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REVIEW

Mechanosensitive Piezo1 Channel Evoked-Mechanical Signals in Atherosclerosis

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Abstract: Recently, more and more works have focused and used extensive resources on atherosclerosis research, which is one of the major causes of death globally. Alongside traditional risk factors, such as hyperlipidemia, smoking, hypertension, obesity, and diabetes, mechanical forces, including shear stress, pressure and stretches exerted on endothelial cells by flow, is proved to be crucial in atherosclerosis development. Studies have recognized the mechanosensitive Piezo1 channel as a special sensor and transducer of various mechanical forces into biochemical signals, and recent studies report its role in atherosclerosis through different mechanical forces in pressure, stretching and turbulent shear stress. Based on our expertise in this field and considering the recent advancement of atherosclerosis research, we will be focusing on the function of Piezo1 and its involvement in various cellular mechanisms and consequent involvement in the development of atherosclerosis in this review. Also, we will discuss various functions of Piezo1 involvement in atherosclerosis and come up with new mechanistic insight for future research. Based on the recent findings, we suggest Piezo1 as a valid candidate for novel therapeutic innovations, in which deep exploration and translating its findings into the clinic will be a new therapeutic strategy for cardiovascular diseases, particularly atherosclerosis.

Keywords: atherogenesis, Piezo1 channel, endothelial cell, inflammation, shear stress, mechanotransduction

Introduction

Atherosclerosis (AS) is a major global killer, and is the basis of cardiovascular diseases (CVDs) comprising myocardial infarction (MI), ischemic heart disease (IHD) and stroke. AS is a multifactorial inflammatory disorder,[1–4] and is the root of cardiovascular disease.[5] AS remains a leading cause of death globally, claiming millions of lives every year, as estimated in the 2015 global burden of disease study (17.9 million) about 30% of whole death globally.[6] There is an increased in its prevalence due to the global rise in obesity and diabetes, with more than half of the world population becoming obese, leading to a steep rise in cardiovascular diseases (CVDs) burden; it is estimated that the global death from CVDs may go beyond 23.6 million by the year 2030. At the onset of AS, endothelial cell (EC) defense is triggered by a number of factors, including mechanical forces such as shear stress and stretching, which leads to EC adaptive responses thereby developing a distinct phenotype to interact with other traditional risk factors,[7] and facilitate the initiation of AS. The significance of mechanical forces in cardiovascular physiology and pathology have been reported for decades. Shear stress mediated by Piezo1 is among the significant factors and the initiator of inflammation and vascular

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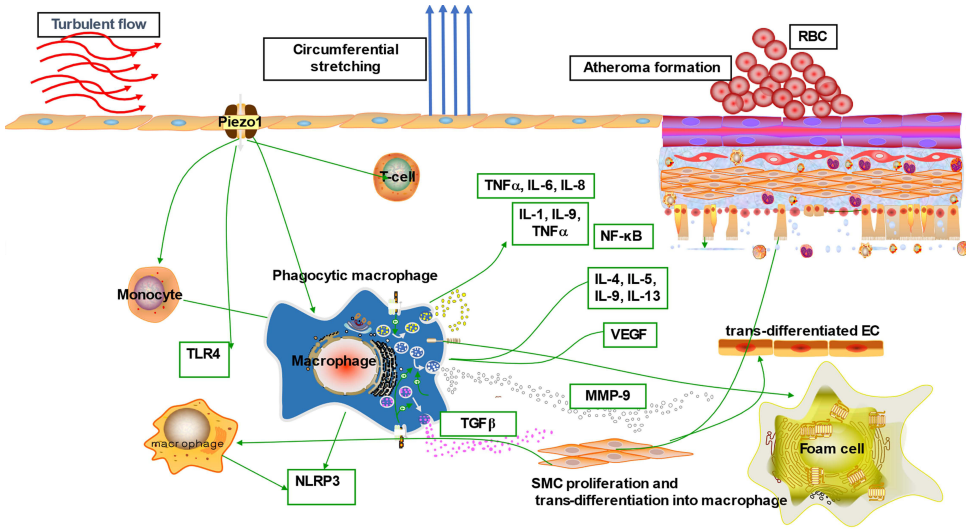
Graphical Abstract



endothelial cell (VEC) dysfunction.[8] Cells detect and liberate mechanical forces using various biochemical and molecular mechanisms. In the cardiovascular system, frictional force and pressure are generated in the vessels, endothelial Piezo1 senses and transduces such forces which are the determinant of the physiological competence of the system throughout life. Piezo1 serves a crucial function in angiogenesis, embryonic development and is crucial for endothelial shear stress-senses, blood pressure regulation, and physical activities during exercise etc.[9] As our knowledge of this field increases, various functions of Piezo1 are emerging. Piezo1 is a significant player in cardiovascular physiology (Figure 1), renal and hematopoietic systems.[10] Its function is known in embryonic vessel development,[11] RBC stability in both human and mouse,[9] control of blood pressure, physical activities,

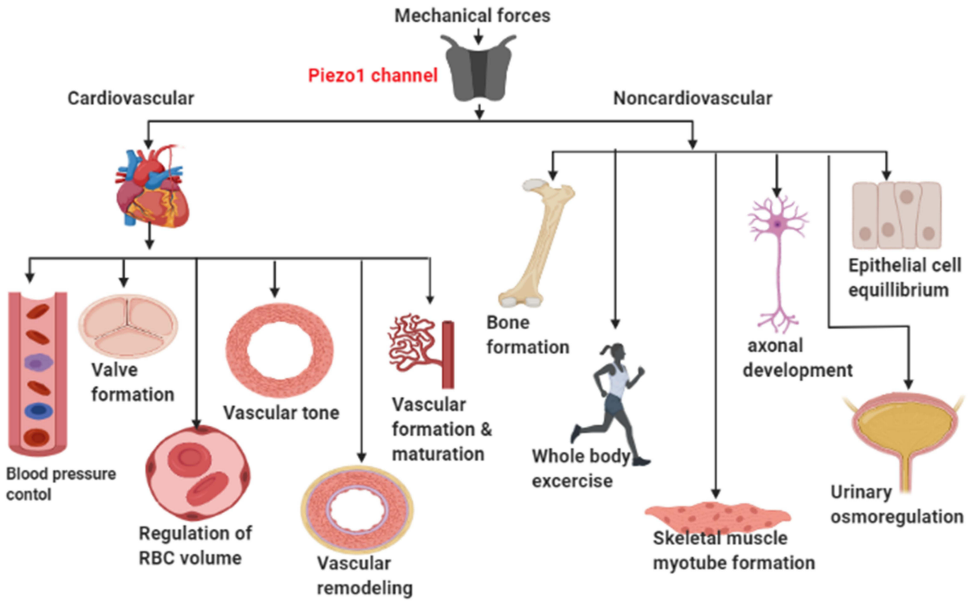


Figure 1 Cardiovascular and non-cardiovascular functions of Piezo1: The schematic diagram demonstrating a wide range of Piezo1 functions in different areas of physiology including cardiovascular and non-cardiovascular roles from the activation of Piezo1 by mechanical force branching from left to right arrows, pointing different organ and cell / tissue.

