternative pathway of the complement system. This activation causes proinflammatory reactions and can elicit an immune response.^[82,83,91] On top of that, they can signal to polymorphonuclear leukocytes (PMNs) and later to macrophages inducing inflammation. The activation of the complement system results in a cascade of reactions and the release of C3a, C4a, and C5 that mediate inflammation and act as chemoattractant for PMNs and monocytes. In the context of blood-contacting medical devices, complement system activation primarily occurs through the alternative and classical pathways, largely influenced by protein adsorption (Figure 3d).^[70] Moreover, the complement sys-

tem and the coagulation cascade are highly interconnected as e.g. platelet activation and aggregation is induced by C3a or thrombin can activate C3 and C5.^[58,92] Furthermore, leukocyte activation is induced not only by the adhesion to the surface, but also by the interaction with adsorbed proteins, and chemical signaling of activated platelets (P-selectin, platelet factor 4), components of the complement system (C3a and C5a), and thrombin.^[93] Once they are activated, they release neutrophil extracellular traps (NETs) that are used to bind to the artificial surface which also provides an anchoring point for more platelets to bind (Figure 3e).^[72,73]

The previous paragraph as well as Figure 3a evidence that all these processes occur simultaneously, are highly interconnected, and exhibit autocatalytic amplification reactions as well as redundant pathways, making it difficult, if not impossible, to stop them once they are set in motion. Consequently, even minute amounts of protein adsorption can disrupt the hemostatic balance and trigger uncontrolled formation of a clot which is directly grown from the surface of blood-contacting medical devices. Not only does this lead to device failure but also triggers cascading reactions in the body that may impact vital organs.

2. Anticoagulants – Friend or Foe of Blood-Contacting Medical Devices

In clinical practice, anticoagulants are administered to mitigate the burden posed by a foreign surface. The overall idea is that these molecules can interfere or stop some of the pathways of coagulation preventing its progression.^[94] Toward this aim, strategies operating via different mechanisms of action have been introduced. These include: i) Vitamin K antagonists (VKAs);^[95] ii) heparin and its fragment derivatives^[96,97] and more recently iii) direct oral anticoagulants (DOACs).^[98] i) VKAs, which include warfarin, phenprocoumon and acenocoumarol operate as indirect anticoagulants.^[99] They form competitive inhibitors for the integral membrane protein vitamin K epoxide reductase.^[100] This enzyme catalyzes the conversion of vitamin K to its active co-factor form for γ -carboxylation – a post translational modification essential to the structural stability of coagulation factors FVII, FIX and FX and prothrombin.^[101] ii) Alternatively, the anticoagulant activity of the naturally occurring glycosaminoglycan, unfractionated heparin, derives from a specific pentasaccharide sequence which is able to bind to the serine protease inhibitor ATIII. This interaction induces a conformational change in the inhibitor, enhancing its activity toward thrombin, FXa and FIXa.^[102] Low-molecular weight derivatives such as enoxaparin have since been developed with more predictable anticoagulant activity compared to the unfractionated form owing to more favorable pharmacokinetic properties; however, these still carry the threat of heparin-induced thrombocytopenia (HIT) which leads to platelet consumption.^[103,104] To reduce this risk, researchers developed a lower molecular weight analogue, fondaparinux, having the same pentasaccharide sequence binding to ATIII but lacking the binding site for thrombin. Thus, fondaparinux targets FXa but not thrombin, having a more predictable profile.^[105,106] Together, VKAs and heparin have formed the mainstay of anticoagulant therapy for over 50 years.^[94] Their narrow therapeutic range, however, has hampered their application with routine monitoring of patients and dose adjustments required to ensure therapeutic levels of anticoagulation.^[107] iii) DOACs constitute a

newer, more predictable alternative to VKAs and heparin that can be administered in fixed doses and have single targets in the coagulation pathway.^[108] They encompass inhibitors of FXa (rivaroxaban, apixaban, edoxaban, and betrixaban) as well as the inhibitor of thrombin (dabigatran).^[109]

While all these agents can effectively mitigate thrombosis; they are aimed at inactivating enzymes at the final stages of the coagulation cascade and thereby have an increased likelihood of perturbing systemic hemostasis.^[110] This can shift the original problem to the other extreme, presenting the patient with hemorrhagic complications.^[111] Moreover, these strategies are based on the myopic idea of coagulation excluding any significance of the surface. Even if some of the pathways for coagulation are blocked, different ways exist for the clot to continue to grow, *e.g.* through the contact system, and surface properties continue to become impaired. Conversely, the most advanced efforts toward anticoagulation therapy in the context of blood-contacting devices are focused on targeting the inactivation of FXIIa and FXIa and stopping coagulation at its root cause.^[15,88,112–118] Despite demonstrating promising results in terms of selectivity and safety in animal models,^[119–121] the inhibition of FXIIa and FXIa still excludes the fact coagulation may be initiated by other means and that the material properties may become impaired by the other reactions highlighted in the previous section.

