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Is the endogenous ligand for PEAR1 a proteoglycan: clues from the sea

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Abstract

Platelet Endothelial Aggregation Receptor 1 (PEAR1) is an orphan receptor of unknown function which mediates powerful activation of platelets and endothelial cells in response to crosslinking by antibodies and sulfated polysaccharides belonging to the dextran and fucoidan families. PEAR1 is a single transmembrane protein composed of 15 epidermal growth factor-like repeat sequences and with a conserved binding motif, YXXM, which when phosphorylated binds to phosphoinositide 3-kinase (PI3K). The 13th of the repeats has a heparin-binding sequence that is the site of interaction with the sulfated fucoidans and the only known endogenous ligand FcεRIα. Crosslinking of PEAR1 drives Src family kinase phosphorylation of the cytosolic tail leading to binding and activation of PI3K. In this Opinion Article, we summarise the literature on PEAR1 expression, structure and signalling, and the search for further endogenous ligands. We highlight one article in which phosphorylation of a 150 kDa platelet protein by heparin-containing ligands has been reported and propose that PEAR1 is a receptor for one or more glycosaminoglycan-conjugated proteins (proteoglycans). The up-regulation of PEAR1 at sites of inflammation in the vasculature and its role in angiogenesis suggests a role in the interplay of inflammation, platelets, coagulation and thromboinflammation. We speculate that this may explain the link between single nucleotide variants in PEAR1 and cardiovascular disease.

PEAR1 in human platelets

PEAR1 was first described in 2005 as a novel aggregation receptor expressed on platelets and endothelial cells [1]. Crosslinking of PEAR1 by a PEAR1-specific antibody generated rapid and full aggregation of platelets that is similar to that of other classical platelet agonists [2]. PEAR1 has since been shown to be a receptor for the sulfated polysaccharides, fucoidans and dextran sulfates, which are found in seaweed and bacteria, respectively [3,4]. The only known endogenous ligand for PEAR1, the high affinity immunoglobulin E receptor subunit α (FcεRIα), increases the magnitude of aggregation by platelet agonists but has no effect on its own [5]. The significance of the increase in aggregation is not known but suggests a potentially important role for FcεRIα in enhancing the sensitivity to activation by other agonists.

The expression level of PEAR1 in human platelets has been estimated using quantitative proteomics to be approximately 1800 copies [6], which is similar to that of the glycoprotein receptors GPVI and CLEC-2. PEAR1 is expressed on both the platelet surface and on α-granules, with the level of expression on the surface being increasing upon platelet activation [2]. Thus, the fusion of α-granules with the platelet membrane provides a pathway to reinforce platelet activation by PEAR1 ligands.

PEAR1 was originally reported to undergo marked tyrosine phosphorylation during platelet aggregation induced by thrombin and collagen [1,2]. This suggested the presence of an endogenous ligand on the platelet surface or the release of a ligand upon activation. However, in our publication in 2019 [3], we were unable to confirm tyrosine phosphorylation in platelets activated by the GPVI agonist convulxin and the CLEC-2 agonist rhodocytin, whereas rapid and marked phosphorylation was seen in response to synthetic glycopolymers (α-L-fucoside pendant glycopolymers) and natural sulfated polysaccharides [3]. We have also been unable to show phosphorylation of PEAR1 in response to thrombin and collagen under both aggregating and non-aggregating conditions (unpublished). The lack of a detectable increase in phosphorylation of PEAR1 is consistent with the absence of a role of PEAR1 in supporting haemostasis or thrombus formation following $FeCl_3$ injury in PEAR1-deficient mice [7]. These observations have led us to speculate that the functional role of PEAR1 in platelets is in pathways other than classical haemostasis.

PEAR1 in other cells

PEAR1 takes its name from its discovery on platelets and on vascular endothelial cells using microarray and proteomics [1]. Two studies using immunohistochemistry have since shown expression of PEAR1 on endothelial cells in human liver, lung, and kidneys [8], and on murine pulmonary microvascular endothelial cells [9]. PEAR1 mRNA expression and protein levels vary between different types of endothelial cells. The highest mRNA expression level was observed in microvascular endothelial cells from the heart, while freshly isolated blood outgrowth endothelial cells have the lowest mRNA level [8]. What governs the differences in expression between the different endothelial cell types is yet to be explored. PEAR1 was shown to be primarily expressed in filopodia and lamellipodia of cultured human umbilical cord vein endothelial cells [8].