hypertension-dependent arterial remodeling, urinary osmoregulation, epithelial equilibrium and axonal development.[11] It also serves the function of adjusting erythrocyte volume,[12–14] and in prostate cancer.[15] Piezo1 global knockout in mice leads to embryonic fatality,[10,12,16–19] indicating its significance during embryogenesis.[20] Additionally, severe defects in vessel maturation and remodeling, and disability in NO production and vessel dilation responding to flow were both observed following Piezo1 global deletion or EC-specific disruption.[21] Also, Piezo1 in partnership with Piezo2 serves the function of baroreceptor reflex as their dual disruption obliterates baroreceptor responses to sodium nitroprusside or phenylephrine.[22] Piezo1 appears to function in a wide area of cell biology, as illustrated in Figure 1, and its pathologic importance in humans was also indicated.[11,23–25] The broad concept of Piezo1 functions was also reviewed in recent articles.[9,26–28] Collectively, Piezo1 remains a significant player in a broad area of cell physiology, considering its expression and functions in diverse tissues, not limited to the cardiovascular system (Figure 1). This indicates that defects or mutations in this channel may impair various functions in ECs and other cell types. Therefore, pharmacological manipulation of either activation or inhibition of this channel may come up with a new trend in clinical practice. Different abnormalities or up/downregulation of cellular activities were observed in several studies following the silencing/blocking, deletion, cell specific or global knockout and deficiency of Piezo1.[9,28–33] Since the recognition of Piezo1 &2 in 2010, they have been regarded as one of the most significant classes of mechanosensory proteins. It is now feasible to investigate the mechanism of Piezo1 engagement in physiological and pathophysiological processes as a result of recent developments in understanding their topology, the identification of the agonists Yoda1, Jedi1&2 as well as the antagonist GsMTx4, Ruthenium Red. Recently, cardiovascular aspects of Piezo1 channel have been reviewed elsewhere, but here we review the current understanding of Piezo1 channel and specifically focus on its immune/inflammatory mechanisms of atherosclerosis involving different mechanotransduction processes as summarized in the graphic abstract, which have not been reviewed to date. We also raise awareness of the realization of its pharmacology and suggested new directions for future research toward the development of advanced therapeutic strategies for prevention and management of atherosclerosis.

Structure of Piezo1 Channel

Human mechanically activated (MA) channel molecular identity was mysterious for a long time until the revolutionary discovery of Piezo1 & 2, which may increase our understanding of cellular signaling and mechanotransduction. Piezo1 proteins are collectively arranged to form a three blade-like propeller inserted within the lipid bilayer which makes the central ion pore that senses mechanical forces.[9,34–36] Its extracellular propeller domain serves as a detector of flow related-shear and other mechanical stress.[16,37] In respect to structural components, Piezo1 can be categorized as follows.

Exceptional 38-TM Topography

With advancement of Piezo1 research, high-resolution structures of mice Piezo1 (mPiezo1) were shortly disclosed, showing that each subdomain has a special 38-TM topography. The inner helixes (IH) and outer helix (OH) of the center of the pore module are the 2 TM subdomains (TM37 and TM38) nearest to the protein's core. The remaining 36 TM regions (TM1-36) are organized into a blade resembling a curved structure with 9 repeating folds comprising four TM regions each, known as transmembrane helical units (THUs).[38–40]

Exceptionally Curving Blades

Each subdomain's 9 peripheral THUs produce bladelike architectures, each twisted clockwise. As seen from a line parallel to the plasma membranous planes, next to the TM25–TM36 and periphery of the TM13-24 these are based at a 100° and a 140° angle, respectively. The L-shaped helical structures produced by TM13, TM17, TM21, TM25, and TM29 are another essential feature of the blades. Both structural characteristics tend to be suitable for inducing regional membrane curvature as well as mechano-sensing. Surprisingly, the peripheral TM13-24 tends to be located inside a strongly bent membrane plane, implying that the Piezo1 channel has the ability to bend the membrane in which it sits. Previous research suggested that cell membrane deflection and tension may control Piezo1.[26,27,38,39,41]

Central Cap

Using topographical predicting simulation, a study by Kamajaya's team,[42] discovered that Piezo1 residues 2210 to 2457 produced an extracellular loop next to the last TM region from the C-terminus, known as C-terminal

extracellular domain (CED). The central cap was not expressed when residues 2218 to 2453 were removed from the Piezo1 protein, implying that this area trimerized to produce the central cap. The central cap comprises the CED in the shape of trimeric complexes that encapsulated the extracellular-vestibule (EV) with apertures, disclosed by another study.[27,38,39,43]

The Ion Conducting Pore

Piezo proteins compose a trimeric ion conducting channel comprising residues 2189 to 2547, that composes the last two TMs. An EV in the cap region, a transmembrane-vestibule (MV) within the membrane, and the intracellular-vestibule (IV) beneath the membrane make up the continuous central channel. The MVs are located on top of and beneath the membrane, and both the EV and IV have an opening that binds them. DEEED (2393–2397), a patch of negative charge residues located in the opening of the extracellular "cap" structure made up of the CED, is necessary for effective ion conducting and determining the preference for cations than anions. Furthermore, divalent calcium ion selectivity, unitary conductance, and aperture blocking can be caused by two essential acidic residues, E2495 and E2496, situated at the CTD-constituting IV.[26,39,40,44]

The Intracellular Beam

Piezo1 possess 3 beam-like structures from intracellular aspect, each measuring 90 nm in length and arranged at a 30° angle to the membranous plane. The beam composition is made up of residues H1300-S1362. The long intracellular THU7-8 loop has about 390 residues, which could supply the beam with a structural foundation for force transmitting. The 3 longer intracellular beams serve as a functional barrier between the distal THUs and the central ion conducting orifice, as well as supporting the entire TM framework. The mutated protein was missing after residues 1280 to 1360 were removed, indicating the beam's structural significance.[26,27,39]

