

Review

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Review

Syndecans in Aortic Aneurysm Pathogenesis and Course: A Narrative Review. Biomarkers and Targets?

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Abstract: Maintenance of the integrity of entire endothelium, glycocalyx included, and therefore of tissue aorta's homeostasis, depends on the expressions of several molecular pathways and their interactions, such as syndecans molecules. Alterations in syndecans, i.e. quantitative or linking to their shedding, contributes to evocate endothelium dysfunction, which causes damage in the vessel wall due to the increased production of growth-stimulating and pro-inflammatory gene products. Inflammatory processes negatively affect the integrity of the endothelial glycocalyx, a dynamic layer of the luminal portion of endothelial cells composed of proteoglycans, glycoproteins, and glycosaminoglycans, i.e. syndecans. In turn, structural alterations of endothelial glycocalyx influence the coagulative state, increasing pro-thrombotic processes. The family of syndecans constitutes the major component of glycocalyx, or better the major source of cell surface heparan sulfate. It encompasses 4 components: syndecan-1, syndecan-2 and syndecan-4 (since syndecan-3 is expressed only in neural tissue), which have a fundamental role in regulating the events of acute and chronic aorta damage subsequently correlated with the formation of aneurysms. Considering such, the aim of our review is to highlight the current knowledge on the roles of syndecans, and based on the most recent literature, to analyze their relationship with the pathological processes of the aortic wall.

Keywords: endothelial glycocalyx; syndecans; aortic aneurysm.

1. Introduction

Aortic aneurysm is a usually silent clinical condition that progresses slowly until it reaches a critical point, beyond which the progression of the diameter can be very rapid, leading to dissection or rupture [1,2]. For this reason, the 5-year survival of untreated patients is 10-20% due to the high rate of lethal ruptures [3].

Unlike abdominal aortic aneurysm, which recognizes etiopathogenesis mostly related to atherosclerotic pathology, in thoracic aortic aneurysm the etiology is extremely variable. Therefore, based on the responsible etiological agent, we can distinguish different categories (sporadic, syndromic and familial non-syndromic aneurysms). In the case of sporadic form, the precise pathogenetic processes related to degeneration of the medial tunica and remodeling of entire aorta wall, are not fully known [3,4]. However, our group has evidenced in the last years the role of diverse pathways, differentially expressed, including for example Notch, TLR4, eNOs, RAS, TGF- β and MMP pathways, as well as the crucial involvement of inflammatory pathways [5–8]. They have been demonstrated to induce the remodeling of the aorta wall, including infiltration of leukocytes, increased levels of systemic parameters related to chronic inflammation, and augmented release of enzymes able to degrade the aortic wall, and to determine thoracic aortic aneurysm formation [9–11].

Recently, numerous data in the literature has demonstrated how the alteration of the endothelial glycocalyx (eGCX) increases inflammatory processes, leukocyte adhesion which augment the risk of vascular diseases [12–16]. The endothelial glycocalyx is a proteoglycan complex, composed of a

protein core (syndecans) and glycosaminoglycans, such as heparan sulfate, chondroitin sulfate and hyaluronan, lining the luminal surface of endothelial cells (ECs) in all blood vessels [17,18]. The integrity of the endothelial glycocalyx is essential for maintaining the homeostasis of the cardiovascular system, as it plays an important role in several functions for blood vessels: semi-permeable barrier, shear stress mechanosensation and mechano-transduction, stimulating the production of nitric oxide, protecting from cellular infiltration and activation of inflammatory processes [19].

Thus, the aim of our review is to analyze the role of endothelial glycocalyx dysfunction, and particularly the relationship of syndecans, in aortic aneurysm (AA) pathogenesis. This might help to identify new biomarkers and targets.