There have been relatively few studies investigating the role of PEAR1 in endothelial cells [8,9]. Vandenbriele *et al.* reported that PEAR1 knockdown increases the proliferation rate of endothelial cells *in vitro* and the neovascularisation in a murine hind limb ischemia model *in vivo* [8]. Interestingly, the vasculature in the PEAR1-deficient mouse prior to ligation was comparable to wild type mice suggesting that PEAR1 does not play a role in angiogenesis during embryological vascular development [8]. PEAR1 expression has also been shown to be upregulated in the pulmonary microvascular endothelial cells in a lung injury model in mice [9]. Both of these studies are characterised by an alteration of shear forces, induction of local hypoxia, production of reactive oxygen species and inflammation. This indicates that the physiological role of PEAR1 may lie in the response to hypoxia or

inflammation. Intriguingly, some receptors, for example Glycoprotein Ibα, is only able to interact to their endogenous ligand, von Willebrand Factor, when the ligand is subjected to a sufficient amount of shear force which exposes the ligand's binding site for the receptor [10]. Whether a possible link with shear is because PEAR1 is a mechanoreceptor, or how ligand interactions are affected by shear, is an interesting area that requires further investigation.

PEAR1 has also been reported to be present in several other cells types in the Human Protein Atlas project (www.proteinatlas.org), including tissue-resident macrophages in the lungs, tissue-resident dendritic cells in the skin (Langerhans cells), and in neurons in the central nervous system. The physiological role of PEAR1 in these cells is not known.

PEAR1 structure and signalling

PEAR1 is a part of the Multiple epidermal growth factor (EGF)-like domain family and is also known as multiple EGF-like domains protein 12 (MEGF12) and JEDI1. PEAR1 is a single transmembrane protein with 15 EGF-like repeats (Figure 1). Crosslinking of PEAR1 in platelets by PEAR1-specific antibodies or sulfated polysaccharides induces Src family kinase phosphorylation of the cytoplasmic tail leading to platelet activation [1,3–5]. One study has predicted six phosphorylation sites on the cytosolic tail of PEAR1, of which three have been experimentally proven; tyrosine 925, serine 953, and serine 1029 [1]. One of the predicted phosphorylation sites is tyrosine 943, which is present in a consensus site, YXXM, for binding to the SH2 domains of the 110 kDa regulatory subunit of the class I family of PI3K. Activation of the P85 catalytic unit by the regulatory subunit generates the lipid messenger phosphatidylinositol 3,4,5-trisphosphate (PIP3) which binds to pleckstrin homology (PH) domains in a variety of proteins, including the serine/threonine kinase Akt (Figure 1). Inhibitors of Src family kinases and PI3K abolish platelet activation induced by antibodies to PEAR1 or sulfated polysaccharides, demonstrating a unique mechanism of activation by a platelet surface glycoprotein [2–4] independent of Syk and PLCγ2, and major Ca^{2+} signalling [3]. PEAR1 has also been shown to activate PI3K in megakaryocytes [11] and in endothelial cells [8,9].

PEAR1 in mouse platelets

In contrast to human platelets, where PEAR1 is upregulated on the surface upon activation [2], the majority of PEAR1 is already present on the surface membrane of mouse platelets [7]. The investigation of signalling by PEAR1 in mouse platelets is limited to the use of PEAR1-specific antibodies as, unlike in human platelets, dextran sulfate activates platelets in mice via both PEAR1 and CLEC-2 [4] and fucoidan activates mouse platelets primarily through CLEC-2 [3,12]. This species difference may reflect the twenty fold greater level of expression of CLEC-2 in mouse relative to human platelets [6]. There are approximately 3100 receptor copies of PEAR1 in mouse platelets [13], while there are about 1800 copies on human platelets [14]. For CLEC-2 the species difference is larger with ~41 000 copies in mouse platelets [13] and 2000 - 4000 in human platelets [14]. However, there may also be sequence variations that cause affinity alterations in the interaction of the sulfated polysaccharides with both receptors. PEAR1 is also expressed on endothelial cells [8,9] and on peripheral glial cells in mice [15].