The Anchor

The OH-IH pair is connected into the C-terminal domains (CTD) planes by a hairpin structure called the anchor, which pushes the OH-CED-IH-composing area of 1 subdomain to the adjacent subdomain in a dextral aspect. Three helices (α1, α2, and α3) make up the anchor. The inverted V-shaped structure formed by helices α1 and α2 was discovered to keep the ion-conducting pore's stability. The longer α3 helical unit interacts with the polar residue-rich α2–3 turning in the anchor and the glutamate-rich portion of the CTD through a lysine-rich anchor-OH linker which runs parallel onto the membranous plane. A few mutations in Piezo1 have been identified to account for serious disorders at regions such as KKKK (2182-K2185), T2143, T2142 (T2127 in human Piezo1), R2514, E2523, and E2522, which are situated at α3 in the anchor. SERCA2, a Piezo-interactor protein, also inhibits Piezo1 by interacting with the anchor-OH linker. These results affirm the anchor portion's structural and functional significance.[26,38,40]

Piezo1 Functions

The Role of Piezo1 in Helical Flow

The circulatory system generates a variety of flow patterns within the vascular beds, including laminar, disturbed or turbulent, and oscillatory or helical flow, depending on the nature of vessel.[8] Piezo1 channel was recently recognized as a specialized mechanosensor that senses blood flow and integrates the signal into a genealogical program for vascular formation and maturation.[45–47] Due to the effects of flow pattern on vascular health, helical flow patterns have received considerable attention in modern days. The helical pattern of flow is symbolized by increased velocity[48] with a high shear stress that is known to be sensed by Piezo1,[9,27] and is now considered as a physiologic type of flow.[48,49] It is now thought to be an atheroprotective flow,[50] considering that it could minimize blood cell adherence to the vessel wall, prohibit LDL buildup, and improve perfusion and oxygen delivery. Furthermore, hemodynamic efficacy of a vascular device is enhanced by helical flow,[48,51] as summarized in Table 1. Piezo1 may sense helical flow and act as a key regulator of vascular health through various mechanisms, as it senses and transduces different flow patterns into biochemical signals. Therefore, through Piezo1 mechanotransductions, the roles of helical flow might minimize the burdens on vasculature as well as protecting it from atherosclerotic pathologies, intimal hyperplasia and thromboembolism, through the suppression of proinflammatory signaling resulting from low and turbulent shear stress.[52] Altogether, these data demonstrate the physiological importance of Piezo1 mediated helical flow, its mechanisms in cardiovascular biology signaling and its therapeutic potentials for targeting atherosclerosis and other CVDs.

Table 1 Summarizing the Suggested Clinical Significance of Helical Flow

Condition(s)	Clinical Significance	Model	References
Endovascular Stent Restenosis	Improvement of hemodynamic efficacy of stent Decrease turbulent flow zone and OS index in stent	Straight endovascular stent	[52]
End-to-Side Anastomosis Restenosis	Abolish the formation of intimal hyperplasia Termination of reduced shear stress zone	S-type arterial bypass graft	[130]
Arterial Bypass Grafting & Arteriovenous Shunts Occlusion	Reduction of thrombosis and IH Amplification of shear stress Reduction of oscillatory shear index	Swirl Graft Helical grafts	[131]
Small Caliber Arterial Prostheses Occlusions	Decreases thrombi development Repression of platelet adhesion	Small diameter arterial prosthesis Glass tube	[132]
Superior Vena Cava Obstruction & Vena Cava Filters Blocking	Clearance of block and obstructions	Spiral vein graft Vena cava filters	[133,134]

Piezo1 in VSMCs Shear Stress-Induced Plaque Formation

Piezo1 is the specialized sensor and transducer of mechanical forces including shear stress. It enables EC,[9,53] and vascular smooth muscle cells (VSMCs),[20] to detect and respond to changes in their environment. Turbulent shear senses via Piezo1,[8] increases EC protein and gene expressions of VSMC mitogens including platelet-derived growth factors (PDGF), ET-1, and vascular endothelial growth factor (VEGF). EC expression of VSMCs migration inhibitor (plasminogen activator inhibitor (PAI)-1) and effective suppressors of cellular growth and migration, such as NO and TGFβ, are all downregulated by turbulent shear. The EC downregulation of these growth inhibitors by disturbed shear encourages VSMCs to migrate into the intima via an interrupted internal elastic lamina (IEL). VSMCs develop synthetic phenotype in the intima, replicate and generate collagen, including other (ECM) proteins. With time, VSMCs[54] together with fibroblast that is known to be regulated by Piezo1,[55] form the fibrous cap along with lipid core, building up what is known as atherosclerosis plaque.

Piezo1 Channel as Shear Sensors

Shear sensing is vital in cardiovascular physiology, and shear stress is among the factors guiding the developing vessel during embryogenesis.[17] Piezo1 is a specialized and authentic shear stress sensor, as proved by much evidence. ECs detect shear stress and convey the signaling inside the cells, which induces cell responses to changes in its surroundings; abnormality in these responses could result in various disorders, including CVDs.[56] In response to shear stress, Piezo1 activates cascades of downstream mechanisms, which alter the cell behavior based on the type of stimuli.[17,57] It senses physiological shear to enhance angiogenesis and vessel maturation.[34] Earlier discoveries about Piezo1 unveiled its importance for shear stress detection.[18] With Piezo1, EC oriented and aligned in the flow direction, while in its absence, EC failed to do so.[12,34] Collectively, these qualify Piezo1 as an authentic shear stress sensor; and tuning Piezo1 through pharmacological approaches may change the story of clinical practice. Shear stress triggers EC Piezo1, which causes Ca^{2+} inflow and phosphorylating of AKT and eNOS, resulting in enhanced NO generation and VSMC-dependent vessel dilatation. Comparatively, VSMC Piezo1 is triggered by stretch and is active in vascular remodeling mechanisms under pathological conditions, resulting in a reduction in vessel diameter. Both Piezo1-dependent processes successfully sustain basal BP control.[58] In human embryonic kidney cells, transfecting Piezo1 caused prompt shear stress–evoked Ca^{2+} influx or ion current, shear stress quickly stimulates endogenous Piezo1 in membrane patches extracted from native endothelium, and Piezo1 knockout disrupts embryonic vascular maturation, which is thought to be caused by shear stress.[9]

Piezo1 Correlation with Inflammation and Atherosclerosis

Increasing evidence has reported Piezo1 involvement in various mechanisms of cell biology, including health and disease.

