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Wider impact

Blood-contacting biomaterials are central to numerous medical technologies, including vascular grafts, stents, extracorporeal circulation systems, and implantable devices. Despite decades of research, thrombosis and incomplete endothelialization remain major limitations, particularly for small-caliber vascular grafts. Marine sulfated polysaccharides (MSPs) represent a structurally diverse and renewable class of biofunctional materials capable of modulating coagulation, inflammation, and vascular cell behavior through mechanisms that extend beyond those of conventional mammalian-derived anticoagulants. By adopting a materials-oriented and application-driven perspective, this review highlights how insights from marine glycobiology can inform the rational design of next-generation blood-contacting interfaces. The concepts discussed are broadly relevant not only to vascular tissue engineering, but also to hemocompatible coatings for cardiovascular implants, microfluidic and extracorporeal devices. Addressing challenges related to MSP standardization, scalability, and regulatory translation may ultimately enable more sustainable and clinically robust biomaterials.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Marine Sulfated Polysaccharides as Biofunctional Agents for Enhancing Hemocompatibility and Endothelialization of Tissue-Engineered Vascular Grafts.

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Abstract

Small-diameter vascular grafts (≤6 mm) continue to face high failure rates due to thrombosis, intimal hyperplasia, and inadequate endothelialization. While bioresorbable and hybrid materials offer promising alternatives to conventional prostheses, challenges in hemocompatibility and host integration remain. Marine sulfated polysaccharides (MSPs)—including fucoidans, carrageenans, and fucosylated chondroitin sulfates—have emerged as biofunctional agents capable of modulating coagulation, inflammation, and vascular cell behavior. These structurally diverse, highly sulfated glycans mimic features of the native endothelial glycocalyx, enabling interactions with coagulation factors and promoting endothelial regeneration. This review brings together current insights into MSPs structure–function relationships, anticoagulant mechanisms, and endothelial support, and discusses how these features can be strategically harnessed for vascular graft design and clinical translation. We examine recent strategies for MSPs functionalization of electrospun and 3D-printed scaffolds and evaluate emerging evidence from *in vitro* and *in vivo* studies. Finally, we explore current challenges and future directions for the clinical application of MSP-functionalized vascular biomaterials. Collectively, these insights position marine sulfated polysaccharides as a versatile and underexplored class of biomolecules with the potential to address long-standing barriers in vascular tissue engineering.

Keywords

Marine sulfated polysaccharides (MSPs); Fucosylated chondroitin sulfate (FCS); Small-diameter vascular graft (sTEVG); Vascular regeneration; Scaffold biofunctionalization; Hemocompatibility

Introduction

The development of small-diameter (≤6 mm) tissue engineered vascular grafts (sTEVG) remains a critical and unresolved challenge in cardiovascular tissue engineering [1,2]. Conventional synthetic prostheses, such as expanded polytetrafluoroethylene (ePTFE) and Dacron, frequently fail due to early thrombosis, intimal hyperplasia, and insufficient endothelialization [3,4], resulting in low long-term patency rates [5,6]. Various strategies have been pursued to improve hemocompatibility of vascular prostheses, including the functionalization of graft surfaces with anticoagulant agents [7], primarily heparin [8], as well as physicochemical surface engineering approaches designed to enhance endothelial cell affinity and reduce thrombogenicity [9]. However, these approaches have only marginally improved long-term clinical outcomes [10]. Resorbable small-caliber grafts have emerged as a promising alternative, offering the potential for *in situ* tissue regeneration through host cell recruitment and extracellular matrix (ECM) deposition, while supporting endothelialization to reduce thrombotic risk [11,12]. However, their clinical translation has been hindered by limitations such as the lack of reliable autologous cell sources, immunogenicity, and incomplete integration with host tissue. Additionally, many synthetic resorbable materials exhibit poor endothelial cell colonization and a high thrombogenic profile [13–16]. To address these shortcomings, hybrid constructs combining synthetic polymers with natural materials have been developed, which improve cell adhesion but often compromise mechanical performance and fail to fully address thrombogenicity [17–20]. Mechanical integrity and degradation kinetics must be precisely tuned: vascular grafts must retain sufficient structural strength to support early neo-tissue formation while degrading in a manner that permits timely cell infiltration and ECM remodeling. Compliance mismatch between the graft and native vessels further contributes to long-term

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failure, highlighting the need for biomaterials that recapitulate the biomechanical properties of native vessels [21–26].

Despite significant advances in antithrombotic pharmacotherapy and surface engineering, the development of durable, off-the-shelf vascular grafts that fully replicate the biological and functional performance of native vessels is challenging using current materials [11,12,27]. One emerging strategy is the biofunctionalization of vascular scaffolds with bioactive molecules that mimic the extracellular environment and actively modulate host responses [28]. Among these, marine-derived sulfated polysaccharides—including fucoidans, fucosylated chondroitin sulfate, and carrageenans—have attracted growing interest due to their structural similarities to glycosaminoglycans found in vertebrates, such as heparin, and their wide-ranging biological activities [29]. Sourced from diverse marine invertebrates and algae—including echinoderms, sponges, and seaweeds—these polysaccharides possess unique sulfation patterns and carbohydrate backbones [30,31], which contribute to anticoagulant [32], antithrombotic [33,34], anti-inflammatory [35], pro-endothelial [36] and antitumoral [37] properties. Their evolutionary adaptation in extreme marine environments has given rise to structurally diverse, highly bioactive compounds, many of which are amenable to scalable extraction or synthetic optimization. Unlike mammalian heparin, marine-derived polysaccharides offer additional advantages such as reduced immunogenicity, non-mammalian origin, and distinctive biologically functional profiles.

This review synthesizes recent advances in the use of marine sulfated polysaccharides (MSPs) as biofunctional agents for vascular biomaterials. We examine their sources, structural features, and mechanisms of hemocompatibility, along with strategies for their incorporation into tissue-engineered vascular scaffolds. Finally, we discuss translational challenges and future directions, positioning these marine biopolymers as promising candidates in the development of next-generation, bioactive vascular grafts.

Marine Sulfated Polysaccharides: Sources and Structural Features

To address the still unmet challenges of effective sTEVG development, research has increasingly turned to naturally derived bioactive materials. Among these, MSPs stand out for their structural resemblance to glycosaminoglycans and their ability to regulate vascular responses. The following section provides an overview of their marine origins and distinctive structural features.

Origins and Diversity

MSPs are a structurally diverse class of biomolecules derived from a wide array of marine organisms, including brown and red algae, sea cucumbers, and sponges (Figure 1 and Table 1). Each class is characterized by distinct monosaccharide compositions, bonding motifs, and sulfation patterns that underline their unique biological activities [38,39].

Among the most studied are fucoidans, primarily extracted from brown seaweeds such as *Fucus vesiculosus*, *Laminaria digitata*, *Saccharina latissima*, and *Cladosiphon okamuranus* [40–42]. These polysaccharides are typically rich in α-L-fucose residues, which are variably substituted with O-sulfate groups, giving rise to highly branched, heterogeneous structures.

Carrageenans, another major group, are linear sulfated galactans found in red algae (phylum *Rhodophyta*) [43] such as *Chondrus crispus*, *Eucheuma spp.*, *Gigartina stellata*, *Iridaea*, *Hypnea*, *Solieria*, *Agardhiella*, and *Sarconema* [44,45]. They consist of repeating disaccharide units of D-galactose linked via alternating β-(1→4) and α-(1→3) glycosidic bonds, with sulfation ranging

from zero to three sulfate groups per disaccharide. At least ten structurally distinct carrageenan types have been identified, each with specific biological and rheological properties [46].

Other MSPs, including ulvans derived from green macroalgae of the Ulva genus, have also attracted increasing interest in biomaterials and regenerative medicine research [47,48]. Ulvans are structurally complex sulfated heteropolysaccharides mainly composed of rhamnose, glucuronic acid, iduronic acid, and xylose residues, whose composition and sulfation patterns strongly depend on species and extraction methodologies [49]. Although their anticoagulant activity is generally less pronounced than that of fucoidans or fucosylated chondroitin sulfates, ulvans have demonstrated immunomodulatory, antioxidant, anti-inflammatory, and tissue-regenerative properties, highlighting their emerging relevance as multifunctional marine glycans for biomedical applications [48,50].