The function of PEAR1 in the mouse has been investigated through the generation of a global knockout. PEAR1-deficient mice, designated $Pear1^{tm1a(KOMP)Wtsi}$, are born with a Mendelian pattern of inheritance and are indistinguishable from littermate controls [7,15]. No abnormalities in platelet count and morphology have been reported. Platelet aggregation to a PAR-4 activating peptide, collagen and ADP is similar to wild type platelets, including to low concentrations. Clot retraction induced by thrombin in platelet rich plasma is also unaltered [7]. In contrast, activation by dextran sulfate is reduced and reversible in PEAR1-deficient mice with the residual response mediated through CLEC-2 [4]. Tail bleeding times and thrombosis in a $FeCl_3$ mesenteric injury model are similar to littermate controls [7], suggesting that PEAR1 does not play a primary role in haemostasis or arterial thrombosis in the mouse.

PEAR1 in cardiovascular disease: GWAS studies

Some of the common variants of PEAR1 and their correlations with platelet function and disease identified by genome wide association studies (GWAS) are summarized in Table 1 [16–21]. Many of the single nucleotide variants (SNVs) are found in introns, which could lead to alternative splicing of PEAR1 but also regulation of other distant genes. One of the variants has been shown to increase expression of PEAR1 [16] (Table 1).

Surprisingly, some of the SNVs correlate with altered platelet aggregation to ADP, collagen, and epinephrine [16,22], despite the lack of evidence for a role of PEAR1 in platelet activation by any of these agonists. One explanation for this is a possible role for PEAR1 in megakaryocyte development or platelet formation, perhaps leading to a change in receptor expression or downstream signalling proteins. Although, this is not supported by the observation that deletion of PEAR1 in mouse platelets does not give rise to altered responses to classical agonists [7]. There may however be a species difference in the role of PEAR1 between human and mouse.

The primary associations of the SNVs in PEAR1 is with cardiovascular diseases, and include an increase in risk for coronary artery aneurysm in patients with Kawasaki disease [17], and following percutaneous coronary intervention treatment for coronary artery disease and acute coronary syndromes [18]. An association with pulmonary thromboembolism in a Chinese family of three generations has also been reported but further case studies are needed to confirm this association [21]. The molecular basis for these associations is not yet known and could be due to the presence of PEAR1 on endothelial and other cell types.

Endogenous ligands

To date, the only proposed endogenous ligand for PEAR1 is FcεR1α which was identified using AVidity-based EXtracellular Interaction Screen (AVEXIS) technology, a protein-based array designed to identify interactions between membrane proteins [5]. A specific interaction was confirmed by surface plasmon resonance giving an estimated K_D for binding of monomeric FcεR1α to PEAR1 of 27 nM [5]. However, care should be taken when comparing affinities of recombinant constructs and native proteins. FcεR1α is a heavily glycosylated protein [23] and the glycosylation pattern may vary between the natural source and the expression system. The pentameric FcεR1α was shown to increase the magnitude of platelet aggregation by collagen, as measured by light transmission aggregometry, but to have no effect on its own [5].

FcεR1α is expressed at high levels on mast cells and eosinophils and therefore could mediate a direct interaction between these two cell types and platelets. FcεR1α has been reported to be expressed at low levels on platelets, but as discussed above, there is no clear evidence for a role of PEAR1 in haemostasis and thrombosis. In addition, the low level of expression of FcεR1α is consistent with the lack of substantial phosphorylation of PEAR1 in activated platelets. The interaction between PEAR1 and FcεR1α is not preserved in mice (YS, unpublished), possibly due to the low sequence homology between mouse and human FcεR1α (46% by identity, sequence alignment, uniprot.org). The amino acid sequence homology between human and mouse PEAR1 is approximately 83% by identity (sequence alignment, uniprot.org) and in both species the receptor contains 15 EGF-like repeats [1].

Exogenous ligands

In recent years, sulfated polysaccharides have been identified as potent ligands for PEAR1 [3,4]. This was first shown by Vandenbriele *et al.* who reported that dextran sulfate, a polysaccharide of bacterial origin, induces aggregation of platelets through PEAR1 [4]. More recently, we have shown that naturally occurring fucoidans and synthetic fucoidan-mimetic glycopolymers activate PEAR1 in human platelets [3].

Dextran sulfates of bacterial origin and fucose-based polysaccharides of seaweed origin have been widely studied in biology due to their anti-viral, anti-cancer and thrombo-modulating properties [24]. However, studying the effect of naturally occurring sulfated polysaccharides is complex due to their heterogenic nature [24]. To circumvent this, we used synthetic fucoidan-mimetic glycopolymers of known chain-lengths and monomeric composition and spacing. We also controlled the degree of sulfation to match that of fucoidan isolated from *Fucus vesiculosus* [3,25]. Both pure fucoidan from *Fucus vesiculosus* (>95% purity) and synthetic glycopolymers mediate activation of human platelets through PEAR1, and not CLEC-2 as previously proposed for naturally occurring fucoidans [26]. The conflicting observation may reflect impurities or differences in extraction methods of commercial preparations [24]. Determining structure-function relationships, and the effect of various preparation techniques, are important areas when studying naturally occurring carbohydrates.