2. Syndecans and Their Role in Disease: What Is the Role in Aortic Aneurysm?

Emerging evidence has demonstrated the contribution of eGCX, with pleiotropic roles, in the onset and progression of cardiovascular diseases (CVD), aneurysm included. eGCX dysfunction is characterized by its degradation and has been observed to happen in diverse CVD, such as AA [20]; therefore, circulating levels of related eGCX degradation products have been proposed as CVD biomarkers. In addition to their role as diagnostic biomarkers, some eGCX fragments act as pathogenic factors in disease progression thus representing potential prognostic biomarkers. This is leading to the development of pharmacological interventions and potential strategies to attenuate eGCX degradation or restore its integrity, maintaining endothelial health into adult life. Among the eGCX degradation products, the syndecans (SDCs), heparan sulfate proteoglycans (HSPGs), have attracted the attention of several researchers [21,22]. The components of the glycocalyx are glycoproteins with short acid oligosaccharides and terminal sialic acids (SA), oligosaccharides and heparan sulphate proteoglycan (HSPGs), such as SDCs, and glycosaminoglycans (GAGs).

The SDCs family include four members: SDC-1, SDC-2, SDC-3, and SDC-4, consisting of a core protein modified by heparan sulfate (HS) chains. Each SDC has defined expression patterns and functions in their respective target tissues. SDC3 is expressed in neuronal and musculoskeletal cells. SDC-3 (N-SDC or *neuronal SDC*) is a transmembrane protein 442 amino acid long. Analysis of SDC-3 in experimental models of inflammation and AD showed that patients with AD have overexpression of SDC-3, not only in the brain but also in the periphery. Consequently, SDC-3 could serve as a basis for the development of future AD diagnostics. Syndecans, core proteins of the endothelial glycocalyx, are a family composed of four cell surface proteoglycans (namely, syndecan-1, -2, -3 and -4). Syndecans interact with a wide variety of molecules, including growth factors, cytokines, proteases, adhesion receptors, and extracellular matrix components, mainly via pendant glycosaminoglycans, such as heparan sulfate and chondroitin sulfate, which sequester and regulate the activity of heparin-binding growth factors, pro-inflammatory chemokines, and proteases [23,24].

2.1. SDCs and Their Expression in Inflammatory Conditions

SDCs expression depends on the release of growth factors and inflammatory molecules. It has been observed that SDC-1 mRNA levels increase in conditions of improved release of growth factors, such as platelet-derived growth factor (PDGF), FGF-2, TGF- β . On the contrary, the SDC-1 levels appear reduced, in the presence of factors that inhibit cell growth (e.g. IFN- γ). Moreover, SDC-2 mRNA increases in response to TGF- β 1 and IL-1 β , while decreases in response to IFN- γ , and remains stable in the presence of other growth factors [25]. SDC-4 synthesis is positively regulated by FGF-2, TGF- β 1, and hypoxia-inducible factor-1 pathway and the p38 MAPK pathway. In case of endothelial damage, an increased release of FGF-2 occurs and evokes an increased cell migration and proliferation to the aim of repairing the damaged site. However, it has been shown that increased synthesis of SDC-1 downregulates SDC-4 synthesis by suppressing the ERK1/2 and p38 MAPK signaling pathways to ensure tissue homeostasis [26].