3. Stealth Surfaces: Toward Prevention of Blood Activation

Since the early stages of biomaterial development, the importance of yielding blood-material interactions with coatings has been recognized. The first examples of these were produced by incubating the materials with blood to create a layer from blood components with the hope of improving further interactions. With the recognition that these adsorbed proteins actually could have a negative effect,^[30,31] efforts shifted toward reducing the driving force to protein adsorption. Whitesides established four minimal requirements for a surface to repel proteins: it should i) be hydrophilic, ii) include hydrogen bond acceptors but iii) exclude donors, and iv) have a neutral overall electrical charge.^[122,123] The hydrophilization of the surface reduces the interfacial energy between blood and the material, which usually involves generating hydrophilic groups either by physicochemical treatments or by applying hydrophilic coating (Figure 4a). This includes plasma treatment,^[124–126] or depositing coatings from hydrophilic molecules bearing zero net charge. Examples include physisorbed polymers,^[127–129] self-assembled monolayers (Figure 4b),^[130–134] plasma polymerized films,^[125,135] etc. These approaches have only succeeded to reduce adsorption from model solutions of a single protein but their repellency is rapidly overcome when in contact with complex media such as serum, plasma, let alone blood.^[136] Improved protection to fouling could be achieved when using high density end-grafted hydrophilic polymer, referred to as polymer brushes (Figure 4c).^[137–139] Their high water content, capacity of the end-groups to interact with water and stretch and crowded conformation results in an enthalpic barrier^[137,140,141] and entropic shielding.^[137,142–144] Moreover, the high density of polymer brushes displays peculiar effects such as the complete exclusion of the very same polymer as a melt applied on top, the so call autophobic effect.^[145,146]

They have been shown to prevent the primary adsorption of macromolecules at their substrate by excluding transport across their chains as well as preventing tertiary adsorption on top of them.^[143,144] Poly(ethylene glycol) (PEG) brushes were among the first of these macromolecular structures to be explored.^[147–149] PEG is a hydrophilic polymer with very high flexibility, which has been highly scrutinized^[130,132,150] and is currently used in the majority of applications, where antifouling properties are sought. However, some recent studies have shown that some proteins, such as apolipoprotein B-100, complement C3, fibrinogen, and albumin, may specifically interact with the PEG surface mediating the adsorption of other blood plasma proteins resulting in activation of the complement system, inflammation and the activation of the coagulation system.^[81–84,151,152] Polyoxazolines have become a promising alternative for PEG.^[153] Recently, the use of cyclic polymer topology based on PEG or polyoxazolines demonstrated the formation of denser brushes resulting in a higher steric barrier that prevents the adsorption of proteins.^[154,155] Whitesides et al. introduced the idea of using kosmotropic groups to reduce fouling.^[134] These groups are capable of binding strongly to water and thus preserving the structure of proteins in close proximity to them.^[134,156–158] Betaines are among the most widely studied kosmotropic groups,^[159] including phosphorylcholine,^[160–163] sulfobetaine,^[136,164,165] and carboxybetaine.^[136,165–172] The latter, having a propyl spacer between the cation and the anion, has shown almost complete repellency to plasma proteins.^[167,171,173–175] Other hydroxyl-functional acrylamides were later introduced demonstrating very high^[150] and even complete prevention of fouling in the case of *N*-(hydroxypropyl) methacrylamide (HPMA).^[171,173,174,176–178] Subsequent experiments, however, have shown that HPMA could lead to plasma fouling by activation of the complement system resulting in possible undesirable immune reactions and inflammatory responses.^[82,179,180] Thus, so far the best compatibility with blood has been achieved with zwitterionic brushes (Table 1).

Despite the clear success of polymer brushes in reducing protein fouling and improving hemocompatibility their translation to medical devices, such as membrane oxygenators, pumps, etc. is challenged by their complex synthesis. Three different techniques have been developed to synthesize polymer brushes: grafting-from, grafting-to and grafting-through.^[137] The grafting-from technique involves initiating polymerization directly from the substrate surface, where surface-bound initiators trigger the growth of polymer chains outward.^[137] The necessary high grafting densities are usually achieved by the simultaneous grafting of polymer chains from the surface using controlled radical polymerizations.^[208–210] Such stringent conditions and the need for specialized material-specific chemistries to anchor the initiators make their translation to industry not yet realistic. This has propelled research toward other synthetically less demanding approaches to mimic their outcome. In contrast, the grafting-to technique attaches pre-formed polymer chains to a functionalized substrate, where polymers with reactive end groups bond covalently to complementary surface groups.^[137] This method simplifies polymer synthesis since polymer chains can be characterized prior to attachment, ensuring known molecular weights and functionalities. Grafting-to usually leads to poor grafting density, although this can be ameliorated if the excluded volume interactions during the grafting process are at a minimum using,

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Table 1. Summary of the most utilized polymers for antifouling polymer brushes.