Structure-function relationship of sulfated polysaccharides and PEAR1

We have shown that sulfation of fucoidans is critical for PEAR1 binding and platelet activation by PEAR1 [3,25]. PEAR1-activating fucoidans have a high degree of sulfation (DS) in the order of 81% which is equivalent to 1.6 sulfates per monomer, while the synthetic glycopolymers (α-L-fucoside pendant glycopolymers) have a DS between 87-89%, which is closer to 2.6 sulfates per monomer [3,25] (Figure 2).

The length of the polysaccharides and glycopolymers is also important for potency. For glycopolymer-mediated PEAR1-driven platelet activation, we have shown that ~13 monomeric units are sufficient to achieve maximal aggregation [3]. Longer glycopolymers with an average chain-length of 329 are ~20-fold more efficient at causing aggregation than those with an average length of 13, in proportion to the greater number of monomeric units [3]. We speculate that the higher potency of the longer glycopolymer, when used at equimolar concentrations, is because it can cause more PEAR1 clustering. A study by Kauskot et al. show that an antibody to the extracellular domain of PEAR1 can cause PEAR1-driven activation [2], which may indicate that a large enough number of activated dimers could be sufficient.

The ligand binding site on PEAR1 is a heparin-binding consensus sequence

We have shown that the synthetic glycopolymers bind to the same EGF repeat on PEAR1, EGF-like repeat 13, as FcεR1α [3,5]. This is the only EGF-like repeat in PEAR1 that has a sequence that resembles a *heparin binding consensus sequence.* The sequence is composed of a cluster of positively charged amino acids (BXXBB, where B is a positively charged amino acid). This sequence is preserved in both human and mouse PEAR1. We predict the sequence to bind to sulfates of the glycopolymers and polysaccharides. This therefore raises the question of whether other sulfated sugars also bind to PEAR1.

Structure-function relations of sulfated polysaccharides

Sulfated polysaccharides are abundantly expressed in biology and include glycosaminoglycans like heparan sulfates, chondroitin sulfates, dermatan sulfates, keratan sulfates, and heparins. Although these differ markedly in their chemical structure, monomer composition, linkage and degree of sulfation (Figure 3). The sulfated polysaccharides can also be linked to proteins in different combinations, also known as proteoglycans.

We know that fucoidan, dextran sulfate, and the synthetic glycopolymers cause human platelet aggregation [3]. However, they are all structurally different as shown in Figure 2. Fucoidan from *Fucus vesiculosus* mainly consists of a backbone of 1-3 or alternating 1-3 and 1-4 linked fucoses, with two potential sulfation sites on either C2 and C3, or C3 and C4, depending on linkage and branching [27,28]. Dextran sulfate in contrast consists of 1-6 linked dextrans with three potential sulfation sites; C2, C3, and C4, depending on branching [29]. The synthetic glycopolymers used in our 2019 study differ from

both [3]. The synthetic glycopolymers are chains of covalently coupled methacrylated α-L-fucoside pendants with three potential O-sulfation sites on C2, C3, and C4 [3,25]. One of the major similarities between all three is that they have approximately two sulfate groups per monomeric residue.

We have investigated which native glycosaminoglycan could be closest in similarity to the known PEAR1-agonists in terms of charge distribution (Figure 3). Heparin is the human glycosaminoglycan with the highest degree of sulfation, and one of the few glycosaminoglycans that can contain two or more sulfates on a single monomer. It also has a unique 3-O sulfation which is essential for its strong interaction with antithrombin III [30,31]. Most of the other glycosaminoglycans only have one sulfate group per monomer [31–35]. Heparan sulfate, one of the most abundantly expressed glycosaminoglycans that coats virtually every cell surface, has <1 one sulfate per disaccharide unit and does not contain the 3-0 sulfation that is unique for heparin [30,33,34].

Chondroitin sulfate is classified by its sulfation pattern with type A and C being the most common in mammals. Chondroitin A, C, and D are only sulfated on one oxygen per monomer, leaving just chondroitin E with a potential of two sulfates on a single monomeric unit [36]. However, the chemical structure of chondroitin E is distinctly different from heparin. Chondroitin sulfate E is generally 2,6 sulfated on the glucuronic acid, and the amine group of the galactosamine is generally acetylated [37]. Most chondroitin chains contain a variation of chondroitin types, resulting in a heterogenous mix of sulfation [36].