2.2. SDCs and Aorta Aneurysms Formation

In Table 1, we summarize the data on the role of SDCs in the onset of aorta aneurysms. Precisely, Wen and colleagues have studied the expression of SDC-1, -2, -4 using 8-week-old male Apo-E deficient mice (mice subjected to an atherogenic diet), and after stimulation of arterial hypertension by infusion of angiotensin II with the aim of inducing the formation of aortic aneurysms. Initially, only the presence of SDC-4 was detected within the smooth muscle cells of the aortic wall media, while the presence of SDC-1 and -2 was not detected. After a week of treatment, and especially during the process of aortic aneurysm formation, an increased synthesis of SDC-1 emerged associated with the infiltration of macrophages, mainly at the level of the periaortic aorta. Precisely, in the created aneurysms an increase in the expression of SDC-2 was evident, while, due to the fragmentation of smooth muscle cells, a heterogeneous distribution of SDC-4 was observed. Considering these results, the authors have hypothesized that the increased release of SDC-1, with associated macrophage infiltration, may stimulate the inflammatory process, which, together with the increase in proteolytic activity, raises the degradation of the ECM, constituting the basic pathogenic process of aneurysm formation [27]. Conversely, SDC-2 enhances the expression of TGF- β I and II [28], resulting in increased synthesis of collagen and elastin fibers, smooth muscle cell proliferation and inhibition of metalloproteases. Thus, its increased expression during the aneurysm formation process could be explained as a compensatory mechanism to reduce dilation. Similar results emerged from the work of Zalghout et al. They conducted an *in-vitro* study on the aortic wall of twenty-five patients undergoing thoracic aortic replacement surgery and compared it with the aortic wall of eleven healthy subjects and it emerged, through RT-qPCR evaluation, ELISA and histological analysis. The data that emerged was a greater expression of syndecan-1 in the media of patients affected by aneurysm especially within the smooth muscle cells. Furthermore, they conducted a further *in vivo* analysis on 3-week-old SDC-1 $+/+$ a SDC 1 $-/-$ divided into 3 groups: the first group without treatment up to 8 weeks of life, the second and third groups treated with β -aminopropionitrile fumarate for 28 days, then infused subcutaneously of angiotensin II. Analyzing the onset of aneurysms in the 3 different groups, they demonstrated an equal incidence of thoracic and abdominal aneurysms in the two different populations; after 3 days from the infusion of angiotensin II no relevant different incidence of aneurysms; after 28 days of treatment an increase in the incidence of thoracic aneurysms in the syndecan-1 $+/+$ population compared to the syndecan-1 $-/-$ population and finally an increased incidence of abdominal aneurysms (8%) of the SDC 1 $-/-$ population compared to the SDC- 1 $+/+$ population (no presence of abdominal aneurysm), demonstrating the protective role of SDC-1 in the onset of abdominal aneurysms. Finally, no significant differences were highlighted between the two populations (SDC-1 $+/+$ and SDC-1 $-/-$) in terms of elastin degradation, collagen fiber fragmentation and leukocyte infiltration [29].

Likewise, Xiao et al, through the administration of elastin and angiotensin II in SDC 1 $-/-$ mice, highlighted during aneurysm formation an increase in macrophages associated with SDC-1, an increase in proteolytic activity, with an increase in MMP-9 and MMP-2 within the aortic wall and, furthermore, the reduction in the expression of IL-10 and Foxp3 demonstrates how the deficit of SDC 1 determines a reduction in the ability to limit the inflammatory process [24].

A key role has emerged for SDC-4 demonstrated in the manuscript by Hu and colleagues. In addition to the reduced expression of SDC-4 in the aortic wall of patients with abdominal aneurysm, they emphasized a very high incidence of abdominal aneurysms and a greater degradation of elastic fibers in SDC4 $-/-$ Apo E $-/-$ mice treated with angiotensin II infusion, compared to the ApoE $-/-$ group. Furthermore, by constructing SDC4 knockdown (SDC4-KD) and SDC4 overexpression (SDC4-OE) viruses capable of infecting smooth cells, they observed in physiological conditions a reduction in the levels of paxillin (cell adhesion protein) in SDC4-KD, an increase in the levels of MMP2, MMP9 and a reduction in the levels of α -SMA, calponin1 and SM-MHC in SDC4-KD treated with angiotensin II. On the contrary no difference was identified in the SDC4-OE population. Similarly, stimulation with angiotensin II determined a rise in the production of IL-1 β , IL6 and TNF- α (inflammatory cytokines) both in the control group, but especially in SDC4-KD, while strongly reduced in the SDC4-OE group. Finally, phenotypic changes in VSMCs via the RhoA- F/G-actin -MRTF-A pathway in the SDC4-KD group were found. These last, by enhancing the secretory characteristics of smooth muscle cells, further increased the risk of abdominal aneurysms [30].