Polymer	Examples	Outcome	References
Poly(ethylene glycol)	Poly(ethylene glycol), Poly(oligo(ethylene glycol) methyl ether methacrylate), Poly(oligo(ethylene glycol) methyl ether acrylate)	Polymer brushes based on this polymer are widely used to provide antifouling properties. These properties stem from the enhanced hydration through hydrogen bonds by its ethylene glycol repeating unit. However, it has been demonstrated that some proteins specifically interact with this polymer mediating the adsorption of other blood plasma proteins. Moreover, there are antibodies against it.	[81–84, 130, 132, 147–152, 181–184]
Poly(vinylpyrrolidone)	Linear, bottlebrush	Its polar lactam structures can tightly bind water molecules resulting in a robust hydration layer that effectively repels proteins. It is used in various biomedical applications.	[185–189]
Polyglycerol	Linear, hyperbranched	Environmentally friendly alternative to PEG. Its multiple hydroxyl groups are responsible for its hydrophilicity, which results in superior antifouling properties compared to PEG.	[190–195]
Poly(2-oxazoline)s	Poly(2-alkyl-oxazoline), Poly(2-aryl-oxazoline)	Their hydrophilicity results in protein repellency. Brushes can be formed linear, as bottle-brush or comb-like and cyclic. Especially, the cyclic structure presents a strong entropic barrier.	[153, 196–202]
Sulfoxide polymers	Poly(2-(methylsulfinyl) ethyl acrylate)	These polymers contain numerous sulfoxide groups within their structures. The highly polar nature of these groups leads to strong interactions with water molecules, which enhances their antifouling properties. They have demonstrated reduced adhesion of BP proteins and platelets.	[203–207]
Zwitterionic polymers	Phosphorylcholine (PC), Sulfobetaine (SB), Carboxybetaine (CB)	These zwitterionic polymers are known for their kosmotropic behavior and showed almost complete repellency to blood plasma proteins in different studies. The ranking of their antifouling properties has been demonstrated as polyCB > polySB > polyPC.	[136, 160–163, 165–175]
Other hydrophilic polymers	Poly(<i>N</i> -(2-hydroxypropyl) methacrylamide	Inspired by the success of this polymer in drug deliver, this polymer was introduced as brushes presenting high or even complete prevention of protein adsorption. Recent studies have shown that the hydroxyl groups may be responsible for the activation of complement system for some donors.	[82, 150, 171, 173, 174, 176–180]

for example, in theta or poor thermodynamic solvents or performing the grafting from melt where polymer behave as if in a theta solvent.^[211–215] Another approach makes use of graft-copolymers where the hydrophilic polymers are attached to a backbone that has affinity to the surface and binds either by physical interactions (ionic)^[196,216–219] or through chemical promoters (Figure 4c), such as phenylazide, alkylphosphates, catechols, silanes, etc.^[216,220–225] However, steric hindrance between large polymer chains reduces the achievable grafting density, and the thickness of the brush layer is typically limited. A less common technique is the grafting-through technique, based on chain-grow polymerization where growing chains in solutions incorporate a monomer that had been linked to a surface thereby incorporating the chain.^[137] Controlling the final thickness and density of these attached polymer can be challenging and not easily to reproduce. Rühe et al. introduced an alternative strategy termed ultrathin surface-attached hydrogels (Figure 4d).^[226] The hydrogels are formed from hydrophilic polymers with a small fraction of comonomers that can be photochemically or thermally activated to generate reactive intermediates. By deposition of these polymers, the reactive intermediates form C–C bonds with

both the substrate and neighboring chains creating a cross-linked polymeric network covalently bound to the surface.^[227–230] Common cross-linking groups include aromatic carbonyls, azides, diaziridines, or diazocarbonyls.^[223,231–234] The benzophenone group, activated by UV irradiation, is widely used for cross-linking.^[227,230] Other functional groups could also be utilized, however, non-covalent bonds usually defy the strong connection with the substrate as needed to have only normal swelling.^[226] We demonstrated that these ultrathin surface-attached hydrogels exhibit dangling chains that segregate in water to the interface forming a brush-like structure^[230] on top of a thin hydrogel that regulates the hydration and stretching of the former.^[235] Moreover, they cannot be penetrated by other macromolecules due to their restricted swelling orthogonal to the substrate.^[236] These coatings have served to improve compatibility with blood as well as general antifouling and lubricious surfaces.^[226,237–240]

A more recent approach has used protein-polymer hybrids to facilitate the modification of various materials and surfaces without any prior treatment (Figure 4e). These hybrids consist of a surface-affine protein (liquid-chromatography-peak-I) and an antifouling polymer block.^[229,241–243] Both parts are

hydrophilic and molecularly dissolved in water. Upon contact with a surface, the protein adapts its conformation to maximize weak interactions with the surface resulting in an effective quasi-irreversible binding,^[243,244] while the polymeric chains segregate away from the surface. This process leads to an oriented immobilization,^[242] where only the protein adsorb, and the adsorption energy is sufficient to overcome the entropic penalty of generating the brush. These coatings excelled at preventing protein adsorption^[229,241–243] and bacterial adhesion^[229,243] but their compatibility with blood is yet to be determined.

While these advancements in macromolecular engineering and nanotechnology have propelled the development of coatings far beyond conventional clinic standards, their passive protection remains insufficient to ensure true hemocompatibility. At the same time, current anticoagulant therapies fail to address the role of the surface in coagulation and the different pathways through which hemostasis can be activated. Therefore, holistic approaches that consider both the need for stealth properties of surfaces and the modulation of coagulation are seen as a challenging but more realistic route toward true improvements in surface hemocompatibility.