Dermatan sulfate (previously known as chondroitin sulfate B), is predominantly sulfated on one residue per disaccharide unit in mammals [31,33,36]. Although keratan sulfate is a very heterogenous glycosaminoglycan and has a maximal potential sulfation of two sulfate groups on a single monomer, it tends to be sulfated on one single position per monomeric unit (6-O-sulfation). The degree of sulfation varies depending on the species and the tissue from which it was derived [32,35,38].

The absence of robust PEAR1-phosphorylation in both human and murine platelets upon activation by convulxin, rhodocytin [3], thrombin, and collagen (unpublished) shows that the most abundantly expressed glycosaminoglycans in platelets and on endothelial cells are unlikely to be endogenous PEAR1 ligands. Platelets would come in contact with them during aggregation. Many of the cartilage and extracellular matrix glycosaminoglycans would also be encountered by the platelets in the mouse tail bleeding model, where the absence of PEAR1 has minimal effect [7]. Taken together, this leaves heparin as the most likely candidate among the endogenous glycosaminoglycans.

Are heparin-based glycosaminoglycans ligands for PEAR1?

One key factor, that sets fucoidan and dextran sulfate apart from native glycosaminoglycans is that they can be branched [27,29] and we speculate that this may be important for the clustering of PEAR1. A recently published paper by Lin et al. shows that branching is important for sulfated polysaccharide-induced platelet activation, although this study did not go on to test weather this was through PEAR1 [39]. One way that a human linear glycosaminoglycan could resemble a branched structure is by attachment to a protein core.

Heparin was discovered in 1916 and is still the most widely used anticoagulant [40,41]. Since its introduction, several groups have reported that heparin modulates platelet activation by other agonists [42–45] but does not induce activation on its own [44]. Heparin alone, or when used in the preparation of platelets, does not stimulate phosphorylation of bands in the PEAR1 kDa region [3,25,44]. Preparing the platelets in the presence of heparin does not inhibit aggregation induced by fucoidan, dextran sulfate, or sulfated polysaccharides [3,25]. This shows that a linear glycosaminoglycan on its own will either not bind to PEAR1 or cause sufficient clustering to induce platelet activation and aggregation. However, a heparin-conjugated proteoglycan-mimetic, known as Dual Platelet and Anticoagulant (APAC), stimulates marked tyrosine phosphorylation of an unknown

band of 150 kDa in platelets which migrates at the position of PEAR1. APAC also binds to the major platelet ITIM inhibitory receptor, G6b-B, preventing activation of platelets [44]. In mouse platelets deficient in G6b-B, APAC stimulates powerful activation [44] and we speculate that this could be mediated through PEAR1. This provides additional, albeit indirect evidence, that the endogenous ligand for PEAR1 is a proteoglycan.

There are very few heparin-conjugated proteoglycans in the human body, with the main candidate as a potential ligand of PEAR1 being serglycin [46,47]. Platelets themselves contain serglycin [48] but granule secretion, or surface-surface contact (which occurs during aggregation), does not cause PEAR1 phosphorylation [3]. We believe that the key to this is the glycosaminoglycan composition of the proteoglycan, that the sulfation ratio of platelet-derived serglycin and the position of the sulfates within glycosaminoglycan chains are not optimal for PEAR1 activation. The major sulfated polysaccharide in platelet serglycin is chondroitin sulfate [48], which has a distinct structure and biological function to heparin [37]. In contrast, there are several reports of similarities between fucoidans and heparins in regard to protein interactions and biological functions [49–51]. Taken together, we propose that the glycosaminoglycan composition of the proteoglycan is of major importance in the interaction with PEAR1.

Mast cells and basophils are the only cell types in the human body that are able to produce heparin, due to the specific sulfotransferases required, and hence the only cell types that can make heparin-conjugated serglycin [46,52]. There is increasing evidence showing mast cell involvement in formation of deep vein thrombosis [53]. Mast cell granule release causes endothelial cell activation, which is crucial for the inflammation driven process which underlies deep vein thrombosis [53,54]. Whether PEAR1 is involved in this and other mast cell-based thromboinflammatory disorders is not known.