Arguably, the most structurally complex and biologically potent MSPs are the fucosylated chondroitin sulfates (FCS), primarily sourced from sea cucumbers (class *Holothuroidea*) [51]. These unique glycosaminoglycans consist of a chondroitin sulfate backbone composed of repeating disaccharide units of β-D-glucuronic acid and N-acetylgalactosamine, branched with sulfated α-L-fucose residues at defined positions [52]. FCSs display species-specific structural variation, particularly in the degree and position of sulfation—commonly at the 2-O, 4-O, and 6-O positions of fucose and backbone sugars—which greatly influence their bioactivity. A growing number of sea cucumber species have been characterized as FCS sources, including *Holothuria tubulosa* [32], *Holothuria stellati* [53], *Massinium magnum* [54], *Holothuria scabra* [55], *Eupentacta fraudatrix* [56], *Cucumaria frondosa* [57], *Cucumaria syracusana* [58], *Acaudina leucoprocta* [59], *Holothuria leucospilota* [60], *Holothuria Mexicana* [61], *Apostichopus japonicus, Actinopyga mauritiana* [62], *Stichopus chloronotus, Stichopus horrens* [63] *and Hemioedema spectabilis* [64]. Considering their wide array of biological activities, FCS oligosaccharides have also been chemically synthesized [65].

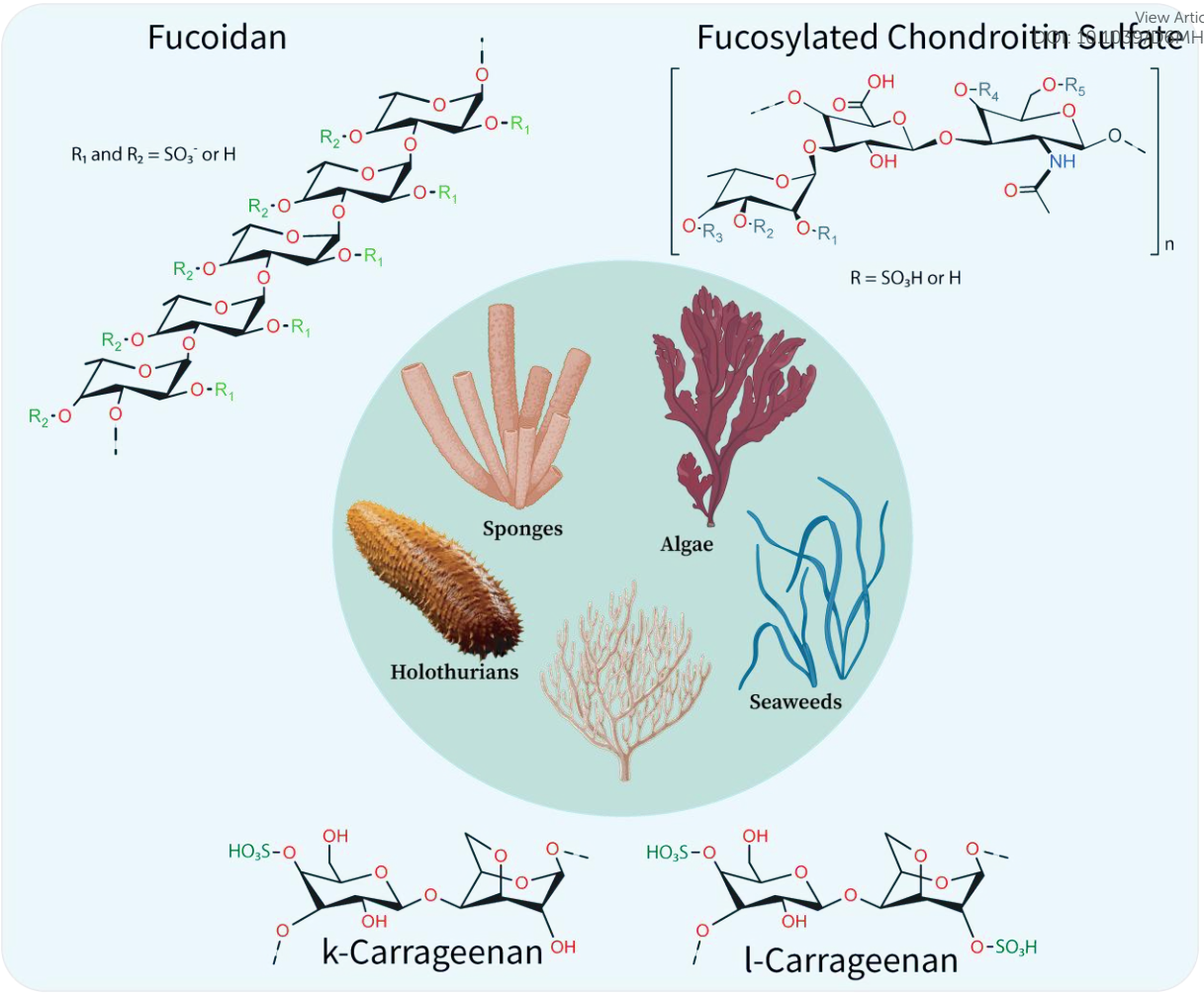

Figure 1. Representative structures of selected major classes of MSPs and their biological sources. Marine-derived glycans, including fucoidan, fucosylated chondroitin sulfate, and carrageenans (κ- and ι-forms), exhibit structural diversity arising from variable sulfation patterns, glycosidic linkages, and monosaccharide compositions. These polysaccharides are predominantly extracted from algae, seaweeds, sponges, and holothurians, and have attracted increasing attention due to their broad spectrum of bioactivities. Figure partially created with BioRender.com under academic license.

MSPs, including glycosaminoglycans (GAGs)-like molecules such as sulfated fucans and sulfated galactans (including carrageenans and related galactose-rich polysaccharides), display a much broader range of monosaccharide composition, sulfation patterns, and backbone structures than mammalian GAGs, even within the same class of molecules [66]. This diversity is especially pronounced in marine invertebrates and algae, leading to unique and structurally distinct polysaccharides compared with their mammalian counterparts [67,68]. Their sulfate content varies widely—fucoidans, for example, can contain between 9% and 40% sulfate by weight, depending on species, seasonal factors, and extraction methodologies [69]. Their molecular weights are equally diverse, spanning from tens to several hundred kilodaltons, contributing to variability in physicochemical and biological properties. In contrast, mammalian heparin—the clinical gold standard for anticoagulation—is a comparatively well-defined GAG composed of repeating disaccharide units of α-L-iduronic acid (or β-D-glucuronic acid) and α-D-glucosamine, with specific sulfation at the N-, 2-O-, and 6-O-positions. Despite

some batch-to-batch variability and the presence of minor GAG contaminants, pharmaceutical-grade heparin displays a much narrower structural and functional profile [70]. By comparison, marine polysaccharides feature a broader array of carbohydrate backbones and sulfation motifs. Fucoidans typically consist of α-(1→3)- and/or α-(1→4)-linked L-fucose units bearing sulfate groups at the 2-O, 3-O, and 4-O positions [71]. Carrageenans, composed of alternating α- and β-linked galactose residues, can possess up to three sulfate groups per disaccharide, leading to highly anionic structures [45,72]. FCSs exhibit a chondroitin sulfate backbone bearing 3-linked, variably sulfated α-L-fucose branches, often carrying multiple sulfates at distinct positions (e.g., 2-O, 3-O, 4-O) on both the side chains and the backbone [51]. This diversity in monosaccharide composition, glycosidic linkages, and sulfation patterns underpins the broad spectrum of biological activities observed for marine-derived sulfated polysaccharides, particularly in modulating coagulation, inflammation, and endothelial function. In addition to the major MSP classes, less extensively characterized glycogen-like acidic polysaccharides have also been sporadically reported, further highlighting the vast and still underexplored structural diversity of marine glycans and their potentially valuable bioactivities [73,74].

A comparative overview of key structural motifs and associated anticoagulant activities is presented in Table 1.

Table 1. Overview of the main structural motifs and anticoagulant activities of representative sulfated polysaccharides. Marine-derived polysaccharides such as fucoidan, carrageenan, and fucosylated chondroitin sulfate display diverse backbones and sulfation patterns compared with mammalian heparin, resulting in variable anticoagulant potency.