4. Biointerfaces that Modulate Hemostasis, Second Generation of Hemocompatible Surfaces

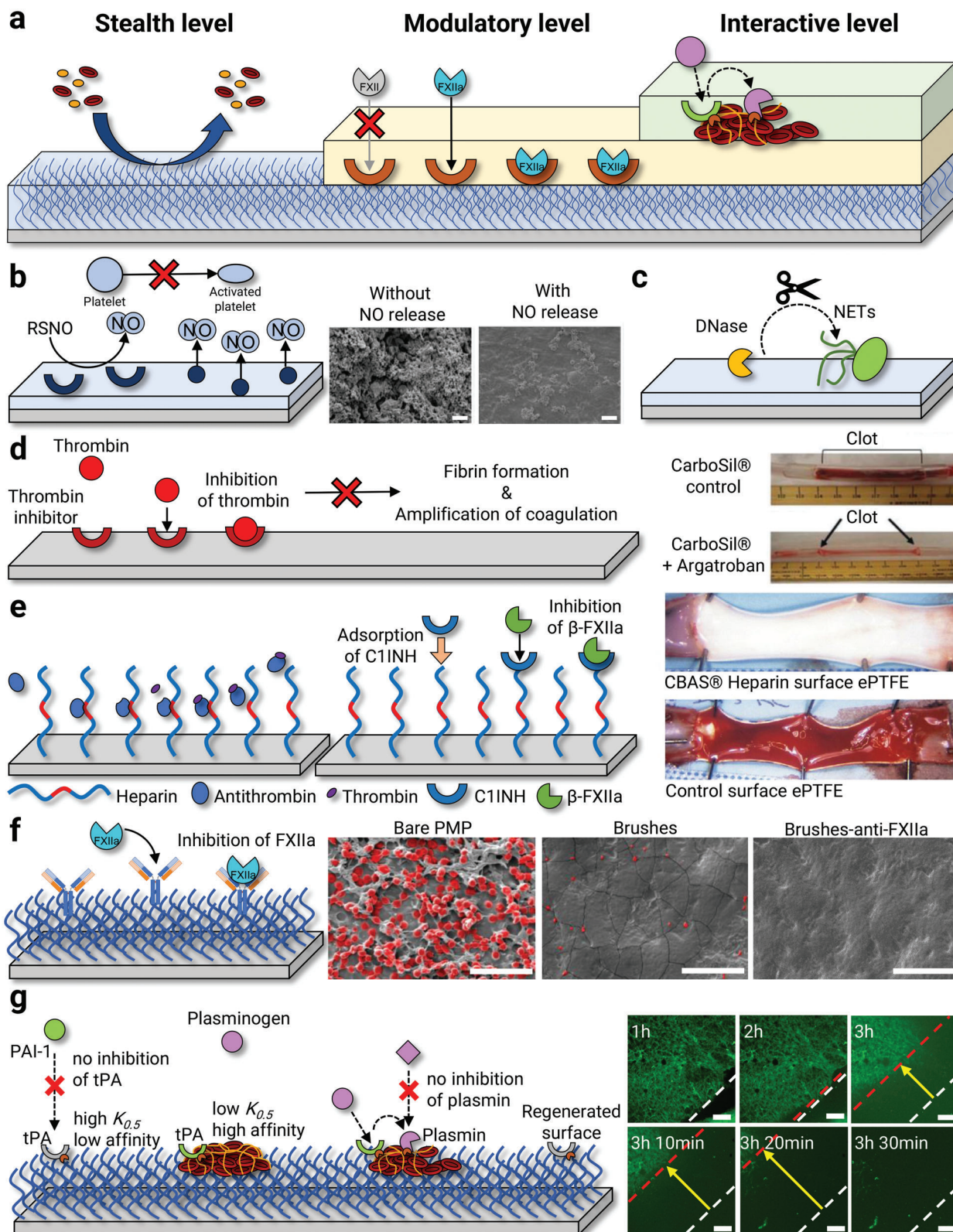
The lining of blood vessels, the endothelium, is stealth to blood, modulates the activation of hemostasis through the different pathways and even has the ability to direct the disintegration of clots. These three distinct functional levels synergistically integrate to create an interface along which blood can flow undisturbed. Contemporary research on hemocompatible coatings has aimed to incorporate these levels in the design of the interface between materials and blood (Figure 5a and Table 2). For the stealth level see Section 3.

For the modulatory level, efforts have been focused on preventing or controlling the surface induced coagulation by targeting platelets, leukocytes, the complement system and mainly on the coagulatory system. For example, the provision of nitric oxide (NO) gas has been explored to turn activated platelets to their quiescent state (Figure 5b).^[247,248] Various coating strategies have been introduced either based on natural or engineered enzymes or synthetic catalysts that convert endogenous substrates in blood into NO.^[249–252] The most prominent examples are S-nitrosothiols^[253–256] and N-diazoniumdiolates,^[257,258] which resulted in an antiplatelet function by the localized release of NO.^[255,257,259] Not only are platelets able to adhere to the surface, but also neutrophils by utilizing their DNA NETs to hold from surfaces.^[260] To circumvent this, DNase, an enzyme that catalyzes the hydrolysis of DNA into oligonucleotides and small molecules, has been immobilized on coatings to reduce neutrophil adhesion or even expel them from the interface (Figure 5c).^[260,261]