Table 1. The recent data about the relationship of syndecans in aorta aneurysm formation.

Authors, Year	Method	Results
Wen et al, 2007	8-week-old male Apo-E deficient mice fed an atherogenic diet, after stimulation of arterial hypertension by infusion of angiotensin II with the aim of inducing the formation of aortic aneurysms	Increased expression of syndecan-1 and -2, inhomogeneous distribution of syndecan-4
Zalghout et al, 2022	<i>in vitro</i> : RT-qPCR evaluation, ELISA and histological analysis of twenty-five patients undergoing thoracic aortic replacement surgery and compared it with the aortic wall of eleven healthy sub <i>in vivo</i> : 3-week-old SDC-1 +/- a SDC 1 -/- mice divided into 3 groups (without treatment; treated with β -aminopropionitrile fumarate for 28 days, then infused subcutaneously of angiotensin II)	Increased expression of syndecan-1 in the media of patients affected by aneurysm; major incidence of thoracic aneurysms in the syndecan-1 +/- population; higher incidence of abdominal aneurysms in SDC 1 -/- population; no significant differences in terms of elastin degradation, collagen fiber fragmentation and leukocyte infiltration
Xiao et al, 2012	<i>in vivo</i> : administration of elastin and angiotensin II in SDC- 1 -/- mice	increase in macrophages associated with syndecan-1, an increase in proteolytic activity, reduction in the ability to limit the inflammatory process
Hu et al, 2021	<i>in vitro</i> : immunofluorescence and western blotting detection of syndecan-4 <i>in vivo</i> : SDC4/-apoe/- mice treated with angiotensin II infusion compared to the apoe/- group	reduced expression of syndecan-4 in the aortic wall of patients with abdominal aneurysm; high incidence of abdominal aneurysms and a greater degradation of elastic fibers in SDC4-/-apoe/- mice treated with angiotensin II; increase in the levels of MMP2, MMP9 and a reduction in the levels of alpha-SMA, calponin1 and SM-MHC in SDC4-KD treated with angiotensin II; increase in the production of IL-1beta, IL6 and TNF-alfa specially in SDC4-KD;phenotypic changes in VSMCs via the RhoA- F/G-actin-MRTF-A pathway in the SDC4-KD group

3. Considerations on the Experimental Results Obtained Until Now

Important results have been obtained in the above-mentioned studies. However, their limited number encourages implementation for clearing all gaps in the research on SDCs in aorta aneurysm, and understanding how they can mediate diverse biological effects, having a differential inflammatory or anti-inflammatory character, and in other words, how can modulate the onset and progression of aorta aneurysm. The data described evidence of a differential role of SDCs during the medial degeneration and the consequent remodeling of aorta wall, as well as the activation and inhibition of diverse cytokines and pathways. Consequently, the study of epigenetic factors able to influence the levels of expression of SDCs in relation to systemic and microenvironmental conditions, and for example in relation to inflammatory conditions, might also be of help. For example, the group of Li and coworkers has recently evidenced the crucial role of miR-17-3p in the interaction of vascular endothelial cells and inflammatory cells, in turn linked to abdominal aorta aneurysm formation [31]. The prominent miR-17-3p expression has been, indeed, associated with the shear stress, representing a significant induction mechanism significantly linked to onset of abdominal aorta aneurysm. However, the precise role of miR-17-3p on and its impact on the glycocalyx remains unclear. Thus, Li and coworkers have used astragaloside IV (AS-IV) (a small-molecule saponin (molecular weight = 784) derived from Astragalus, is noted for its anti-inflammatory properties), in 40 Sprague–Dawley rats with abdominal aorta aneurysm, established using porcine pancreatic elastase. Their aim was to elucidate the AS-IV mechanism of action, focusing on the shedding of the glycocalyx in aortic endothelial cells. The results obtained have evidenced that AS-IV limited aortic damage in such rats, by decreasing both the aortic diameter and glycocalyx damage. In addition, AS-IV inhibited the boost in miR-17-3p expression and induced the SDC1 expression. Thus, they have affirmed that miR-17-3p may damage the glycocalyx of aortic endothelial cells by targeting SDC-1. AS-IV may raise SDC1 expression by inhibiting miR-17-3p, thereby protecting the glycocalyx and alleviating the onset of aorta aneurysm. In another recent study, Zhang and coworkers have demonstrated that SDC-4 is a target of miR-629-5p in case of pediatric acute respiratory distress syndromes (PARDS). While the group of dos Santos has shown that miR-126 in case of laminar shear stress (LSS) on human endothelial cells (HUVECs), has a role in up- and downregulation of genes