Nearly all cells, tissues and organs are exposed to various degrees of mechanical forces, and Piezo1 is the principal mechano-sensor in various cells and tissues, thus linking Piezo1 to multiple mechanisms of inflammation and various disease pathogenesis particularly atherosclerosis. Mechanical forces, including shear stress, are the primary stimuli for cell physiology, since they supply signaling for cellular homeostasis. Piezo1 is known to mediate wide varieties of such forces, therefore dysregulation of Piezo1 signal may alter homeostasis and result in disease processes such as atherosclerosis. ECs respond to these stimuli such as laminar or turbulent shear mediated by Piezo1, and this triggers pro- or anti-inflammatory signals leading to inflammation and atherosclerosis depending on the flow pattern. Piezo1's significance in cardiovascular physiology and pathology is becoming more widely recognized, hence the next section will discuss in detail the Piezo1 mechanisms in inflammation and atherosclerosis. Furthermore, evidence shows that unidirectional and turbulent flow senses by Piezo1, causes distinct signaling in ECs, leading to an anti- or pro-atherogenic phenotype.[8] Each of the unidirectional and turbulent flow triggers initiate signal thoroughfare involving Piezo1.[8,59] The trigger of NF-κB upregulates proinflammatory as well as pro-atherogenic genes,[60,61] leading to growth of AS, while KLF triggering sustains vessel architecture (Figures 2 and 3). Furthermore, various *in vivo* and *ex vivo* studies on pre-flowed ECs culture, demonstrate that unidirectional and turbulent flow-induced athero-protective and atherogenic signals both require Piezo1.

Piezo1 Mediated Mechanisms in the Initiation and Progression of Inflammation and Atherosclerosis

The majority of prior studies on atherosclerosis pointed to elevated LDL levels as the primary culprit.[62] Only recent works recognized that hypercholesterolemia and atherosclerosis development are linked via inflammatory processes. Therefore, immunological response and inflammation have been regarded as key contributors in the initiation and amplification of atherosclerosis.[63,64] Mechanosensitive Piezo1 channel was recently reported to play a crucial role in immune cells and inflammatory processes.[65–68] Over time, research has shed more light on inflammatory responses in atherosclerosis, providing strong evidence that inflammation is a major factor in all stages of atherogenesis.[69] Furthermore, inflammatory signaling increases thrombosis, which is responsible for ischemic heart disease and the majority of myocardial infarctions and cerebrovascular diseases.

Stages of Atheroma Formation

(A) Initially EC undergo inflammatory triggers in response to noxious stimuli,[70] including atherogenic shear from flow

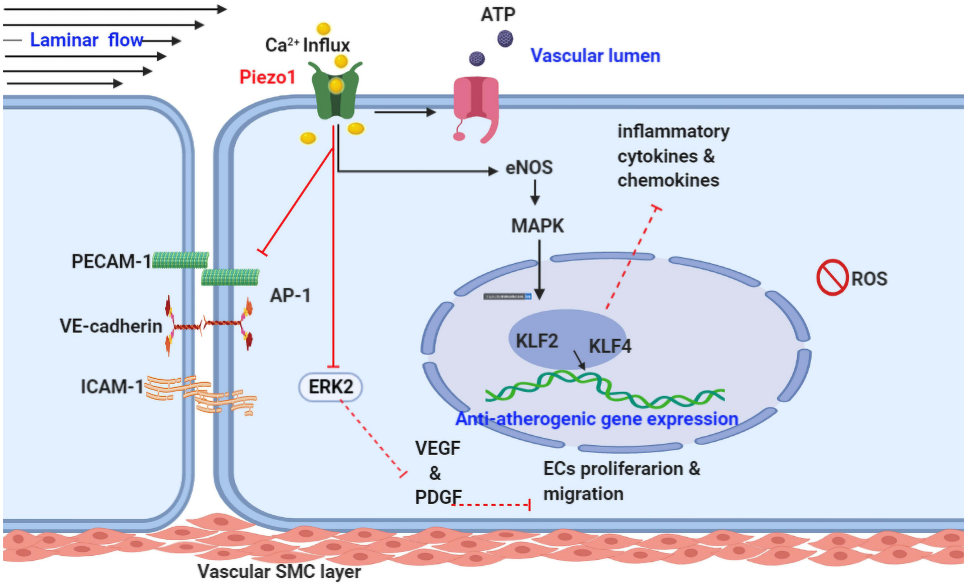


Figure 2 Piezo1 flow induced anti-atherogenic signaling mechanism: schematic diagram, demonstrating laminar flow (anti-atherogenic flow) activates Piezo1 channel, leading to Ca^{2+} influx and then triggers the generation of eNOS that leads to the expression of KLF2 & KLF4 through MAPK and results in the deactivation of adhesion molecules and AP-1 (red inhibition arrow) as well as downregulations of growth factors VEGF/PDGF, proinflammatory chemokines and cytokines, cell proliferation and migration followed by anti-atherogenic gene expression and athero-protection.

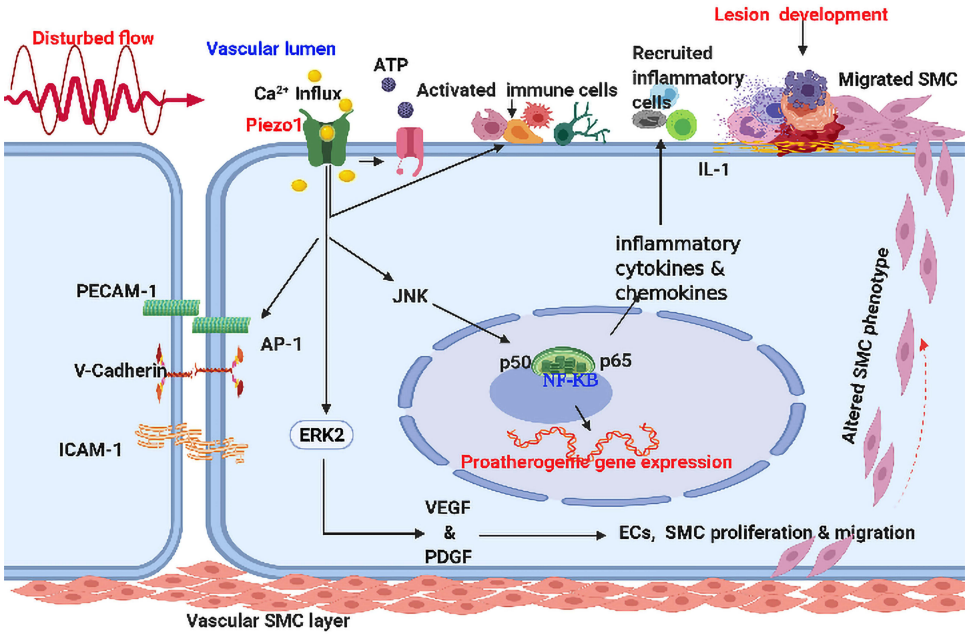


Figure 3 Piezo1 flow induced proatherogenic signaling mechanism: schematic diagram demonstrating disturbed/oscillatory (pro-atherogenic flow) activation of the Piezo1 channel, leading to Ca^{2+} influx followed by the activation of JNK, NF-KB, p50 and p65, ERK2 pathway. And the atherogenic gene expression, growth factors VEGF/PDGF, proinflammatory chemokines, cytokines. And cellular adhesion molecules, which result in the activation of immune cells, inflammatory cell recruitment, and ECs and SMCs proliferation and migration, leading to endothelial inflammation, increased permeability, cell damage, plaque formation, and atherosclerosis development.