However, as alluded in Section 1, the biggest challenge is the modulation of coagulation at the surface, a seemingly unsurmountable task. Toward this aim, a number of works have demonstrated the immobilization of different coagulation factor inhibitors on coatings. The first concepts aimed at inactivating thrombin (Figure 5d) with the rationale that

this enzyme produces the building blocks for the formation of the clot^[262–269] using, for example, hirudin,^[262,263] thrombomodulin,^[252,264,265] or synthetic inhibitors such as benzamidines,^[266,267] Argatroban,^[268] or D-Phe-Pro-Arg-chloromethylketone.^[269] The most successful example is the use of heparin.^[69,270–272] Initially, heparin was either physisorbed or chemically-linked to the surface through functional groups along its backbone. This approach resulted in the hydrophilization of the surface and an overall modest improvement of the compatibility with blood.^[273] A drastic improvement in compatibility, however, was observed when heparin was ligated from one end, constituting the most widely used coating technology for blood-contacting surfaces (Carmeda).^[274–276] Hundreds of thousands medical devices coated with heparin are used every year including Carmeda Bioactive Surface, DuraFlo II, BioLine, AOTHEL, AVECOT and Corline coatings.^[274,277–280] The improved hemocompatibility was proposed to be associated with a higher mobility of the heparin chain that would enable the simultaneous capture of antithrombin and thrombin, leading to the inactivation of the latter (Figure 5e).^[277] The proposed mechanism tacitly assumes that the immobilized heparin works in the same way as when molecularly dissolved. Although, later evidence suggests the effectiveness of immobilized heparin could be related to its ability to sequester inhibitors of FXIIa naturally present in blood, particularly the C1-esterase inhibitor (C1INH)^[69,270,281–283] that deactivates β -FXIIa.^[284–286] In this way, immobilized heparin, through the capture of C1INH, stops the autocatalytic amplification mechanism of FXII activation – the root cause of surface-induced coagulation (Figure 5e and Section 1). Even though the use of heparin coatings is widespread and cost-effective their performance in clinical studies did not demonstrate a significant improvement when compared to an uncoated surface.^[287–289] A more advanced example of a heparin system was developed by Maitz et al., consisting of a hydrogel of star-PEG and heparin that in the presence of thrombin is degraded to release heparin aimed at locally inhibiting the protease's activity.^[272] This new interactive approach holds promise due to the effectivity of soluble heparin but presents challenges as it is a delivery system which has the potential to affect systemic hemostasis. Conversely, the observation that the presence of inhibitors of FXII on heparin coatings improved hemocompatibility sparked the idea that their immobilization on a synthetic coating could stop initiation and propagation of coagulation. Thus, several studies have focused on the use of FXII inhibitor,^[221,290–292] including recombinant proteins,^[293] synthetic peptides,^[89,116,121,294–296] small molecular weight FXIIa inhibitors,^[297] antibodies,^[115,117,119,298] aptamers,^[299] and antisense oligonucleotides.^[300] These inhibitors can be grouped in two types; those that target the zymogen and the active factor and those that only tackle the latter. The inhibitors that capture FXII and FXIIa are likely to become rapidly saturated, thereby losing the surface hemocompatibility. On the other hand, those inhibitors capturing only the active form can provide a longer protective effect as they have to capture fewer molecules.

Recent approaches include the immobilization of FXIIa inhibitors such as corn trypsin inhibitor (CTI),^[290,301] C1INH,^[291] or an antibody against FXIIa (Figure 5f).^[221] C1INH is particularly interesting as it captures β -FXIIa and PK, thus reducing the activation of inflammation.^[292] Moreover, the aforementioned



tioned antibody against FXIIa, has been argued to be the most advanced anticoagulant in the frame of surface-induced coagulation, promising the prevention of thrombosis without risk of bleeding.^[114,115,117]

Finally, the interactive level aims at a more subtle interaction with blood. It is no longer the surface that performs the action but rather directs blood to act on itself. The most explored example is the establishment of a proto-fibrinolytic system on the coating.^[302–311] The first approaches comprised the non-covalent immobilization of tPA and uPA on cationic coatings.^[308,312] The seminal works from Brash demonstrated that the selective binding of plasminogen and later tPA, however these strategies failed with prolonged plasma exposure due to tPA depletion and protein adsorption.^[303,308,313,314] Later, Witzdam et al. devised the combination of stealth brushes with immobilized tPA. The synergy between these two levels enabled the realization of a self-regulated coating that could sense the presence of a clot and change from a dormant to active state, in which it could direct blood to initiate its fibrinolytic system (Figure 5g). This concomitantly enabled an amplification cascade that endowed the coating consisting of only few ng cm⁻² of active substance with the ability to drive the digestion of macroscopic clots.^[310] These results highlight the importance of integrating more than one functional level to achieve an improved outcome and extended effect.

5. The Ultimate Dream of a Surface that Contacts Blood

With the endothelium providing the only true hemocompatible interface a vast number of works have logically been directed toward populating surfaces with endothelial cells or endothelial progenitor cells (EPCs) to generate de novo endothelium. These approaches mainly relied on the formation of a hydrophilic coating, natural or synthetic, which presents biological cues to ensure that the seeded endothelial cells recognize the surface as a surrogate form of its extracellular matrix.^[316–321] This biological paradigm has proven nothing short of challenging. First, there is a need for autologous cells and often the supplementation of proangiogenic cytokines and growth factors.^[319,322] Second, using mature endothelial cells requires biopsy and culture while EPCs

require collection and appropriate differentiation. Moreover, the formation of a healthy endothelium is linked to multiple factors, most of them interconnected, such as the type of biological cue, its specificity (most peptide integrin receptors are conserved among many types of cells), distance between them, pattern, type and chemistry of the surface, the mechanics at the molecular, nano- and mesoscale, as well as external effects like shear.^[323–325] Thus, the replication of such a complex system is prone to imperfections, which in turn result in regions of the surface lacking endothelium. These uncovered areas can provide a site for activation of coagulation and local generation of thrombin. This protease modifies membrane receptors of endothelial cells turning the surface of those of them near the defect thrombogenic. This causes even more production of thrombin and progressive damage of the endothelium coating.^[1,326] Thus, the uncovered areas, even if small, can produce substantial damage to the endothelium. Therefore, despite its promise, an endothelial coating capable of effectively functioning on medical devices and that remain viable for prolong time has still remained elusive.