involved in atherosclerosis, by evoking a high SDC-4 expression. Such evidence demonstrates that further and deep research is imperative, and it might clear the role as biomarkers and targets of aorta aneurysm.

4. Conclusions and Perspective: SDCs as Biomarkers and Targets in Aorta Aneurysms

Therefore, eGCX injury appears to be a fundamental driver in the onset and progression of the diverse CVDs, including AA. This evidence has led researchers to hypothesize that its products of degradation, such as SDCs, as abovementioned, can represent potential biomarkers of CVDs, AA included, despite the limited evidence until now. In addition, the heterogeneous expression of such molecules in course of AA leads to propose that SDCs can also constitute optimal prognostic biomarkers. Certainly, further studies are needed to support such clinical applications. Furthermore, the researchers suppose that they can represent optimal targets to develop new approaches and therapeutic strategies to restore eGCX and its functions. Accordingly, an approach might be represented by the reduction of the activity of cytokines and leukocyte extravasation, considered to be an emerging therapeutic strategy to limit tissue-damaging inflammatory responses and restore immune homeostasis in inflammatory diseases, AA included. For example, it has been proved that soluble forms of SDC-1 exert helpful anti-inflammatory effects by removing chemokines, suppression of proinflammatory cytokine expression and leukocyte migration, and induction of autophagy of proinflammatory macrophages [32]. In contrast, endogenous SDC-2 appears to exert proinflammatory effects, and SDC-4 to mediate beneficial anti-inflammatory effects and regulates Hh and Wnt signaling pathways involved in systemic inflammatory responses. Taken together, targeting the vascular eGCX-derived products, such as soluble SDC-1, SDC-2, and SDC-4, might represent a potential therapeutic strategy to suppress overstimulated cytokine and leukocyte responses in aorta wall, by limiting or stopping the consequent degeneration and remodeling.

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References

1. Cikach F, Desai MY, Roselli EE, Kalahasti V., "Thoracic aortic aneurysm: How to counsel, when to refer.," *Cleve Clin J Med.*, Vols. 85(6):481-492, 2018.
2. Senser EM, Misra S, Henkin S., "Thoracic Aortic Aneurysm: A Clinical Review," *Cardiol Clin.*, Vols. 39(4):505-515. , 2021.
3. Juvonen T, Ergin MA, Galla JD, Lansman SL, Nguyen KH, McCullough JN, Levy D, de Asla RA, Bodian CA, Griep RB., "Prospective study of the natural history of thoracic aortic aneurysms.," *Ann Thorac Surg.*, Vols. 63(6):1533-45., 1997.
4. Balmforth D, Harky A, Adams B, Yap J, Shipolini A, Roberts N, Uppal R, Bashir M., "Is there a role for biomarkers in thoracic aortic aneurysm disease?," *Gen Thorac Cardiovasc Surg.* Vols. 67(1):12-19., 2019.
5. Balistreri CR, "Genetic contribution in sporadic thoracic aortic aneurysm? Emerging evidence of genetic variants related to TLR-4-mediated signaling pathway as risk determinants.," *Vascul Pharmacol.* , Vols. 74:1-10. , 2015.
6. Ruvolo G, Pisano C, Candore G, Lio D, Palmeri C, Maresi E, Balistreri CR. , " Can the TLR-4-mediated signaling pathway be "a key inflammatory promoter for sporadic TAA"?," *Mediators Inflamm.* , vol. 2014:349476., 2014.
7. Balistreri CR, Crapanzano F, Schirone L, Allegra A, Pisano C, Ruvolo G, Forte M, Greco E, Cavarretta E, Marullo AGM, Sciarretta S, Frati G., "Deregulation of Notch1 pathway and circulating endothelial progenitor cell (EPC) number in patients with bicuspid aortic valve with and without ascending aorta aneurysm.," *Sci Rep*, vol. 8(1):13834. , 2018.
8. Scola L, Di Maggio FM, Vaccarino L, Bova M, Forte GI, Pisano C, Candore G, Colonna-Romano G, Lio D, Ruvolo G, Balistreri CR., "Role of TGF- β pathway polymorphisms in sporadic thoracic aortic aneurysm:

- rs900 TGF- β 2 is a marker of differential gender susceptibility," *Mediators Inflamm.*, vol. 2014:165758, 2014.
9. Treska V, Kocova J, Boudova L, Neprasova P, Topolcan O, Pecan L, Tonar Z, "Inflammation in the wall of abdominal aortic aneurysm and its role in the symptomatology of aneurysm," *Cytokines Cell Mol Ther.*, Vols. 7(3):91-7, 2002.
 10. Nordon IM, Hinchliffe RJ, Loftus IM, Thompson MM, "Pathophysiology and epidemiology of abdominal aortic aneurysms," *Nat Rev Cardiol.*, Vols. eb;8(2):92-102., 2011.
 11. Nosoudi N, Nahar-Gohad P, Sinha A, Chowdhury A, Gerard P, Carsten CG, Gray BH, Vyavahare NR, "Prevention of abdominal aortic aneurysm progression by targeted inhibition of matrix metalloproteinase activity with batimastat-loaded nanoparticles," *Circ Res*, Vols. 117(11):e80-9., 2015.
 12. Kolářová H, Ambrúžová B, Sviháľková Šindlerová L, Klinke A, Kubala L, "Modulation of endothelial glycocalyx structure under inflammatory conditions," *Mediators Inflamm*, vol. 2014:694312, 2014.
 13. Mortazavi CM, Hoyt JM, Patel A, Chignalia AZ, "The glycocalyx and calcium dynamics in endothelial cells," *Curr Top Membr.*, Vols. 91:21-41., 2023.
 14. Sieve I, Münster-Kühnel AK, Hilfiker-Kleiner D, "Regulation and function of endothelial glycocalyx layer in vascular diseases," *Vascul Pharmacol.*, Vols. 100:26-33., 2018.
 15. Qu J, Cheng Y, Wu W, Yuan L, Liu X, "Glycocalyx Impairment in Vascular Disease: Focus on Inflammation," *Front Cell Dev Biol.*, vol. 9:730621., 2021.
 16. McDonald KK, Cooper S, Danielzak L, Leask RL, "Glycocalyx Degradation Induces a Proinflammatory Phenotype and Increased Leukocyte Adhesion in Cultured Endothelial Cells under Flow," *PLoS One.*, vol. 11(12):e0167576, 2016.
 17. Milusev A, Rieben R, Sorvillo N, "The Endothelial Glycocalyx: A Possible Therapeutic Target in Cardiovascular Disorders," *Front Cardiovasc Med*, vol. 9:897087., 2022.
 18. Rabia B, Thanigaimani S, Golledge J, "The potential involvement of glycocalyx disruption in abdominal aortic aneurysm pathogenesis," *Cardiovasc Pathol.*, vol. 70:107629., 2024.
 19. Foote CA, Soares RN, Ramirez-Perez FI, Ghiarone T, Aroor A, Manrique-Acevedo C, Padilla J, Martinez-Lemus L, "Endothelial Glycocalyx," *Compr Physiol.*, Vols. 12(4):3781-3811., 2022.
 20. Thota LNR, Chignalia AZ, "The role of the glypican and syndecan families of heparan sulfate proteoglycans in cardiovascular function and disease," *Am J Physiol Cell Physiol.*, Vols. 323(4):C1052-C1060., 2022.
 21. Balistreri CR, Di Giorgi L, Monastero R, "Focus of endothelial glycocalyx dysfunction in ischemic stroke and Alzheimer's disease: Possible intervention strategies," *Ageing Res Rev.*, vol. 99:102362, 2024.