mediated by Piezo1,[71] as discussed in Piezo1 Mediated Shear-Induced Inflammation and Atherosclerosis; (B) monocytes recruitment to atheroma region discussed in 5.3; (C) cytokines and chemoattractive molecules engaged in promoting the recruiting of additional immune/inflammatory cells to the intima discussed in 5.5; (D) later monocyte differentiates into macrophages and engulfs lipoprotein particles to transform into lipid engorged foam cells; (E) then foam cells release proinflammatory molecules, and growth factors including reactive leading to the proliferation, migration, discussed in 5.5, and phenotypic switching or transdifferentiation of VSMCs into SMC derived macrophages in the intima.[72,73] (F) Apoptosis of macrophages leading to the development of "necrotic" core of the mature plaque; (G) macrophages and SMC augment the process,[74] through secretion of matrix metalloproteinases (MMPs) particularly MMP-9,[75] which leads to the degradation of extracellular matrix, resulting in the plaque's fibrous cap thinning; (H) plaque rupture due to weakness of the fibrous cap leading to thrombogenic coagulation and finally thrombosis and obstruction of vessel lumen,[76] which limits the tissue perfusion and results in ischemic heart disease.[69,70] Piezo1 signaling is known to play crucial roles in other immune/inflammatory mechanisms of atherosclerosis as discussed in 5.4.

Piezo1 Mediated Shear-Induced Inflammation and Atherosclerosis

Beside the established risk factors of atherosclerosis, it is convincing that turbulent shear mediated by Piezo1 is crucial for EC activation, leading to initiating of inflammation and atherosclerosis.[8,77,78] Disturbed flow sensed via Piezo1 produces turbulent shear, which is a considerable risk for atherosclerosis, as studies reported its effect on EC.[78,79] Turbulent shear[80] triggers pro-inflammatory EC phenotype; disorders such as AS appeared to originate from such EC phenotypes.[8] Numerous studies suggested Piezo1 associates with different inflammatory pathways and signaling mechanisms in the development of AS (Figure 3). Piezo1 was recently found to be expressed and function in inflammatory cells including monocytes, macrophages[65] and T-cells.[81] Studies reported that activation of monocytes and macrophage by Piezo1 triggers proinflammatory signals leading to expression of various cytokines and chemokines,[65–67] a crucial event during atherogenesis. Cytokines such as TNF-α, IL-1, 2, 3, 6, 10, 12, 15, 18, CXCL8, IFN-γ, M-CSF, TGF-β1, 2, and 3 are critical components of inflammation and play a significant role in AS pathogenesis. The most interesting fact is that in the lack of Piezo1, inflammatory cytokines and chemokines, as well as the transcriptional factor, hypoxia-inducible factor

1 (HIF-1), were not expressed by macrophages and monocytes subjected to pressure cycles. Additionally, PECAM-1, VCAM-1 and ICAM-1[81] are also found in disturbed flow regions of ECs, and reduced shear upregulates the P-selectin[82] and monocyte chemotactic protein-1 (MCP-1) mRNA expression in correlation with an increased number of monocytes bounded to EC. Interestingly, following the loss of Piezo1, the rise in Vcam-1 expression and the number of CD68-positive cells was markedly decreased, and turbulent flow-evoked inflammation signals were also blocked. Comparatively, subjecting human umbilical artery endothelial cells (HUA ECs) to turbulent flow leads to NF-κB triggering, as evidenced by p65 phosphorylating at serine 536. Furthermore, in athero-susceptible sites, there were less integrin activities, inflammatory signals and atherosclerosis, following the selective depletion of endothelial Piezo1 or Gq/G11 in mouse. Both *in vivo* and *ex vivo* EC Piezo1 and Gq/G11 mediate inflammatory EC signal in response to turbulent flow, leading to EC dysfunction and AS, also equal signaling pathway detects laminar flow and triggers eNOS.[21,81,83] Hence, turbulent and laminar flow tend to stimulate Piezo1- and Gq/G11-mediating signals, which mediates both athero-protective and proatherogenic signals, described in the figure legends[8,84–86] (Figures 2 and 3). In AS, inflammation involves several mechanisms and cross-talk between various pathways, therefore targeting inflammation through Piezo1 approach could be wise. Altogether, these findings support the idea that Piezo1 might not just mediate unidirectional flow-evoked anti-atherogenic signals but is also necessary for turbulent flow-mediated endothelial inflammation and atherogenesis.

Piezo1 Mediated Immune/ Inflammatory Response in Atherosclerosis

Mechanical stress exerted on EC in the form of disturbed flow is among the primary activators of the endothelial immune defense system. Activation of EC is always followed by the recruitment of immune cells such as monocytes, which later differentiate into macrophages and transform to lipid-engorged foam cells, the hallmark of AS. Numerous studies reported the dominance of immune cells on the site of an earlier plaque. Triggered T cells, including macrophages, have been revealed to reside on early and part of matured AS plaques, and their transcription components speed up the plaque advancement, indicating the significant function served by innate and adaptive immunity in AS cytopathology.[64,87,88] Turbulent flow is thought to activate the endothelial immune system that initiates the process of AS. Traditionally ECs oppose adherence of inflammatory cells, but EC exposure to turbulent shear mediated by Piezo1 activates the endothelial expressions of adhesive molecules that promote the attaching of immune cells (Figure 3). Studies reported the significant role of mechanical force on immune cell functioning, and Piezo1 appears to be crucial in T-cell activation and recruitment.[89,90] Additionally, findings by Solis et al. revealed the physiologic function of Piezo1, including mechano-sensing in immunity.[65] Adaptive immunity has a significant effect on atherogenesis, with pro- and anti-atherogenic impacts exerted by T cells sub-classes.[91] As reported by Solis, Piezo1 detects oscillatory pressure in myeloid cells, and triggers pro-inflammatory responses. Mechanical activation of macrophages, including monocytes, stimulates expressions of pro-inflammatory and chemo-attractive mediators, which all rely on Piezo1.[65] Intriguingly, in lack of Piezo1, macrophages, including monocytes subjected to cyclical pressure, could not express inflammatory cytokines and chemokines.[67] Altogether these findings demonstrated that Piezo1 is crucial for immune response during atherogenesis (Figure 3).