Concluding remarks

In this short article, we have set out the basis for our proposal that the endogenous ligand for PEAR1 is likely to be a proteoglycan fitted with glycosaminoglycans containing di-sulfated monomeric residues. The native glycosaminoglycan with the highest degree of sulfation is heparin [30], and the major heparin-conjugated proteoglycan is serglycin [46]. There are many knowledge gaps to be filled, and hypotheses to be tested, but one thing is clear: PEAR1 is a fascinating orphan signalling receptor which is implicated in inflammatory processes and cardiovascular disease.

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Table 1

Table 1 Selection of the most commonly mentioned PEAR1 variants and their correlations.

Variant	Correlation	Ref
rs12041331 (Intron)	Increased PEAR1 receptor expression. Increased platelet aggregation to ADP, collagen, and epinephrine in the presence and absence of aspirin.	[16]
	Increased risk for coronary artery aneurysm in patients with Kawasaki disease.	[17]
rs12566888 (Intron)	Increased platelet aggregation to ADP, collagen, and epinephrine in the presence and absence of aspirin.	[16]
	Trend for increased risk of adverse events following PCI treatment for stable CAD and ACS in men.	[18]
rs2768759	Increased platelet aggregation to ADP, collagen, epinephrine, and arachidonic acid.	[19]
(Downstream of gene)	Homozygous carriers have increased risk of adverse events following PCI treatment for CAD and ACS	[18]
rs3737224 (Coding-syn)	Increased platelet aggregation to high dose ADP, collagen, and epinephrine.	[16]
	Increased platelet P-selectin expression to XL-CRP-stimulation, increased platelet fibrinogen binding to XL-CRP- and ADP-stimulation.	[20]
rs41273215 (Intron)	Decreased platelet count and lower reactivity in TRAP-induced platelet aggregation in CAD and ACS patients.	[18]
	Increased platelet P-selectin expression and fibrinogen binding to XL-CRP-stimulation.	[20]
rs778026543 (Splice region)	Association with pulmonary thromboembolism in a Chinese family of three generations.	[21]

PCI = Percutaneous coronary intervention, CAD = Coronary artery disease, ACS = Acute coronary syndrome

Figure 1

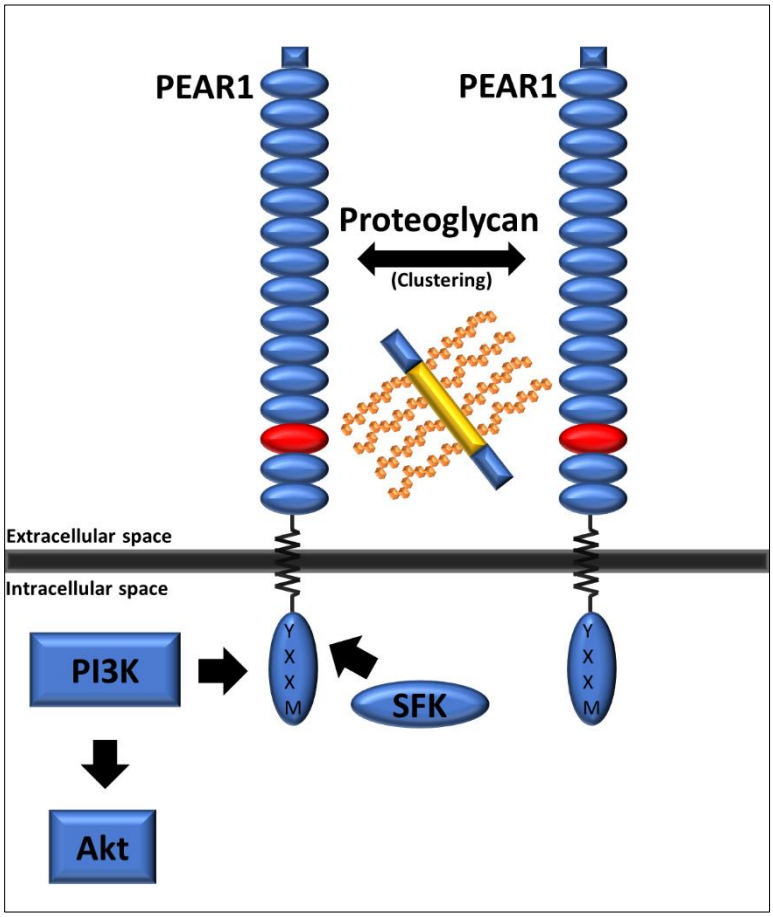

Figure 1 Schematic overview of PEAR1 signalling in platelets induced by theoretical proteoglycan clustering.