Polysaccharide	*Source*	*Backbone and Glycosidic Linkages*	*Sulfation Pattern*	*Anticoagulant Activity (Mechanism)*	*Relevance for Vascular Grafts*
Fucoidan *41*	Brown algae (*Fucus, Laminaria, Saccharina*)	Predominantly α-L-fucopyranose units linked via (1→3) or alternating (1→3)/(1→4) linkages; occasional branching at C2	Mainly O-sulfation at C2 and/or C4, less frequently C3; highly heterogeneous	Potentiates ATIII and HCII; inhibits thrombin (IIa) and Factor Xa; interferes with P-selectin-mediated platelet adhesion	Reduces platelet adhesion and thrombin generation; promotes EC proliferation; anti-inflammatory
Carrageenan (κ, ι, λ) *44,45*	Red algae (*Chondrus, Eucheuma*)	Linear chains of repeating disaccharides: β-D-galactose (1→4) linked to α-D-galactose (1→3); presence of 3,6-anhydrogalactose (κ, ι types)	κ: sulfate at C4; ι: sulfates at C4 and C2; λ: higher sulfation (e.g., C2, C6)	Weak anticoagulant effect; limited interaction with ATIII; mainly electrostatic interference with coagulation proteins	Limited hemocompatibility improvement
Fucosylated Chondroitin Sulfate *32,51,52*	Sea cucumber (*Holothuria, Cucumaria*)	Backbone: repeating β-D-glucuronic acid (1→3) β-D-N-acetylgalactosamine (1→4); α-L-fucose branches linked to O-3 of GlcA	Fucose branches: 2-O, 4-O, and/or 3-O sulfation; GalNAc residues: 4-O and/or 6-O sulfation	Strong activation of ATIII and HCII; potent inhibition of thrombin and Factor Xa; high-affinity binding to coagulation proteins	Excellent hemocompatibility; inhibits platelet adhesion; supports EC monolayer formation and vascular cell integration
Ulvan *47–49*	Green algae *(Ulva spp.)*	Sulfated heteropolysaccharide mainly composed of rhamnose, glucuronic acid, iduronic acid, and	Variable sulfation primarily on rhamnose residues; species- and	Mild-to-moderate anticoagulant activity acting predominantly through the	Promising for regenerative vascular biomaterials due to immunomodulatory

		xylose with heterogeneous glycosidic linkages	extraction-dependent	intrinsic and common coagulation pathways	, antioxidant, and endothelial-supportive effects
Sulfated Arabinogalactans/ Galactoarabinan [75–77]	Green algae (*Codium fragile*, others)	Branched polysaccharides composed of β-D-galactopyranose and α-L-arabinofuranose units; linkages include (1→3), (1→6)	Sulfation on galactose and/or arabinose residues (position-dependent, variable)	Interferes with intrinsic coagulation cascade	Limited data for vascular graft applications
Acidic Glycogen/ Glycogen-like acidic polysaccharides [73,74]	Sea sponge (*Aplysina fulva*)	Branched α-D-glucopyranose polymer with α-(1→4)-linked backbone and α-(1→6)-linked branching	5% of Sulfated D-Glc; 50% of sulfated non-reducing ends	Not yet investigated	Poorly characterized; relevance to vascular grafts remains unclear
Heparin [78]	Mammalian (Porcine intestine)	α-L-iduronic acid or β-D-glucuronic acid + *N*-acetylated glucosamine or *N*-sulfated glucosamine	Highly sulfated: 2-*O*,6-*O*, N-sulfation	Strong ATIII-mediated inhibition of thrombin and Factor Xa	Clinical gold standard for anticoagulation; limited endothelialization effect

Structure–Anticoagulation Relationships

As the structure plays a defining role in bioactivity, the mechanistic basis of MSPs anticoagulant function lies in their specific interactions with the coagulation cascade and platelets. How do these glycans influence clotting pathways and cellular responses at the blood–material interface? The structural diversity of MSPs—reflected in their sugar backbones, molecular weights, and sulfation motifs—is key to their functional behavior [79]. The anticoagulant potency of MSPs is closely linked to their structural features, particularly the degree and pattern of sulfation. Higher sulfate content generally enhances anticoagulant activity, but the specific position of sulfate groups on sugar residues is also critical. For example, sulfation at certain positions (such as C-2/C-4 of rhamnose or galactose units) significantly increases the ability to inhibit coagulation factors [76,77,80–82]. The molecular weight of these polysaccharides also plays a role: higher molecular weight fractions tend to show stronger anticoagulant effects, while depolymerization can reduce activity [65,81–83]. Additionally, unique structural motifs—such as the presence of L-fucose branching, and uronic acid residues—can modulate binding to coagulation proteins and influence the mechanism of action [84–87]. In particular, the 2,4-disulfated fucosyl branches [88,89], especially sulfation at the 4-position of fucosyl branches, appear to play a critical role in coagulation inhibition, as suggested by computational studies [90].

Specific Interactions with the Coagulation Cascade

Blood coagulation is a tightly regulated cascade of enzymatic reactions that culminates in the formation of a stable fibrin clot (Figure 2). This cascade is classically divided into three interconnected pathways: the intrinsic, extrinsic, and common pathways. The extrinsic pathway is rapidly activated by external trauma that exposes tissue factor (TF) to circulating factor VII, forming a TF–VIIa complex that directly activates factor X. The intrinsic pathway, on the other hand, is initiated by contact with negatively charged surfaces, leading to sequential activation of factors XII, XI, IX, and VIII, ultimately converging at factor X. Both pathways feed into the common pathway, where activated factor X (Xa) converts prothrombin (factor II) into thrombin (factor IIa), which in turn converts fibrinogen into fibrin, forming the structural backbone of a clot [91,92]. MSPs exert anticoagulant effects primarily by potentiating serpin inhibitors such as antithrombin III (ATIII) and heparin cofactor II (HCII), leading to accelerated inhibition of thrombin (factor IIa) and factor Xa within the common pathway [93–95]. Certain sulfated galactoarabinan and arabinogalactan structures from green algae strongly inhibit intrinsic

pathway factors (XII, XI, IX, VIII) and promote thrombin and factor Xa inhibition via ATIII and HCII [75–77]. Some MSPs also enhance plasminogen activation, contributing to thrombolytic activity and clot breakdown [82,96]. While initial attraction is largely electrostatic, specific binding and activation are regulated by the stereochemical properties of the polysaccharide, including sulfation pattern, degree of sulfation, and backbone structure, rather than simply overall negative charge [77,97,98].