 22. Balistreri CR, "Promising Strategies for Preserving Adult Endothelium Health and Reversing Its Dysfunction: From Liquid Biopsy to New Omics Technologies and Noninvasive Circulating Biomarkers," *Int J Mol Sci.*, vol. 23(14):7548, 2022.
 23. Bartlett AH, Hayashida K, Park PW, "Molecular and cellular mechanisms of syndecans in tissue injury and inflammation," *Mol Cells.*, Vols. 24(2):153-66, 2007.
 24. Xiao J, Angsana J, Wen J, Smith SV, Park PW, Ford ML, Haller CA, Chaikof EL, "Syndecan-1 displays a protective role in aortic aneurysm formation by modulating T cell-mediated responses," *Arterioscler Thromb Vasc Biol.*, Vols. 32(2):386-96, 2012.
 25. Worapamorn W, Haase HR, Li H, Bartold PM, "Growth factors and cytokines modulate gene expression of cell-surface proteoglycans in human periodontal ligament cells," *J Cell Physiol*, Vols. 186(3):448-56, 2001.
 26. Hara T, Sato A, Yamamoto C, Kaji T, "Syndecan-1 downregulates syndecan-4 expression by suppressing the ERK1/2 and p38 MAPK signaling pathways in cultured vascular endothelial cells," *Biochem Biophys Rep.*, vol. 26:101001., 2021.
 27. Wen J, Wang P, Smith SV, Haller CA, Chaikof EL, "Syndecans are differentially expressed during the course of aortic aneurysm formation," *J Vasc Surg*, Vols. 46(5):1014-25., 2007.
 28. Chen L, Klass C, Woods A, "Syndecan-2 regulates transforming growth factor-beta signaling," *J Biol Chem*, Vols. 279(16):15715-8., 2004.
 29. Zalgout S, Vo S, Arocas V, Jadoui S, Hamade E, Badran B, Oudar O, Charnaux N, Longrois D, Boulaftali Y, Bouton MC, Richard B, "Syndecan-1 Is Overexpressed in Human Thoracic Aneurysm but Is Dispensable for the Disease Progression in a Mouse Model," *Front Cardiovasc Med.*, vol. 9:839743., 2022.
 30. Hu J, Li Y, Wei Z, Chen H, Sun X, Zhou Q, Zhang Q, Yin Y, Guo M, Chen J, Zhai G, Xu B, Xie J, "A reduction in the vascular smooth muscle cell focal adhesion component syndecan-4 is associated with abdominal aortic aneurysm formation," *Clin Transl Med*, vol. 11(12):e605, 2021.

31. Li G, Yang Q, Luo K, Xu A, Hou L, Li Z, Du L., "Astragaloside IV Protects against Shear Stress-Induced Glycocalyx Damage and Alleviates Abdominal Aortic Aneurysm by Regulating miR-17-3p/Syndecan-1," *Anal Cell Pathol (Amst)*, vol. 2024:2348336., 2024.
32. Kunnathattil M, Rahul P, Skaria T. , "Soluble vascular endothelial glycocalyx proteoglycans as potential therapeutic targets in inflammatory diseases," *Immunol Cell Biol*, Vols. 102(2):97-116., 2024.

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