Piezo1 Activation of NLRP3 Inflammasome and TLR4 Signaling in Regulation of Inflammation and Atherosclerosist

Atherosclerosis is a chronic progressive inflammatory disorder that is believed to be linked to the triggering of NLRP3 inflammasome and TLRs signaling. According to a growing body of data, NLRP3 inflammasome and TLR4 appears to have a causal role in the onset and advance of atherosclerosis.[92,93] Given the importance of mechanical forces in regulating cellular and tissue growth, as well as in disease pathogenesis,[94] including atherosclerosis, mechanosensitive Piezo1 channel could be considered as a crucial player in various mechanisms of CVDs particularly atherosclerosis.[28] Piezo1 channel was reported to be expressed and function in vascular cells including ECs,[95] VSMCs,[20] as well as immune cells (myeloid cells) such as monocyte, macrophages,[65] B and T cells.[68,90] On the other hand, NLRP3 and TLRs,[96,97] are also expressed by both immune cells and endothelium. NLRP3 inflammasomes and TLRs are well-known multi-protein complex immunological sensors that augment inflammation in response to a variety of danger-signaling ligands inclusive of pathogen-associated molecular patterns (PAMPs) from invading microbes (e.g., LPS) or mislocated commensal pathogens,

as well as danger-associated molecular patterns (DAMPs) or alarmins like endogenous factors,[98] inclusive of RNA and DNA, HMGB1, amyloid-β, cholesterol crystals, mitochondrial damage, or ROS, as well as noxious stimuli like disturbed shear mediated by Piezo1, which results in accumulation and triggering of caspase-1. Innate immune responses mainly rely on the detection of PAMPs and DAMPs via the pattern-recognition receptors (PPR), including Toll-like receptors and NLRs, particularly TRL4 and NLRP3. A recent study shows that application of Yoda1 in BV2 cell upregulates the expressions of TLR4, moreover, significant elevation of TLR4 and Piezo1 expressions were seen following the application of Yoda1 and LPS; this finding suggest that Piezo1 is crucial for TRL4 signaling.[99] NLRP3 activators are thought to cause one or more downstream cellular processes or diseases rather than directly interacting with NLRP3. The NLRP3 inflammasome is triggered by two distinct signals: toll-like receptor 4 (TLR4) ligands lipopolysaccharide (LPS) binding to its receptor, which causes NLRP3 and pro-IL-1 transcriptional upregulating via NF-B (1st signaling). TLR4 can also deliver 1st signaling independently of new protein synthesis through its adaptors myeloid differentiation factor 88 (MyD88), interleukin 1 receptor-associated kinase 1 (IRAK1), and IRAK4. NLRP3 activation requires a posttranscriptional alteration; NLRP3 deubiquitination mediates by BRCA1/BRCA2-containing complex subunit 3 (BRCC3) (2nd signaling). The NLRP3 inflammasome is assembled and activated by the second signal through NLRP3-activating substances (e.g., ATP, ROS, oxidized mitochondrial DNA (mtDNA), and other noxious stimuli including mechanical stretch and disturbed or oscillatory shear mediated by Piezo1, followed by proinflammatory caspase-mediated pyroptosis.[97,100] Recent findings[92,100–102] suggested that in ECs, various insults like disturbed flow, initiate the NLRP3 inflammasome triggering, and Piezo1 is a newly discovered mechanosensitive channel that senses and transduces different flow patterns into biochemical signals.[103,104] In ECs simulation of turbulent flow and oscillating shear extensively intensifies the generation of active caspase-1 and IL-1β.[105] Furthermore, Sun et al. reported that Piezo1 triggering enhances the assembly of NLRP3 inflammasome, as indicated by caspase 1 upregulating and generation of IL-1β which was reversed after Piezo1 siRNA transfecting. Interestingly, the abrogation of Piezo1 dependent NLRP3 inflammasome trigger was observed following the Ca^{2+}/NF-κB pathway suppression. The author further revealed that mechanical stretching enhanced expression of Piezo1 and intracellular Ca^{2+} accumulation that upregulates NLRP3 through the NF-B pathway triggering. It also acts as a direct secondary stimulus, promoting NLRP3 assembly, caspase-1 triggering, and the generation of IL-1β.[106] In tissue-resident mice alveolar macrophages, Wu et al. found that cyclical stretching known to be mediated by Piezo1, triggers the NLRP3 inflammasome through mitochondrial ROS generation, suggesting that this mechanism might be connected to lung inflammation caused by mechanical ventilation. Mechanical stress appears to be a risk factor for NLRP3 inflammasome activation, according to this study.[107] Whereas another study found that application of prolonged compressive stress to epidermal tissue increased NLRP3 and caspase-1 protein expressions while reduced IL-1β expression.[108] Contrarily, another study revealed that in macrophages, cyclical stretching inhibits the NLRP3 inflammasome.[109] This implies that further studies are necessary to explain these contradictory findings. The mechanosensitive Piezo1 channel appeared as principal transducer of mechanical cues into Ca^{2+} dependent signaling, and Ca^{2+} signaling was critical in various cellular physiology and pathologies. Piezo1 triggering is necessary for various Ca^{2+} dependent pathways. Many downstream pathways including that of TLR4, NF-B, mTOR, and JNK1,[110] which are controlled by intracellular Ca^{2+} signals, have been demonstrated to be the major molecular processes involved in immune processes including inflammation and atherosclerosis.