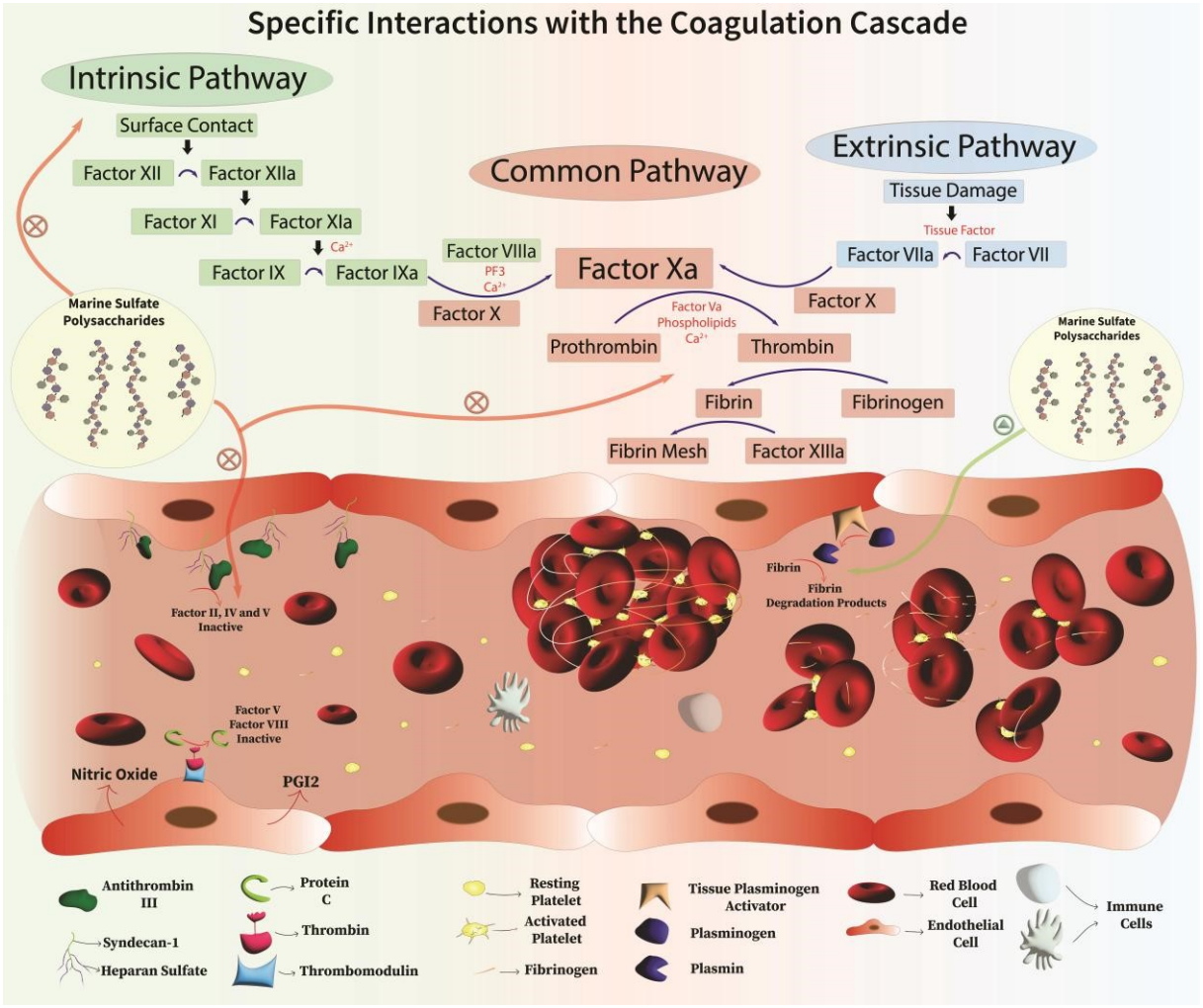

Figure 2. Schematic representation of the coagulation cascade and the modulatory effects of MSPs. The coagulation process proceeds through two main initiation routes—the intrinsic pathway (triggered by surface contact) and the extrinsic pathway (activated by tissue damage)—which converge at the common pathway, leading to the activation of Factor Xa and subsequent conversion of prothrombin to thrombin. Thrombin then cleaves fibrinogen into fibrin, which polymerizes into a fibrin mesh stabilized by Factor XIIIa, ultimately resulting in clot formation. MSPs can interfere with this process at multiple stages, particularly by inhibiting thrombin generation, Factor Xa activity, and fibrin formation, thereby reducing clot stability. Original schematic created by the authors using Adobe Illustrator.

Effects on Platelet Adhesion and Aggregation

MSPs exhibit anticoagulant activity not only through interactions with coagulation cascade proteins but also by significantly inhibiting platelet adhesion and aggregation (Figure 3). Unlike native vascular endothelium, biomaterial surfaces lack natural adhesive ligands and rapidly adsorb plasma proteins upon blood contact (the Vroman effect), including fibrinogen, albumin,

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fibronectin, and von Willebrand factor (vWF). The conformation of these adsorbed proteins—particularly fibrinogen—is a key determinant of platelet adhesion. Current evidence indicates that platelet adhesion is governed more by protein conformational changes than by the absolute amount of protein adsorbed. Unfolded fibrinogen exposes cryptic binding sites for platelet integrins, notably αIIbβ3, which can result in stronger platelet adhesion compared with native tissue [13,99–101].

Although GpIb–vWF interactions can still occur if vWF is adsorbed and partially unfolded on the biomaterial surface, platelet adhesion on artificial materials is often dominated by direct fibrinogen–integrin interactions due to the higher plasma concentration of fibrinogen. In native vessels, the initial tethering of platelets under flow is mediated by GpIbα binding to the A1 domain of vWF immobilized on collagen. On biomaterials, this mechanism is less prominent unless vWF is appropriately adsorbed and conformationally active. Surface characteristics—such as chemistry, roughness, and hydrophobicity—strongly influence protein adsorption and conformation, thereby modulating platelet adhesion. Strategies including hydrophilic coatings, nanoscale topographies, and endothelialization (e.g., HUVEC monolayers) have been shown to mitigate platelet adhesion by maintaining protein conformation or replicating the antithrombotic properties of native endothelium [102–105].

MSPs also interfere with P-selectin-mediated interactions and collagen-induced platelet activation. By attenuating P-selectin–dependent platelet–leukocyte crosstalk, MSPs can reduce downstream vascular inflammation and thrombus propagation. This dual functionality—combining anticoagulant and anti-inflammatory effects—positions MSPs as promising biologically functional agents for vascular grafts and other blood-contacting devices [106–108]. Although P-selectin is not directly involved in the initial platelet adhesion to biomaterial surfaces, its expression on activated platelets and endothelial cells plays a critical role in later stages of thrombus formation and in linking platelet activation to immune cell recruitment via P-selectin Glycoprotein Ligand-1 (PSGL-1) [106,109].

Importantly, hemocompatibility and endothelialization should not be viewed as isolated phenomena in regenerative vascular graft remodeling, but rather as interconnected processes that collectively influence graft integration and long-term patency. While some non-fouling synthetic biomaterials, such as zwitterionic or highly anti-adhesive surfaces, aim to minimize protein adsorption and cellular interactions to reduce thrombogenicity, tissue-engineered vascular grafts instead require controlled bioactivity capable of supporting both blood compatibility and vascular regeneration. In this context, early blood–material interactions strongly influence endothelial cell recruitment, adhesion, and maturation, whereas successful endothelialization progressively restores the antithrombotic and anti-inflammatory functions of the native vascular interface. The multifunctional nature of MSPs is therefore particularly attractive, as these biomolecules may simultaneously modulate thrombogenicity, inflammation, and endothelial regeneration within a single bioactive platform.

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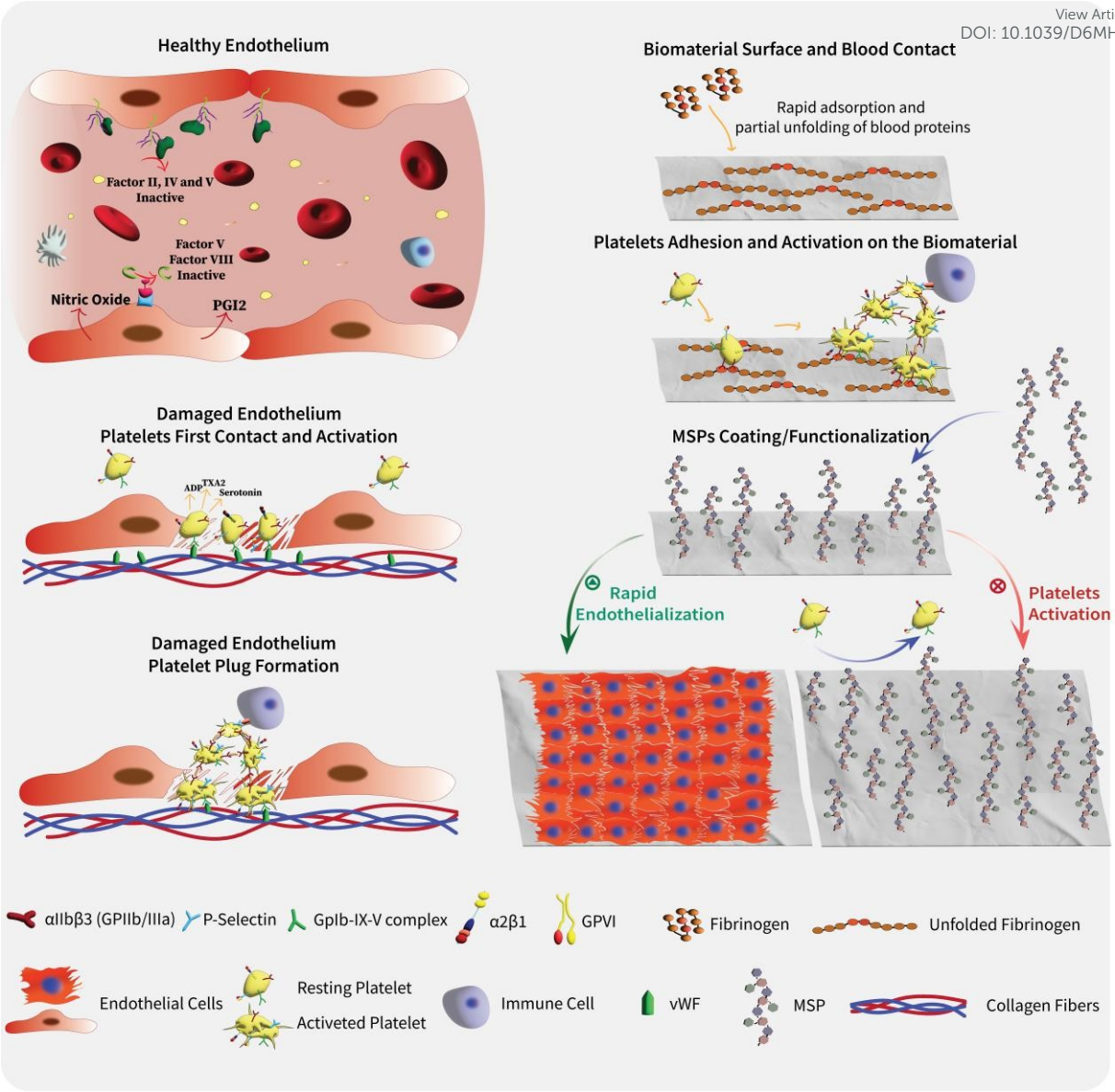

Figure 3. Comparison of hemostatic responses in healthy endothelium versus biomaterial surfaces, and the modulatory role of MSPs. Under physiological conditions, the healthy endothelium maintains blood fluidity by releasing nitric oxide (NO) and prostacyclin (PGI_2), maintaining an antithrombotic microenvironment that prevents coagulation and platelet activation. In contrast, endothelial damage exposes subendothelial collagen, triggering platelet adhesion through receptors such as GPIb-IX-V, αIIbβ3, α2β1, and GPVI, followed by platelet activation and platelet plug formation. Similarly, when blood contacts a biomaterial surface, rapid adsorption and partial unfolding of plasma proteins (e.g., fibrinogen, von Willebrand factor) initiate platelet adhesion and activation, potentially leading to thrombus formation. Functionalization of biomaterials with MSPs can modulate this response: (i) by inhibiting platelet adhesion and activation, reducing thrombotic risk, and (ii) by promoting rapid endothelialization, thereby restoring an antithrombotic surface similar to native endothelium. This dual mechanism highlights the therapeutic relevance of MSP-based coatings for the development of hemocompatible vascular grafts. Original schematic created by the authors using Adobe Illustrator.