The Platelet Endothelial Aggregation Receptor 1 (PEAR1) is a 15 epidermal growth factor (EGF)-like repeat receptor, where the 13th EGF-like repeat has been shown to interact with sulfated glycopolymers (red). We propose that PEAR1 can be activated by proteoglycans conjugated with highly sulfated glycosaminoglycans (orange). The specific glycosaminoglycan presented in the image is serglycin, it has a Ser-Gly repeat sequence (yellow) that holds maximum 8 glycosaminoglycan chains in humans (orange). Upon activation, PEAR1 will be phosphorylated by a Src family kinase (SFK), followed by a direct interaction of the regulatory unit of phosphoinositide 3-kinase (PI3K) with the YXXM motif of the intracellular domain of PEAR1. The activation of PI3K will lead to subsequent AKT phosphorylation. PEAR1-induced signalling downstream of PI3K/AKT in platelets has not yet been studied. However, PEAR1-induced platelet activation eventually leads to platelet aggregation and secretion.

Figure 2

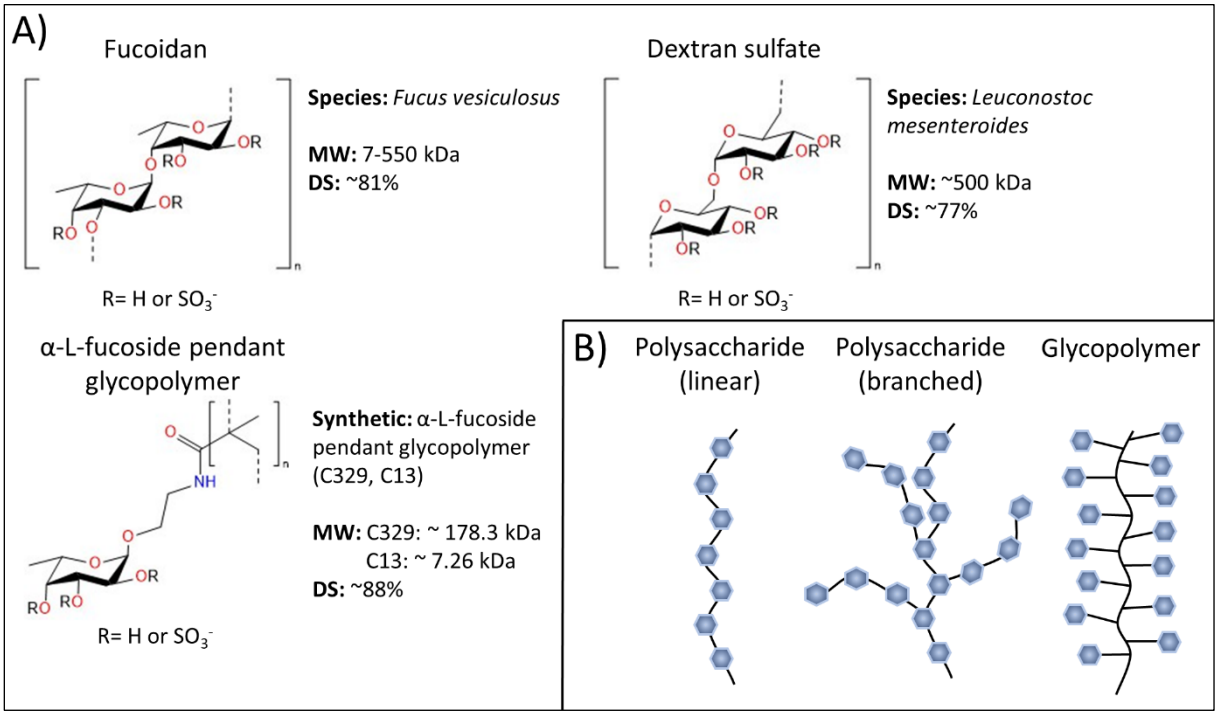

Figure 2 Chemical structure of fucoidan, dextran sulfate, and synthetic α-L-fucoside pendant glycopolymers.

A) Chemical structures of the most common sugar residues of fucoidan from *Fucus vesiculosus* and dextran sulfate from *Leuconostock mesenteroides*, and a monomeric unit of the α-L-fucoside pendant glycopolymer. Both the molecular weights (MW) and the degree of sulfation (DS) are presented as an average value. C13 and C329 are synthetic glycopolymers with names that represent their average degree of polymerisation. C13 is ~13 monomeric residues, while C329 is ~C329 monomeric residues in average, their polydispersity is 1.23 and 1.32 respectively [3,25].