Piezo1 Mechanical Trigger of Proliferation, Migration and Apoptosis in Atherogenesis

Owing to the pulsative aspect of blood supply, vascular cells (VECs & VSMCs) are exposed to hemodynamic forces in the form of shear stress, pressure, circumferential/distention or stretches. Mechanosensitive Piezo1 senses such forces in various intensities, allowing their translation into biological signals within the cell, leading to triggering of downstream pathways.[9,111,112] Depending on whether the cells are subjected to physiologic or sub-physiologic/supraphysiologic mechanical forces, this trigger can differ. Significant physiological mechanical force is crucial in maintaining vascular homeostasis.[72] While sub-physiologic or supraphysiologic forces may induce alterations in gene expression that encourage inflammation, cell proliferation, migration, apoptosis and vascular remodeling, that are

pivotal process in atherosclerosis development.[113,114] Multiple studies demonstrated the effects of Piezo1-mediated mechanical signals on vascular and other cells (immune/inflammatory cells) involving proliferation, migration, apoptosis and remodeling during disease pathogenesis,[65,66,68,90,105] particularly atherosclerosis (Figure 4). Pathological inflammation, cell proliferation, migration and apoptosis of EC, VSMCs and macrophages is the hallmark of atherosclerosis pathogenesis, including several CVDs.[115] Piezo1 is necessary for sensing and transduction of various mechanical forces including shear stress, pressure, and cyclic stretch. VSMCs proliferation was reported to be increased by cyclic stretch *in vitro*.[72,73] Piezo1 is a well-recognized mechanically triggered channel that enables Ca^{2+} influx,[47,116] and Ca^{2+} is a highly recognized modulator of cell proliferation, migration and apoptosis, thus, it serves a crucial function in atherogenesis.[8,9] Additionally, ERK and Akt/mTOR pathways are crucial for cell survival, differentiation, proliferation, migrating and apoptosis,[117–119] and intracellular Ca^{2+} signaling can control these pathways.[120] Stretching was shown to enhance mice and rabbit VSMCs proliferation by activating the extracellular signal-regulated-kinase (ERK) pathway in a synergistic manner with oxidized LDL and norepinephrine. Furthermore, 15% stretching of mouse aortic SMCs exhibited higher ERK and Akt triggering, as well as an increase in insulin-induced cellular proliferation.[72] In pathological stretching, however, unregulated proliferation of ECs was seen due to upregulating of oncogene c-Myc expression in human umbilical vein endothelial cells (HUVEC). HUVECs depleted in Piezo1 display decreased expression of VEGF, cell proliferation, and migration in stationary states, demonstrating the significance of Piezo1 in this mechanism.[12] When ECs were stretched, they transdifferentiated into SMCs as elevated expression of specific SMC marker genes (SM22, -SMA, caldesmon-1, SM MHC, and calponin) was observed, while endothelial markers were reduced. The appearance of SMC markers on EC means that during mechanical stretching, EC plasticity towards the SMC phenotype occurs, which may lead to the plaque progression.[73] Comparatively, Piezo1 overexpression or dysregulation can lead to increase in Ca^{2+} overload. The elevated level of intracellular Ca^{2+} can activate the Akt/mTOR pathways through calmodulin (CaM) or CaM-dependent protein kinase II (CaMKII) and, as a result, accelerate cellular proliferation and migration, important processes in plaque formation and cancer. Piezo1 plays a crucial role in cell migration, as MCF-7 cells can migrate better when Piezo1 is overexpressed. While application of Piezo1 agonist GsMTx-4 impaired the migrating of MCF-7 breast cancer cells.[28] Collectively, these results demonstrate that Piezo1 is needed for inflammation cell proliferation, migration, apoptosis and, that these are critical stages in the development of AS.

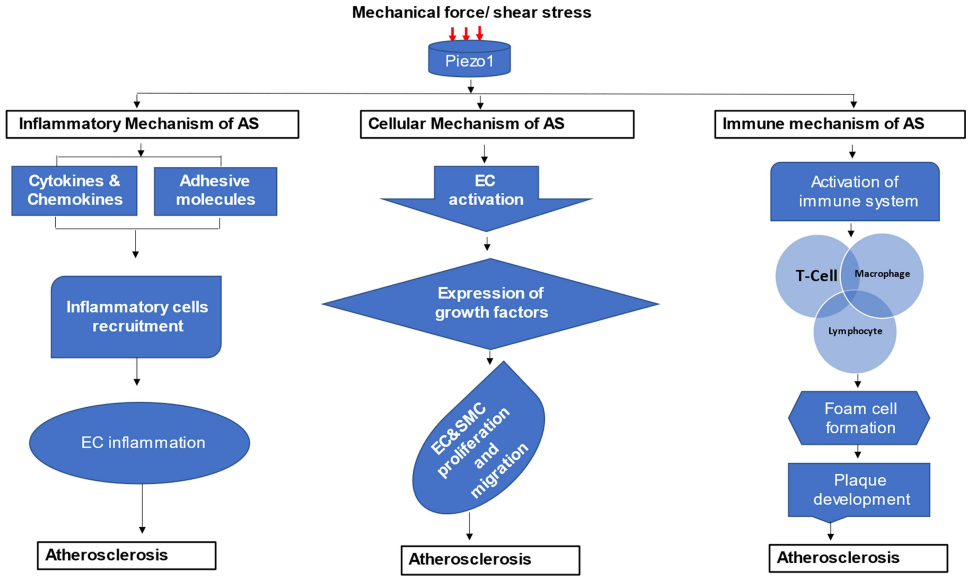


Figure 4 Different mechanosignaling mechanisms of atherosclerosis: schematic diagram demonstrating different signaling thoroughfares and stages of atherosclerotic development from Piezo1 activation by mechanical force, the arrow branching to inflammatory, cellular proliferation and migration, and immune atherosclerosis development.

Piezo1 Pharmacology

The accumulated reports and preceding experiments collectively demonstrate the mechanosensitive value of Piezo1 in both physiology and pathology, particularly atherosclerosis. They may be used as diagnostic biomarkers, as well as pharmacologic and genetic targets for innovative and advanced therapeutic approaches. Despite the infancy of Piezo1 research and its pharmacology, the rapid discovery of its pharmacologic agents presents an outstanding therapeutic opportunity. Recent studies reported the recognition of a few molecules including Yoda1,[121] and Jedi1/2,[122] as potent activators of Piezo1, and GsMTx-4,[123–126] Ruthenium Red (RR)[47,127] as its non-specific inhibitors, inclusive of Yoda1 analog called Dooku1,[11] and the most recent molecule Tubeimoside1 (TBMS1),[128] that have reversible antagonizing capacity of Yoda1-evoked Piezo1 trigger, as well as the binding site including activating mechanisms.[112] Altogether, the agonistic and antagonistic capability of the molecules on Piezo1 demonstrated the medicinal and pathophysiological significance of Piezo1 in atherosclerosis and including cancer and other disorders. Nevertheless, Piezo1 drug targeting for therapeutic approaches remains challenging and a difficult task that requires further investigations.