A central question, thus, remains open: can we ever fully recapitulate the ability of natural endothelium to be compatible with blood? We envision that the field of bottom-up synthetic biology may hold an answer, providing a means to engineer cell mimics, which can alleviate some of the current limitations of their natural form's inclusion in coatings. The idea of a synthetic cell (synCell) and its use in medicine was coined by TMS Chang in 1957.^[327–330] These first rudimentary but revolutionary synCells could capture the most basic biological function of natural erythrocytes, the transport of oxygen, and served as blood substitutes.^[327–329,331–335] Currently a number of different synCells are being developed for medical purposes such immune activation, targeted delivery, chemotaxis, etc.^[336–340] In a similar vein, would it be possible for synthetic cells to cross fertilize the field of hemocompatibility? It is conceivable that such synCells could be designed to assemble into a confluent layer at the surface of blood-contacting medical devices and function as synthetic endothelium (synEndothelium). Compared to natural cells, the synthetic surrogates cannot proliferate, posing no risk to become cancerous and offer an unparallel programmability. The latter is a huge advantage for the design of medical solu-

Figure 5. Steps toward mimicking basic functionalities of endothelium. a) Scheme of the three hierarchical levels, stealth, modulatory, and interactive, proposed to be needed to achieve hemocompatibility on artificial interfaces. b) Scheme of NO-releasing coatings that are capable of converting blood components into NO. Released NO modulates the activation of platelets. SEM images of surface after contact with blood with and without NO release show a significant improvement in the case of the latter. Scale bars represent 10 μm. Reprinted with permission from.^[259] Copyright 2016, Acta Biomaterialia, Elsevier. c) Scheme of a coating capable of digesting neutrophils' NET. DNase is immobilized on a hydrophilic coating. The enzyme can digest NETs thereby reducing the attachment of neutrophils. d) Depiction of coatings capable of inhibiting thrombin. Hemocompatibility studies on CarboSil® surface demonstrated less thrombus formation in the case of immobilized Argatroban (direct thrombin inhibitor). Reproduced from^[268] with permission. Copyright 2016, Royal Society of Chemistry. e) Schemes of proposed mechanisms of action of heparin end-tethered to surfaces. Left: Immobilized heparin is assumed to work in the same way as unbound one where AT binds to heparin, change its conformation and thereby increasing its affinity for thrombin, which is subsequently captured and inhibited.^[277] Other research suggest that the improvement in surface hemocompatibility stemmed from the biospecific adsorption of plasma proteins, in particular C1INH, that inhibit FXIIa and thereby preventing the contact activation. The commercial Carmeda BioActive Surface (CBAS®) showed a clean surface after blood contact compared to uncoated ePTFE. Reproduced with permission from.^[315] Copyright 2017, W.L. Gore & Associates, Elsevier. f) Immobilization of monoclonal antibody against FXIIa (one of the most advanced anticoagulants)^[112,114,115] on antifouling surfaces can deactivate the root cause of surface-induced coagulation. Static hemocompatibility studies showed no clot formation on the coating system. This indicates a massive improvement compared to the unmodified surface. Scale bars represent 30 μm. Reproduced with permission from.^[221] Copyright 2022, Quandt et al. Advanced Materials Interfaces, Wiley-VCH GmbH. g) Example of the interactive level realized on polymer brushes. The scheme shows a fibrinolytic coating that can switch between dormant and active state to produce plasmin once it detects a clot. In the active state plasmin is continuously produced and released from tPA allowing for fast digestion of the clot. After the clot is disintegrated, tPA returns to its dormant state. Confocal laser scanning microscopy images show the successful digestion of a macroscopic clot after only 3 h. Scale bars represent 20 μm. Reprinted with permission from.^[310] Copyright 2024, American Chemical Society.

Table 2. Overview of current coating strategies to improve the hemocompatibility of medical devices.