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Modulation of endothelialization

MSPs exhibit structural similarities to mammalian glycosaminoglycans (GAGs) but possess distinct sulfation patterns and carbohydrate backbones that confer potent anticoagulant properties [110]. In addition to their anticoagulant and hemocompatible properties, these polysaccharides have also been shown to promote endothelial cell adhesion, proliferation, and functional maturation [111]. Earlier mechanistic studies on related sulfated glycoconjugates—particularly sulfatides—demonstrated that these molecules can mediate cell adhesion through highly specific interactions with ECM proteins such as laminin and thrombospondin [112]. These interactions are not merely adhesive but functionally significant: sulfatide–laminin binding supports both cell attachment and spreading, whereas sulfatide–thrombospondin binding enables initial adhesion without promoting cell spreading, suggesting distinct roles in regulating cellular behavior [113]. Such findings underscore that sulfated glycolipids and polysaccharides do not act as passive structural elements, but instead actively modulate cellular responses through selective, structure-dependent recognition of matrix components. This supports the emerging view that marine sulfated polysaccharides can serve as functional analogs of the endothelial glycocalyx, influencing not only hemocompatibility but also vascular regeneration.

Immunomodulation and Inflammatory Control

Beyond hemocompatibility, MSPs exhibit notable immunomodulatory activity [114], a key factor in the success of vascular implants. Effective immunoregulation is essential in vascular tissue engineering, where promoting anti-inflammatory and pro-regenerative macrophage responses while limiting pro-inflammatory activation is critical for constructive remodeling [115,116]. Certain fucoidans have been shown to modulate macrophage phenotype and reduce pro-inflammatory cytokine expression to levels comparable to the anti-inflammatory cytokine IL-10, suggesting a role in dampening post-implantation inflammation [117]. Additionally, MSPs can interact directly with immune cells: sulfated glycans from marine sources have been reported to bind specific receptors on macrophages and lymphocytes, triggering intracellular signaling cascades that modulate immune cell proliferation and cytokine production [118–120]. These immunoregulatory functions may help mitigate the foreign body response, enhance tissue remodeling, and support long-term graft acceptance.

Pro-Angiogenic Support via Growth Factor Modulation

The capacity of MSPs to modulate pro-angiogenic signaling also holds relevance for graft integration and long-term function. Several MSPs, particularly fucoidans, have demonstrated the ability to bind and stabilize key angiogenic growth factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF). By mimicking heparan sulfate, fucoidans prolong the half-life of these growth factors and enhance their receptor-mediated signaling [121,122].

In the context of TEVGs, such interactions may support the recruitment of endothelial cells to the graft lumen and promote localized neovascularization at the graft–host interface—processes essential for restoring perfusion and promoting functional anastomosis. Experimental studies have shown that fucoidan can enhance endothelial cell tube formation *in vitro* and stimulate neovascularization *in vivo* [123,124], reinforcing its potential role in improving vascular integration of bioengineered grafts.

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Scientific Potential and Therapeutic Promise

Multiple *in vitro* and *in vivo* studies show low toxicity and good cell compatibility of MSPs, making them suitable for biomedical applications [125,126]. MSPs represent a compelling alternative to conventional anticoagulants like heparin, offering multiple advantages. Sourced from marine algae and invertebrates rather than mammals, such as swine or bovine, they avoid risks of zoonotic contamination, prion transmission, and batch variability commonly associated with mammalian-derived heparin [127–129]. Moreover, MSPs exhibit high structural diversity, particularly in their sulfation patterns and molecular weights, which allows for the fine-tuning of anticoagulant potency and specificity—for example, selectively enhancing inhibition of factor Xa or thrombin (IIa) depending on sulfation degree and position [41,82].

MSPs such as fucoidan generally demonstrate low intrinsic toxicity and may present a lower bleeding risk compared with unfractionated heparin, making them attractive candidates for safer anticoagulant therapies. This is because their anticoagulant effect is mediated by weaker, multi-target interactions—such as partial inhibition of thrombin or factor Xa via both ATIII and HCII rather than the strong, high-affinity binding seen with heparin, reducing the risk of uncontrolled bleeding [130,131]. Low molecular weight fucoidan (LMWF) fractions often exhibit additional antiplatelet or antiproliferative effects, by interfering with P-selectin–mediated platelet adhesion. LMWF also inhibits growth factor signaling in vascular smooth muscle cells, contributing to antiproliferative effects and potentially reducing restenosis risk after vascular injury [132,133].

Importantly, their reduced risk of heparin-induced thrombocytopenia (HIT), combined with customizable bioactivity, positions marine polysaccharides as promising scaffolds for the next generation of anticoagulant and vascular graft functionalization strategies [134,135]. Ongoing research into their structure–function relationships and mechanistic pathways will be critical to unlocking their full therapeutic potential and accelerating their translation into clinical applications.

Given their unique structural features and multifunctional bioactivity, MSPs are increasingly recognized as promising candidates for regenerative medicine and biomedical engineering applications. In particular, their incorporation into surface-modified sTEVG has attracted growing interest as a strategy to address major limitations of current synthetic grafts, including early thrombosis, poor endothelialization, and chronic inflammation. This review highlights the potential of MSPs to biofunctionalize the luminal surface of sTEVG, exploiting their anticoagulant and antiplatelet properties to reduce thrombus formation while simultaneously promoting rapid and stable endothelialization. The highly anionic character of these polysaccharides, resulting from dense and site-specific sulfation, closely mimics the negative charge of the native endothelial glycocalyx, which plays a pivotal role in preventing activation of the intrinsic coagulation cascade [136,137]. By emulating this natural biochemical barrier, MSPs may provide localized anticoagulant activity while minimizing the risk of systemic anticoagulation-related side effects. Their structural motifs can support selective interactions with coagulation factors, including thrombin and factor Xa, while reducing nonspecific protein adsorption and subsequent platelet activation [138]. The improved hemocompatibility associated with MSP-functionalized biomaterials is largely governed by their highly sulfated and negatively charged structure, which enables interactions with key regulators of the coagulation cascade and can also improve the typically low hydrophilicity of synthetic biomaterials. This altered surface chemistry influences the composition and conformation of adsorbed plasma proteins, particularly fibrinogen, thereby modulating platelet adhesion and activation [13]. Similar

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to heparin, MSPs such as fucoidan and FCS potentiate the activity of ATIII and HCII, leading to inhibition of thrombin (factor IIa) and factor Xa. These interactions are strongly dependent on sulfate density, sulfation position, and molecular conformation. Beyond coagulation control, MSPs can further regulate platelet behavior by reducing fibrinogen adsorption and interfering with P-selectin-mediated platelet adhesion, contributing to the formation of a glycocalyx-mimetic microenvironment at the blood–material interface. In addition to their hemocompatibility, MSPs can contribute to a bioactive microenvironment favorable to vascular regeneration. Their negatively charged domains, similarly to heparin, may bind and stabilize pro-angiogenic growth factors such as VEGF and FGF in their bioactive conformation, thereby enhancing local growth factor retention, endothelial cell recruitment, and proliferation [98,139,140]. Furthermore, their carbohydrate-rich surfaces may provide specific adhesion sites for integrin-mediated cell attachment and colonization, further promoting graft endothelialization.

Importantly, several MSPs also exhibit anti-inflammatory and antimicrobial properties, which could help mitigate post-implantation inflammation and prevent graft-related infections—two critical complications in the long-term success of vascular implants [1]. Overall, the stereochemistry and sulfation patterns of MSPs are central to these biointeractions, reinforcing the concept that these marine-derived glycans can act as functional analogs of the endothelial surface, offering a versatile and tunable platform for next-generation vascular biomaterials.