B) The lower right corner of the figure contains a schematic overview of the difference in structure of a glycopolymers and a polysaccharide.

Figure 3

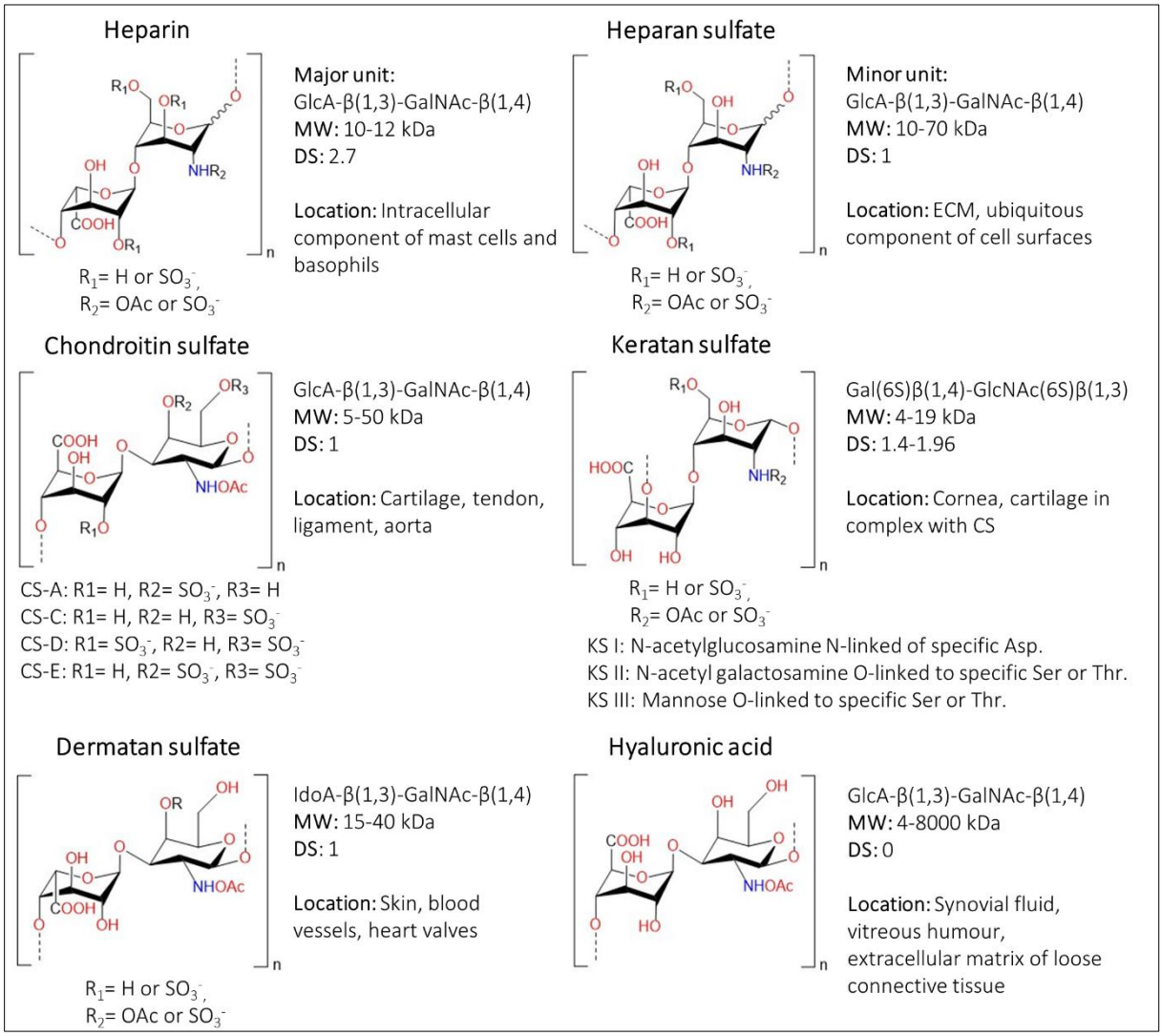

Figure 3 Chemical structure of the human glycosaminoglycan disaccharide units with highest sulfation potential.

Molecular weight (MW) is presented as a range, while the degree of sulfation (DS) is presented as the average number of sulfates per disaccharide unit.