	Coating strategies	Description	Outcome	References
Stealth	Hydrophilization	Introduction of hydroxyl, amine or carboxyl amine by plasma treatment or deposition of hydrophilic polymers.	Reduction of adsorption from model solutions of a single protein.	[124–129]
	Self-assembled monolayers	Molecules that consist of hydrophilic functional headgroup and hydrophilic tails. Ideally, they form on Au or Ag surfaces by alkanethiols.	Reduction of adsorption from model solutions of a single protein.	[130–134]
	Polymer brushes	Tightly packed polymer chains that are tethered by one end to the surface. They can be formed using grafting-from, grafting-to or grafting-through technique.	The most advanced polymer brushes have shown almost complete repellency to blood plasma proteins.	[137–139, 167, 171, 173–178]
	Surface-attached hydrogels	Ultra-thin surface-attached hydrogels exhibit dangling chains that form a brush-like structure at the interface while being easily applicable on polymeric surfaces.	Their repellency against blood plasma proteins is in the same range as the best hydrophilic polymer brushes.	[226–230, 235–240]
	Protein-polymer hybrid	The combination of a surface affine peptide and an antifouling polymer brush allows for the formation of a brush-like coating. While the peptide strongly binds to the surface the polymer chains segregate away from the surface.	These coatings showed excellent repellency against blood plasma proteins and prevented bacterial adhesion.	[229, 241–243]
Modulatory	Nitric oxide release	The release of nitric oxide is based on enzymes or synthetic catalysts that interact with endogenous substrates in blood.	It has been demonstrated that these coating systems can reduce platelet activation.	[247–250, 255, 257, 259]
	DNAse	DNAse is immobilized to hydrolyze the DNA of NETs.	Such coatings reduced neutrophil adhesion or even expelled them from the surface.	[260, 261]
	Thrombin inhibitors	Different thrombin inhibitors such as hirudin, thrombomodulin or heparin were immobilized on the surface to block the formation of the clot.	Immobilization of thrombin inhibitors showed improved compatibility with blood but did not solve the problem of surface-induced coagulation.	[262–269, 274–276, 287–289]
	FXIIa inhibitors	Inactivation of FXIIa by inhibitors such as CTI, C1INH or specific antibodies helps to stop the initiation and propagation of surface-induced coagulation.	Immobilization of FXIIa and/or FXIa inhibitors improved the hemocompatibility and prevented protein adsorption and cell adhesion.	[221, 290, 291, 301]
Interactive	Fibrinolytic coatings	Immobilized uPA or tPA can convert plasminogen into plasmin. In this way the blood clot can be digested by using blood's own mechanism.	These coating systems were able to digest even macroscopic clots.	[302–310, 313, 314]

tions to develop fully customized coating toward personalized medicine. The concept of a synEndothelium is a completely new paradigm that will require the contributions of a number of fields and holds promise to knock down barriers for the design of quasi-living materials and interfaces that can better interface with their living counterparts. This concept will demand designing synCell-based prototissues that meet the following requirements (Figure 6):

a) **Vesicles that Mimic the Membrane of Endothelial Cells:** The synCell's membrane must be stealth by displaying a periphery that prohibits the adsorption of proteins and blood cells to prevent activation of coagulation. They should be able to harbor glycan and natural or synthetic receptors to be used for sensing the state of blood (Figure 6a). Moreover, they should mimic the most salient physical properties of the membrane, such as the thickness flexibility, and dynamics while being stable to withstand shear and they should allow the introduction of mechanism to gate pores to allow the release of molecu-

lar messengers. These features demand to go beyond state-of-the-art liposomes and polymersomes.

- b) **Assembly into Confluent Monolayer:** The synCells should assemble at the surface of the blood-contacting medical device as a confluent monolayer with the aid of a non-thrombogenic synthetic extracellular matrix (synECM). This matrix should protect the integrity of the synCells and promote their cooperative behavior. The latter can be done by mechanically coupling them imitating the integrin-ECM binding or by promoting the formation of tight-junction-like connections between neighboring synCells (Figure 6b).
- c) **Ability to Communicate with Blood and Modulate Hemostasis:** The overall aim is that the synEndothelium senses the biochemical signals arising from activation of coagulation and releases inhibitors or activators of hemostasis in a self-regulated manner (Figure 6c). This autonomous behavior will require coupling the sensing event at each synCell membrane with reaction networks in their lumen that can be programmed to have a proportional response. Moreover, these