Marine Sulfated Polysaccharides Integration into Vascular Grafts

Realizing the therapeutic promise of MSPs requires effective integration into vascular scaffold systems. In the following sections, we highlight current approaches for functionalizing sTEVGs with MSPs and evaluate how these designs influence biological performance and clinical applicability. Marine sulfated glycans, particularly fucoidans and FCSs, provide a potent combination of antithrombotic and pro-endothelial cues that can be leveraged to improve small-diameter vascular grafts [36].

Scaffold Technologies for MSPs Integration: Advantages and Features

Electrospinning and 3D printing techniques offer unique advantages for the fabrication of engineered vascular grafts with MSPs integration. Electrospinning generates nanofibrous scaffolds with high surface-to-volume ratios, mimicking the architecture of the native ECM and providing abundant binding sites for sulfated polysaccharides and cell colonization [5,27]. To this aim, both naturally derived biomaterials and synthetic polymeric platforms have been widely investigated for tissue engineering applications, leveraging the bioactivity of natural systems and the tunable mechanical and manufacturing properties of synthetic materials. Beyond conventional polymers such as PCL, emerging electrospun polyester systems, including PBCE-based aliphatic copolymers and bio-based aromatic PBF/PBI materials, have also shown promising endothelialization, and mechanical performance for small-diameter vascular graft applications, while supporting smooth muscle cell compatibility and maintenance of a contractile phenotype, highlighting their potential to promote both vascular wall regeneration and luminal endothelialization [141,142].

3D printing, on the other hand, enables precise control of lumen geometry, porosity, and multilayer architectures, which are essential to balance mechanical strength with endothelialization potential [143]. Together, these technologies produce reproducible, tunable supports that can stably incorporate MSPs while preserving compliance and long-term patency features that are difficult to achieve with conventional vascular prostheses. Although electrospinning and additive manufacturing represent the most widely explored approaches for

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MSP-functionalized vascular grafts, MSP integration is not limited to these technologies and has also been investigated in hydrogels, surface coatings, multilayer systems, and decellularized matrices.

Functionalization Strategies for MSPs Integration

Engineering the luminal surface of vascular grafts with MSPs has already yielded promising results, with several studies demonstrating comparable or superior performance to traditional heparin-based coatings in terms of inhibition of platelet activation and hemocompatibility [36,144]. Representative studies employing MSP-functionalized vascular biomaterials are summarized in Table 2.

To harness the bioactivity of marine sulfated polysaccharides, researchers have developed a variety of graft functionalization strategies. One notable example involves the incorporation of fucoidan into poly(vinyl alcohol) (PVA) hydrogels using sodium trimetaphosphate (STMP) as a crosslinking agent, resulting in a stable PVA–fucoidan network while preserving the native mechanical properties of the polymer [145]. This modification significantly enhanced endothelial cell adhesion and proliferation while reducing platelet adhesion and thrombin generation *in vitro*. Moreover, in a rabbit carotid artery model, the fucoidan-incorporated grafts achieved superior patency compared with commercial ePTFE grafts after one month of implantation, demonstrating the translational potential of this approach [145]. Similarly, Bračič et al. studied the use of fucoidan and carrageenan, when applied as surface coatings on polyester substrates, effectively reduced nonspecific protein adsorption and mitigated thrombogenic activation. However, their capacity to support endothelial cell proliferation and exert direct anticoagulant effects *in vitro* was more limited than that of heparin and dextran sulfate coatings, which offered a more favorable balance between hemocompatibility and endothelialization [146]. This difference may reflect the lower degree or distinct pattern of sulfation in fucoidan and carrageenan, which could reduce their ability to bind and present growth factors or coagulation mediators as effectively as FCS or heparin. In another strategy, polyelectrolyte multilayers composed of laminin and fucoidan were constructed via layer-by-layer (LbL) self-assembly. These constructs used fucoidan as the terminal layer to minimize platelet adhesion, while laminin-rich surfaces promoted HUVEC attachment and spreading [147]. Recently, FCS from *Holothuria tubulosa*, along with a structurally related sulfated polysaccharide from the sponge *Sarcotragus spinosulus*, were covalently bound to electrospun PCL scaffolds via EDC/NHS chemistry (Figure 4). This chemical modification generated a stable, hydrophilic, and negatively charged surface that mimics key features of the native endothelial glycocalyx. The resulting scaffolds significantly reduced platelet adhesion and supported endothelial cell viability and monolayer formation, further demonstrating the potential of MSPs to enhance both hemocompatibility and endothelialization in small-diameter vascular grafts [36]. While simple physical adsorption or dip-coating can confer bioactivity, these methods typically yield weaker surface retention and limited durability. The choice between covalent binding, LbL assembly, or adsorption should be guided by the desired stability, release profile, and functional longevity of the graft.

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452 Table 2. Strategies for integrating marine sulfated polysaccharides into vascular graft systems
453 and their reported biological outcomes

Scaffold Material	Fabrication Method	MSPs Type	Functionalization Strategy	Main Biological Outcomes	Ref.
Poly(vinyl alcohol) (PVA) hydrogel	Bulk hydrogel fabrication	Fucoidan	Bulk incorporation of fucoidan during STMP-mediated co-crosslinking of PVA hydrogels	↑ EC adhesion and proliferation; ↓ thrombin generation; improved hemocompatibility and *in vivo* patency.	145
PVA tubular grafts	Bulk hydrogel fabrication with luminal microtopography	Fucoidan	CDI-mediated covalent immobilization of aminated fucoidan	↑ in situ endothelialization; ↑ EC migration and alignment; ↓ thrombogenicity; improved graft patency *in vivo*	148
Polyester substrate	Surface coating	Fucoidan/ Carrageenan	Surface adsorption/coating	↓ nonspecific protein adsorption and thrombogenic activation; limited endothelialization compared to heparin and dextran sulfate	146
Laminin/fucoidan multilayer membranes	Layer-by-layer (LbL) assembly	Fucoidan	Sequential LbL assembly of laminin and fucoidan onto functionalized substrates	↓ platelet adhesion; ↑ HUVEC attachment and spreading	147
Electrospun PCL scaffold	Electrospinning	FCS from *Holothuria tubulosa*	Covalent immobilization via EDC/NHS chemistry	↓ platelet adhesion; ↑ endothelialization	36,143
Electrospun PCL scaffold	Electrospinning	Sulfated polysaccharide from *Sarcotragus spinosulus*	Covalent immobilization via EDC/NHS chemistry	↓ platelet adhesion; ↑ endothelialization	36
Multi-layered PCL-based sTEVG	Electrospinning + 4-axis printing	FCS from *Holothuria tubulosa*	Covalent immobilization via EDC/NHS chemistry	Mature endothelial layer formation; ↑ SMC spreading, alignment, and contractile phenotype; ↓ platelet activation	143
Fucoidan–PCL nanofibrous meshes	Electrospinning	Fucoidan	Blend incorporation of fucoidan into electrospun PCL nanofibers	↑ angiogenesis and regenerative potential in chick chorioallantoic membrane (CAM) model	111
Decellularized porcine pericardium	Decellularization and surface biofunctionalization	Ulvan	Covalent ulvan immobilization via EDC/NHS coupling, followed by	Reduced platelet adhesion, inflammatory response, and	50

Scaffold Material	Fabrication Method	MSPs Type	Functionalization Strategy	Main Biological Outcomes	Ref.
(bioprosthetic heart valve model)			endothelial-targeting biomolecule conjugation	calcification; improved endothelialization and tissue integration	