Future Research

Piezo1 channel is a newly identified ion channel, which touches many areas in cell biology. It is expressed in different cell types, and its function may differ in different species, tissues, and local cellular environments. Despite the rapid advancement in Piezo1 research, more roles are yet to be explored. Piezo1 will be a novel candidate for global researchers to further explore its physiological and pathological functions as well as thorough understanding of its pharmacology. Additionally, future investigation on Piezo1 regulation of accompanying mechanisms related to AS will shine a light toward the future prospective and promising therapeutic strategies that may help to reduce the burden of disease and cost of treatment in various conditions, particularly AS in CVDs.

Conclusion

Atherosclerosis is the basis of CVDs, and the critical subject in cardiovascular research and the long-term major issue of global health care. Great efforts and advancement in biomedical as well as clinical research have brought significant achievements in the management of CVDs burden, particularly AS. Despite these remarkable achievements, residual risks yet remain, as many individuals suffer the disability of heart functions leading to the increased CVDs epidemic. AS is a multifactorial disorder; that makes it a complex disease which requires multiple approaches beyond lipid-lowering and lifestyle improvement. Besides these primary and other risks, considering mechanical forces including shear stress in form of disturbed flow should also be crucial. Consistent with the accumulating evidence that specific plaque location is in the curved and branching regions of the arteries where the flow is low and disturbed,[129] and immune/inflammatory mechanisms involving Piezo1 signaling play critical role during the process, this shows that even newborn babies are counted in this risk, due to the branching and curved nature of blood vessels. This indicates the importance of turbulent shear, mediated by Piezo1 in the development and progression of atherosclerosis. There have been several experiments that have elucidated the mechanisms of Piezo1 signaling and its regulatory roles in the trigger of various inflammatory signals that initiate downstream events including activation of NLRP3 inflammasome and TLR4. However, we need to be clear that the initiation of signaling necessary inflammatory mechanisms and their downstream effects in NLRP3 inflammasome triggering play critical roles at different stages of triggering and the impacts they generate are miscellaneous. Piezo1 signaling has various impacts on inflammatory cells and their function including the initiation of inflammatory mechanisms and downstream triggering of the NLRP3 inflammasome, TLR4 and related Ca^{2+} dependent signaling which play crucial roles in the initiation and progression of atherosclerosis. This paper provides a new perspective where not just Piezo1 inflammatory signals and the downstream activation of TLR4 and NLRP3 inflammasome but also the signaling hubs between them are promising strategies to target against atherosclerosis that are worthwhile for future research. In this regard the scientific community should come up with new strategies using interdisciplinary approaches to resolve the challenges of disparity between *in vivo* physiological systems that have heterogeneity in cell behavior across vascular beds compared with our current homogenic *in vitro* experimental system. To achieve this, the following arguments should be considered.

Endothelial Model

HUVEC is the most commonly used model in research; the disparity of endothelial heterogeneity across vascular beds is rarely taken into account, in which endothelium

from other origins could give different outcomes to the same approach. Indeed for clarity, a single study approach should be tested on endothelial models of multiple origin, as the cell behavior is spatially different across vascular beds.

Individual Mechano-Sensing Protein, Its Correlation with Other Proteins and Signaling Pathways

Several studies reported Piezo1 as an independent mechanosensor and transducer of itself, independent of other ancillary proteins, while other works reported Piezo1 functions in correlation with other mechanosensitive proteins, such as TRPV4. This could be due to the cross-talk between different proteins in different cellular mechanisms and correlation with signaling pathways in a particular cell activity. Therefore, new approaches and strategies are required to resolve this argument. Further study targeting several mechanisms involving various proteins and their correlation in regulating multiple cellular signaling pathways are necessary, to elucidate more on particular function of each protein individually, and in correlation with others in different mechanism of cellular physiology.

Physiological Model of Flow in Different Vascular Beds and Rhythmic Changes

With physiological flow *in vivo*, shear pattern is transiently dynamic due to physiological variations in vascular bed, cardiac output or other metabolic needs, compared with *ex vivo* experimental systems that are commonly employed, the laminar or oscillatory shear pattern applied is always steady with no variation in intensity, amplitude or pattern (seen with *in vivo*) throughout the experiment. This creates a considerable gap among *ex vivo* and *in vivo* systems. Therefore, the shear sensing of Piezo1, the downstream impact, endothelial response and consequent gene expression may vary between *ex vivo* and *in vivo*. The transient variations of shear intensity and amplitude which commonly happen with *in vivo* should be considered when using *in vitro* experimental systems, since the common experimental systems used only apply steady, laminar, oscillatory or low turbulent shear which is not enough to precisely symbolize *in vivo* physiological shear experienced by EC. Here arises the requirement for advancing the current *ex vivo* experimental system to precisely meet the conditions similar to that of the *in vivo* physiological flow system.

In summary, Piezo1 is a promising candidate in cardiovascular research, due to the evidence already available on its physiological and pathological relevance in various angle of cardiovascular, regardless of its novelty. Its broad expression makes it likely to serve vital functions in regulating undiscovered aspects of cardiovascular physiology and pathology, and produce multiple functional outcomes depending on cell type and mechanisms involved. Therefore, innovative strategies through Piezo1 pharmacological approach will be advantageous for multiple therapies in cardiovascular disease, especially atherosclerosis.

Lastly, an intriguing fact in the Piezo1 pharmacology is the recent discovery of its activator (Yoda1), and inhibitor Grammostola spatulata mechano-toxin 4 (GsMTx4). It shows that with deep understanding of both Piezo1 and its pharmacology, their translation into the clinic may unlock the door and could be the promising therapeutic target for AS burden and other CVDs.

Abbreviations

AS, atherosclerosis; CVDs, cardiovascular disease; MI, myocardial infarction; IHD, ischemic heart disease; ECs, endothelial cells; VEC, vascular endothelial cell; RBCs, red blood cells; VEGF, vascular endothelial growth factor; PDGF, platelet derived growth factor; IFN-γ, interferon gamma; IL, interleukin; MCP-1, monocyte chemotactic protein-1; PECAM-1, platelet endothelial cell adhesion molecule; ICAM-1, intercellular adhesion molecule; VCAM, vascular cell adhesion molecule; KLF, Kruppel like factor; NF-κB, nuclear factor kappa B; eNOS, endothelial nitric oxide synthase; GM-CSF, granulocyte-macrophage colony-stimulating factor; ROX, reactive oxygen species; HUVECs, human umbilical vein endothelial cells.

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Author Contributions

All authors made a significant contribution to the work reported, right from conception, study design, execution, acquisition of data, analysis and interpretation, and took part in drafting, revising and critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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