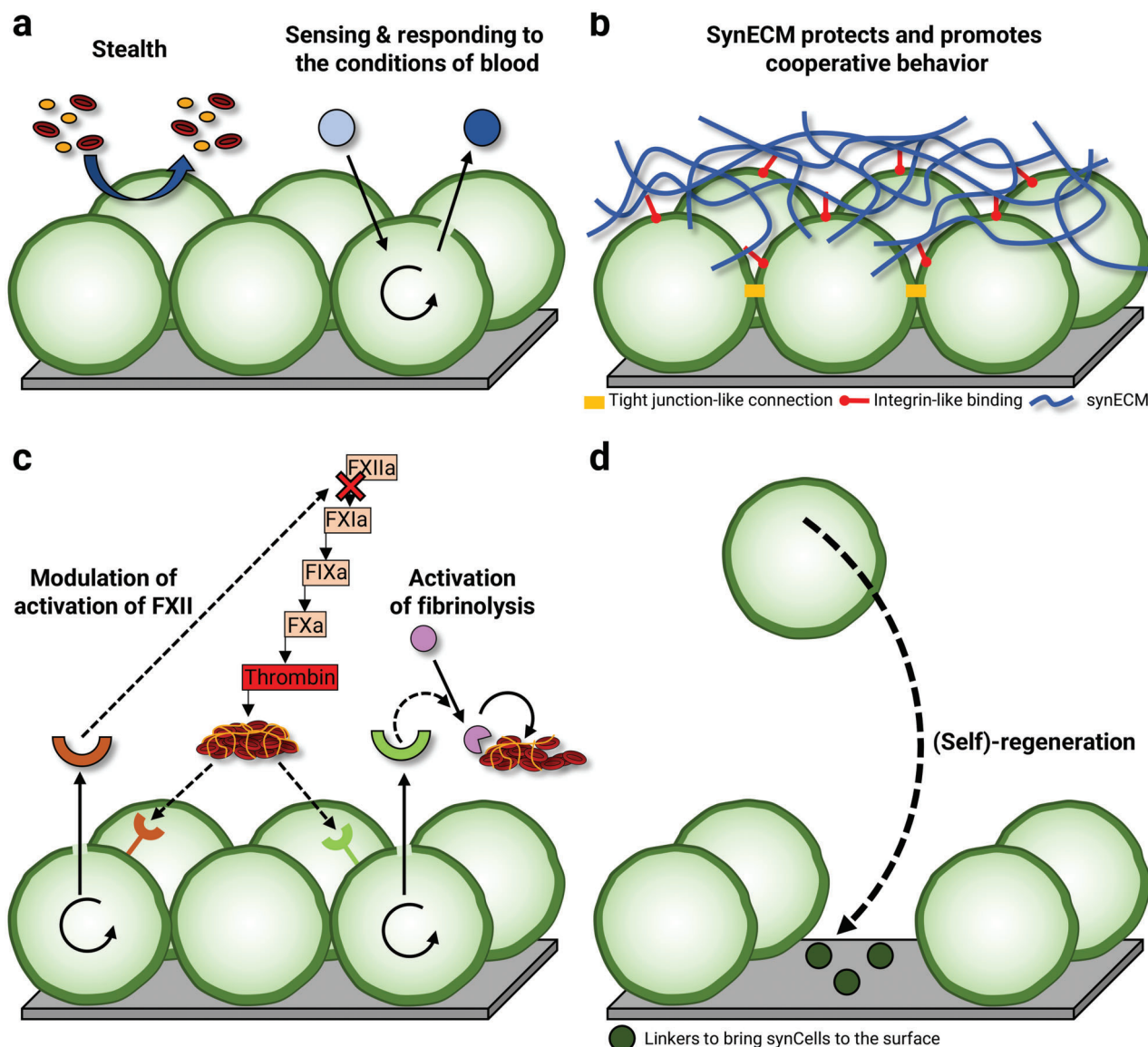


Figure 6. Scheme of the necessary requirements for the formation of synEndothelium. a) The synEndothelium should consist of stealth synCells that mimic that can sense the conditions of blood similar to natural endothelial cells. b) The synCells are connected by synECM that protects the synCells and promotes their cooperative behavior. c) Communication through different receptors allows directed responses to different blood conditions. This allows the modulation of hemostasis by inhibiting the activation of FXII or activating the fibrinolytic system. d) Damages in the confluent layer due to long-term application can be repaired through (self)-regeneration of the synEndothelium by recruiting synCells or natural endothelial cells.

responses must be coordinated between the synCells, which must work as consortia rather than as isolated elements.

- d) SynEndothelium Capable of (self)-Regeneration: The proto-tissue should be able to recruit natural/synthetic cells to repair any damage that occurred with time of operation (Figure 6d).

The feasibility of synCells was first demonstrated by Prof. TMS Chang in 1957,^[329] supported by a vast number of cell surrogates –artificial red blood cells,^[331,332] cells producing insulin,^[333,341] encapsulation of living hepatocytes^[342] so why, 66 years later, do we not have any tissue engineered comprising synCells? Arguably, this is the result of the classical separation between mate-

rial science and biology and perhaps also lack of synthetic tools. But we are now at a pivotal point in time, where material science is capable of integrating nature's blueprints to fabricate materials of unparalleled functionality, interactivity, and information content, exploiting synthetic strategies that transcend the formation of covalent bonds.^[343–345] This makes the fabrication of a synEndothelium, devoid of the complexity of the natural form but instead assembled from self-programmed synthetic cells, conceivable and supported by the leap-forward strides of this new emerging field.

New concepts for synCell membranes, assembled from xenobiotic components, have been developed that faithfully recapitulate the physical properties of natural ones and allowed

the seamless integration of natural receptors, control of permeability and porosity while having enhanced stability.^[346–355] These new synCells have been able to harbor cell machinery and perform cell-like and completely new functions such as their use as smart drug carrier,^[345] for immunotherapy,^[343] and protein synthesis to favor angiogenesis.^[339] SynCells have already been coupled together and through synthetic extracellular matrices to drive their synergistic and cooperative behavior as cell consortia mimicking natural tissues.^[356–358] Moreover, recently synCells have been endowed with the ability to sense and to react upon external physical^[359–363] and biochemical signals.^[364,365] Further steps in this direction included the introduction of artificial signaling pathways and even the ability to communicate with and control living cells.^[338,339,366–370] Such communication has been argued to be the most important hallmark that set living and non-living apart.^[371]

6. Conclusion and Outlook

In conclusion, this perspective elucidates the multifaceted challenges inherent in the interaction between blood and the surface of medical device surfaces, while also presenting recent strides made in the realm of hemocompatible coatings. Furthermore, it offers a compelling vision for the future, wherein the creation of truly hemocompatible surfaces becomes a tangible reality. We have discussed various classes of hemocompatible coatings, underlining the imperative of emulating key functions of healthy endothelium to achieve optimal hemocompatibility. Notably, we underscore the critical importance of imbuing such coatings with stealth properties, alongside the capacity to modulate hemostasis and interact with blood, ideally all in a synergistic manner. In line with this we introduce the idea of developing synEndothelium, underpinned by the groundbreaking advancements in bottom-up synthetic biology. We delineate the minimal requisites for such proto-tissue to ensure hemocompatibility, while elucidating how recent breakthroughs have laid the groundwork for realizing a quasi-living surrogate of healthy endothelium. This surrogate holds the potential to supplant natural endothelium or serve as a secure intermediary until natural regeneration occurs. In essence, our perspective not only sheds light on the existing landscape but also proposes a pathway toward the development of next-generation hemocompatible surfaces.

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Conflict of Interest

The authors declare no conflict of interest.

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