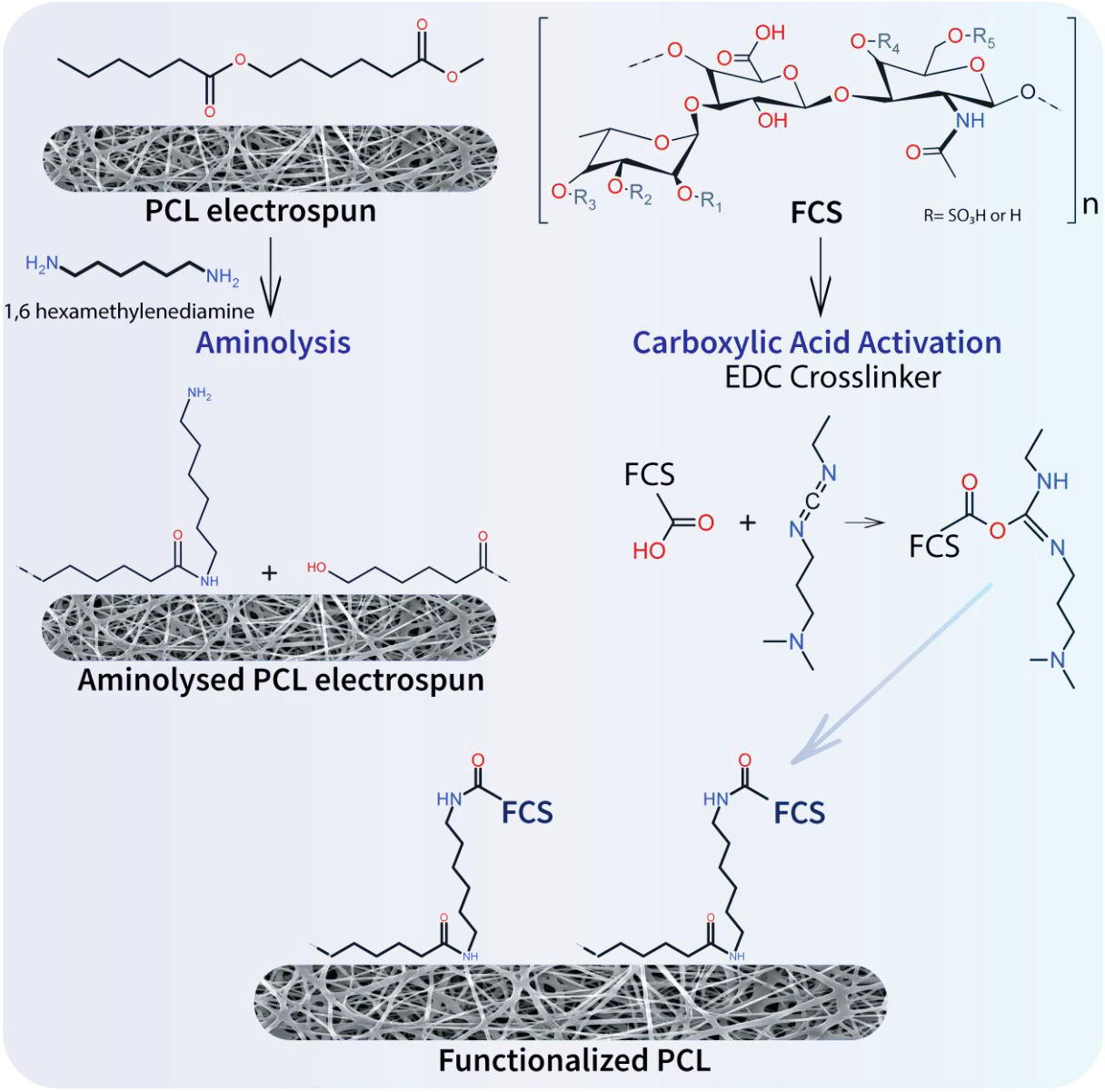

Figure 4. Schematic representation of PCL electrospun scaffold functionalization with sulfated polysaccharides. PCL fibers are first subjected to aminolysis using 1,6-hexamethylenediamine, introducing surface amine groups. In parallel, sulfated polysaccharides (FCS) are activated at their carboxylic acid residues via EDC crosslinking chemistry. The activated polysaccharides are then covalently conjugated to the aminolyzed PCL scaffold, resulting in a functionalized surface presenting bioactive FCS motifs. Original schematic created by the authors using Adobe Illustrator based on literature reports and concepts discussed in Refs [36,149,150].

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In Vitro Studies

Recent *in vitro* studies have demonstrated that MSPs can be efficiently and stably immobilized on electrospun PCL scaffolds, yielding marked improvements in hemocompatibility and endothelialization. For example, chemically crosslinked FCS from *Holothuria tubulosa* and a sulfated polysaccharide from *Sarcotragus spinosulus* were shown to significantly accelerate the formation of a confluent endothelial monolayer compared with unmodified PCL or PCL functionalized with unfractionated porcine heparin. In addition to enhanced endothelial coverage, MSP-functionalized scaffolds exhibited a pronounced reduction in platelet adhesion and activation [36]. A very recent study by the same team further highlighted the impact of surface chemistry on vascular cell behavior [143]. The authors, who developed a tunable multi-layered PCL-based sTEVG functionalized with FCS from *Holothuria tubulosa,* demonstrated that while heparin-functionalized grafts inhibited SMC proliferation and induced a spherical cell morphology with disorganized cytoskeletal architecture, consistent with literature [151,152], FCS-modified scaffolds supported robust SMC spreading, alignment, and contractile phenotype, with abundant α-SMA fibers, as well as the formation of a mature endothelium on the luminal surface. Together, these findings suggest that MSP-functionalized vascular grafts not only promote rapid endothelialization but also foster stable medial integration, addressing two critical requirements for long-term graft patency and function [143].

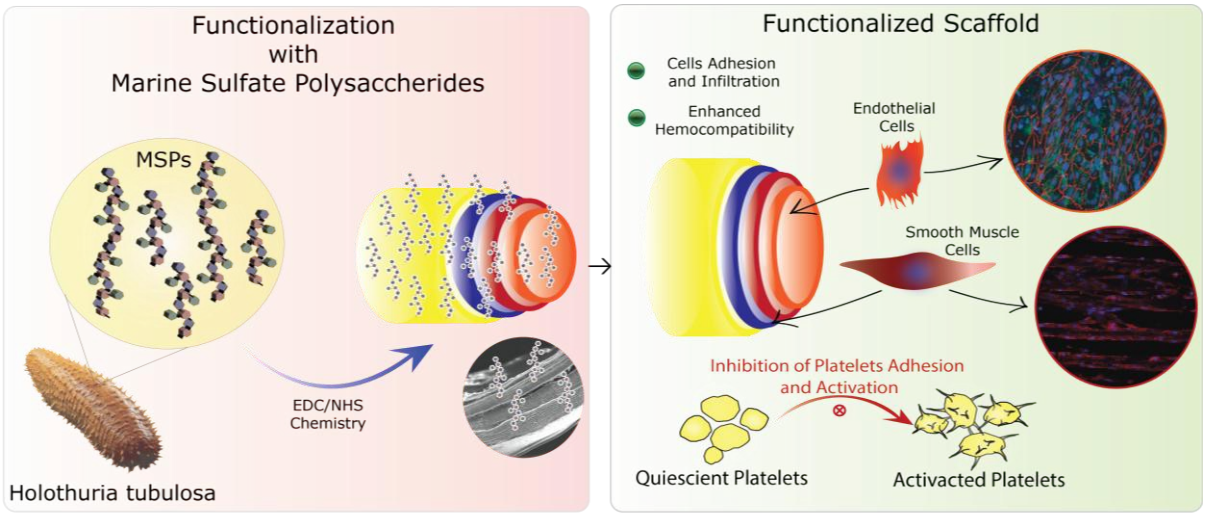

Figure 5. Functionalization of multi-layered vascular scaffolds, obtained by a combination of electrospinning and 4-Axis printing, with MSPs. Covalent crosslink of MSPs from *Holothuria tubulosa* onto polymeric scaffolds (EDC/NHS chemistry) creates a bioactive interface that inhibits platelet activation while driving endothelialization and smooth muscle cell integration, key determinants of long-term graft patency (Adapted from Obino et al [36,143]).

In Vivo Evidence and Translational Progress

While the integration of MSPs into sTEVGs remains at an early stage, emerging *in vivo* evidence indicates encouraging translational potential. In a rabbit carotid artery model, fucoidan-functionalized polyvinyl alcohol (PVA) grafts maintained full patency and supported endothelialization, whereas unmodified grafts occluded rapidly due to thrombotic events. Moreover, fucoidan-coated grafts significantly reduced intimal hyperplasia, suggesting improved vascular healing and remodeling [145]. In a subsequent study by the same team, the combination of fucoidan functionalization with luminal micro-gratings further enhanced in situ

endothelialization, resulting in substantially increased endothelial coverage along the graft lumen and improved graft patency in the same rabbit carotid artery model [148]. These findings underscore the translational relevance of integrating MSP-based biochemical cues with topographical guidance to overcome the limited endothelialization of synthetic vascular grafts. Similarly, by short-term implantation in chick chorioallantoic membrane, fucoidan–PCL nanofibrous meshes were shown to promote angiogenesis, further supporting the regenerative potential of MSP-based materials [111].

Beyond fucoidan-based systems, other MSPs have also demonstrated promising translational potential in cardiovascular biomaterials. In a subcutaneous implantation model in rats, ulvan-based functionalization of decellularized porcine pericardium significantly enhanced endothelialization while reducing inflammatory cell infiltration and calcification compared with unmodified constructs [50]. *In vitro*, the same functionalized scaffolds promoted endothelial cell adhesion, migration, and proliferation while simultaneously reducing platelet adhesion and inflammatory responses, highlighting the multifunctional role of ulvan as both a bioactive and hemocompatible interface for cardiovascular tissue engineering [50].

A critical translational requirement is the preservation of mechanical integrity following MSPs incorporation. Encouragingly, MSPs functionalization—whether via surface adsorption, covalent conjugation, or blending—does not compromise graft mechanical properties within the ranges tested. Fucoidan incorporation did not alter the crosslinking density or tensile strength of PVA scaffolds [145], and electrospun PCL grafts retained porosity and burst strength after MSPs coating [143].

From a regulatory and clinical perspective, MSP-functionalized grafts benefit from inherent biodegradability and favorable blood-contact compatibility. MSPs such as fucoidan and FCS are generally considered biodegradable and have shown favorable biocompatibility profiles with minimal cytotoxicity and immunogenicity reported in preliminary studies. However, rigorous preclinical evaluation remains essential to confirm long-term safety, particularly regarding immunomodulation and degradation byproducts.

Challenges in Standardization and Clinical Translation

Clinical translation of MSPs is constrained less by lack of bioactivity than by the difficulty of producing chemically comparable materials. Fucoidans and sea-cucumber fucosylated glycans vary substantially with species, geographic and environmental conditions, harvesting season, and downstream extraction or purification procedures [153,154]. Moreover, the absence of harmonized extraction, purification, and analytical workflows across laboratories frequently results in substantial differences in monosaccharide composition, uronic-acid content, acetylation, sulfation pattern, and molecular-weight distribution, even among nominally related MSP preparations. Consequently, reproducible structure–activity relationships and reliable cross-study comparisons remain challenging to establish [155,156].

Purity control represents an additional translational challenge because crude marine extracts may contain co-isolated polysaccharides, proteins, phenolic compounds, and endotoxin contaminants capable of influencing biological responses and immunological readouts. Consequently, rigorous purification and analytical characterization are essential to accurately evaluate MSP bioactivity and ensure reproducibility across studies. Standardization and optimization of the techniques commonly used for the purification, such as anion-exchange chromatography, molecular-weight-based fractionation, and multistep purification workflows can substantially improve compositional definition and reduce contaminants, supporting the development of clinically translatable MSP-based biomaterials [156–159].

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Among the structural parameters governing MSP bioactivity, molecular weight represents an important modulator of biological function. Anticoagulant activity is primarily dictated by sulfation degree, sulfation pattern, monosaccharide composition, and the specific interactions established with coagulation proteins and ionic species. However, molecular weight can strongly influence polysaccharide conformation, steric accessibility, and multivalent binding behavior, thereby modulating biological responses. Within matched fucoidan or fucosylated glycan series, decreasing chain length generally attenuates HCII/ATIII-mediated thrombin and factor Xa inhibition, whereas longer or native polysaccharide chains often exhibit stronger anticoagulant activity [160–163]. Conversely, controlled depolymerization of fucosylated glycans may preserve selective antithrombotic activity while reducing contact-pathway activation, platelet aggregation, and hemorrhagic liability [164]. Although immunomodulatory and regenerative effects have been reported across multiple molecular-weight ranges, several studies suggest that low-molecular-weight fucoidans may display enhanced anti-inflammatory, pro-angiogenic, and endothelial-supportive activity by modulating inflammatory signaling, cytokine-associated pathways, immune-cell recruitment, and endothelial repair mechanisms in vascular models [123,164–168].

These observations highlight the importance of developing more standardized and reproducible workflows for the future clinical translation of MSP-based biomaterials. A deeper understanding of structure–function relationships will be essential, particularly regarding how molecular weight, sulfation patterns, and polysaccharide composition influence biological activity. In this context, advanced analytical techniques, including nuclear magnetic resonance (NMR), molecular-weight analysis, and mass spectrometry, will play an important role in improving structural characterization, cross-study comparability, and reproducibility of MSPs preparations [169–174]. In parallel, controllable depolymerization, selective chemical modification, and the development of synthetic or semi-synthetic MSP analogues may represent promising strategies to improve reproducibility, tune biological activity, and facilitate the future clinical translation of marine glycan-based biomaterials.

Manufacturing challenges further complicate the translational pathway of MSP-based technologies, particularly with regard to batch-to-batch consistency, endotoxin-free purification, and precise characterization of sulfation and molecular weight distributions. These hurdles are magnified when sourcing MSPs from wild marine organisms, where seasonal and environmental variability can significantly influence polysaccharide composition and biological activity. In this context, experimental mariculture of different porifera species has been developed successfully, allowing for sustainable harvesting of specimens in a controlled setting, fully aligned with the blue economy principles [175]. Particularly intriguing is the Integrated Multi-Trophic Aquaculture (IMTA) system, a new generation aquaculture that, by combining organisms from different trophic levels within biomimetic ecosystems, may provide a scalable and environmentally sustainable route for MSP production from different sources while simultaneously reducing waste and contributing to bioremediation [176]. From a regulatory perspective, MSP-functionalized vascular grafts will likely require classification as combination products, necessitating extensive evaluation of biocompatibility, sterility, reproducibility, and therapeutic efficacy. Although fucoidan is currently marketed as an FDA-approved dietary supplement, no MSP-based therapeutic or blood-contacting medical device has yet received regulatory approval for cardiovascular applications [177].

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Future Perspectives

The future of scaffold functionalization for vascular regeneration lies in the convergence of biomimetic materials, immunomodulation, advanced fabrication technologies, and smart, multifunctional systems, with a strong emphasis on translational research and clinical validation. MSPs have moved beyond proof-of-concept and now consistently demonstrate anticoagulant, antiplatelet, and pro-endothelial activity when integrated into vascular grafts. The challenge ahead is not whether MSPs are bioactive, but how to harness that bioactivity in a standardized, tunable, and clinically reproducible way. Establishing clear correlations between sulfation motifs, molecular weight, and defined biological outcomes under physiological flow will be essential for rational design.

On the translational side, manufacturing and regulatory hurdles remain major barriers. Natural extracts are intrinsically heterogeneous, with batch-to-batch variability in sulfation, backbone composition, and molecular weight. Sustainable sourcing (e.g., aquaculture, biorefinery pipelines) or synthetic analogues will be required for scalability and reproducibility. Regulatory approval will also demand harmonized protocols for characterization, sterility, and large-animal validation, as most current studies remain short-term and small-scale. While preclinical results are promising, future research must address challenges in scaling up, long-term patency, and performance in disease or aging models. Large animal studies and clinical trials will be essential to validate the translational potential of these advanced scaffolds.

Looking forward, MSPs should be envisioned not as replacements for heparin or other mammalian GAGs, but as versatile, lumen-facing biointerfaces capable of modulating thrombosis, endothelialization, inflammation, and even local angiogenesis. A particularly exciting frontier is the possibility of tailoring MSPs functionalization to the different stages of graft healing. One could envision distinct MSPs chemistries deployed sequentially with highly sulfated domains to ensure immediate hemocompatibility, followed by less sulfated motifs that favor endothelial migration, and later structural variants that stabilize mature endothelium and dampen inflammation. Time-dependent presentation, achieved through degradable linkers or stimuli-responsive release, could transform MSPs into dynamic instructive cues rather than static coatings.

Another promising direction is the use of layer-by-layer functionalization to reflect the natural complexity of the vessel wall. For instance, luminal MSPs might be optimized for endothelial quiescence, medial MSPs for preserving contractile SMC phenotype, and adventitial MSPs for guiding fibroblast remodeling or local angiogenesis. Such stratified design would create a crosstalk among the biomaterial and multiple cell types, orchestrating vascular regeneration in a spatiotemporally controlled manner. Moreover, MSPs could act as smart linkers, exploiting their sulfate-dependent binding affinities to anchor and release growth factors, peptides, or extracellular vesicles locally. This would enable spatially programmed reservoirs that deliver bioactive signals only where needed, such as at sites of flow disturbance or high inflammatory burden.

If a clear understanding of structure–function relationships, reproducible manufacturing, and long-term validation will be achieved, MSPs could evolve into a new class of precision biomolecules for vascular medicine: not static coatings, but adaptive biointerfaces capable of guiding complex cellular processes across time, space, and tissue compartments.

Conclusion

In conclusion, recent findings validate the core premise that MSPs coating, functionalization, or incorporation can impart antithrombotic and pro-endothelial properties to synthetic vascular

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grafts without compromising mechanical performance. As structure–function relationships become clearer, rational design of MSP-functionalized scaffolds may overcome long-standing limitations in small-diameter TEVGs. With continued progress in standardization, safety validation, and regulatory navigation, MSPs hold strong potential to transform vascular biomaterials and advance the field of regenerative medicine.

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