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Review Article

A narrative review on the biology of piezo1 with platelet-rich plasma in cardiac cell regeneration

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ABSTRACT

Cardiomyocyte regeneration following cardiac damage is challenging to study because of the inflammatory process, the multiplication of cells in the stroma, and the creation of scar tissue. In addition to the initial damage, the subsequent decrease in cardiac myocytes adds to heart failure. Piezo1 is remarkably understudied in the heart, which may be related to its recent discovery. Despite this, Piezo1 is expressed in a variety of cardiovascular cell populations, notably epithelial cells (EC), cardiac fibroblasts (CF), and cardiac myocytes (CM), in both animal and human samples, with fibroblasts expressing more than myocytes. Researchers have recently shown that disrupting Piezo1 signaling causes defects in zebrafish developing the outflow tract (OFT) and aortic valves. Platelet plasma membranes may provide lipid substrates, such as phosphatidylinositol bisphosphate, that aid in activating the piezo 1 ion channel in the cardiovascular system. In addition, CXC chemokine ligand 8/CXC chemokine receptor 1/2 (CXCL8-CXCR1/2) signaling was identified to establish the proliferation of coronary endothelial cells during cardiac regeneration. Notably, all these pathways are calcium-dependent, and cell proliferation and angiogenesis were necessary to recover myocardial cells. This review will examine the most current findings to understand further how platelet-rich plasma (PRP) and the piezo 1 channel might aid in cardiomyocyte regeneration.

1. Introduction

The proliferation of cardiomyocytes in the early postnatal period enlarges the mouse's heart (hyperplastic growth). Myocardial damage generates a regenerative response in mice within a limited postnatal window of seven days, culminating in replacing destroyed cardiomyocytes with new ones. Following the findings of fate mapping investigations, cardiomyocyte proliferation is the primary mechanism of action in this kind of cardiac tissue regeneration [1,2]. However, this regeneration window has yet to be discovered in big animals or humans.

Many research findings indicate that cardiomyocyte renewal occurs in the clinically healthy Myocardium due to a moderate degree of previously established cardiomyocyte mitosis [3]. In addition, cardiac myocyte regeneration rates may increase the following insult compared to normal settings [4]. This idea is supported by trials conducted on zebrafish, newts [5], and other animals [5], in which cardiomyocyte regeneration is more robust than in mammals. Manipulating cell cycle regulators, using redox regulators, using growth agents that operate

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through cell surface receptors, or moving nucleic acids intracellularly can all help increase endogenous cardiomyocyte proliferative capacity [6,7]. However, research on cardiomyocyte renewal following a cardiac injury can be complex because of the inflammatory process, the proliferation of cells in the stroma, and scar tissue development (Fig. 1).

Blood flow exerts a frictional force on the vascular wall, resulting in wall distension in response to transmural pressure fluctuations [8,9]. Shear stress can develop in the vasculature due to the laminar flow of blood. These mechanical pressures have a significant impact on the development and physiology of the vascular system and are associated with various disease conditions. Numerous mechanosensory have been identified within cardiomyocytes, including adhesion molecules, cytoskeletal components, the endothelium junctional complex, extracellular matrix components, various ion channels [10–12], G protein-coupled receptors [13], and many signaling molecules, for example, small GTPases and their effectors, which results in the generation of mechanical forces. Since cardiomyocytes are permanently differentiated cells, cells have a limited capacity to renew and repair the damage. As a result of the increased cell death, the damaged heart develops increasingly severe pathological characteristics. Adding insult to injury, the resulting reduction in cardiac myocytes contributes to cardiac failure. Therefore, the review explores the most recent research on the ability of platelet-rich plasma and the role of the piezo 1 channel on cardiomyocyte regeneration.

2. Selection of literature review

As of March 2022, the literature review was conducted using PubMed and other secondary sources like Scopus and Google Scholar. Platelet-rich plasma, cardiac cell regeneration, and cardiac regeneration process are essential terms used in this study's literature search, as are Piezo 1 ion channels and cardiac cell regeneration. The publications were selected based on their relevance to the global cardiac injury-induced loss of functional cardiac myocyte. During this first search, we discovered works published in contemporary scientific journals. Additionally, only English-language publications were selected using the language filter.

3. Biological overview of piezo channel

Following a brief introduction to mechanosensory and the regenerative response within cardiomyocytes, it focuses on the most recent piezo ion channels and Ca2+ handling proteins that have been studied and then on the novel mechanism of action for platelet-rich plasma that biophysically modulates cardiac regeneration, to comprehend the ion channel-cardiac regeneration interaction better.

Piezo1 and 2 are cation channels that are essential sensors of shear stress. They are big transmembrane trimeric biomolecules with a propeller-like structure and three edges arranged around a central pore. These channels create a nonselective positively charged ion current in response to mechanical stressors, including elevated fluid flow, membrane strain, pressure, or hardness. They are leaky to Sodium ions, potassium ions, calcium ions, and other divalent cations [14,15].

Surprisingly very little is documented about Piezo1's involvement in the Myocardium, which may result from its recent discovery. In this, Piezo1 was expressed in a range of cardiac cell types, including epithelial cells (EC), cardiac fibroblasts (CF), and cardiac myocytes (CM) in both human and animal samples, with a higher expression level in fibroblasts than myocytes [16,17] (Fig. 2).

These observations may be used to calculate the rate of Ca2+ accumulation, the latency, and the time required to achieve the peak concentration. The whole contribution is characterized by the combined action of the initial Ca2+ influx via shear-sensitive channels and the subsequently released internal reserves. When shear stress is activated, it is critical to understand the potential paths for the total Ca2+ responses that might be detected. The release of Ca2+ from storage is a frequent mechanism for increasing cytosolic Ca2+ concentrations. ATP-dependent pumps transport calcium from the cytosol to calcium reserves in the endoplasmic reticulum (ER) and mitochondria to maintain cell calcium homeostasis. According to one theory, activation of calcium oscillations by mechanical force may result from calcium influx-induced calcium release. Previous research has demonstrated that a ventricular myocyte's diastolic stretch of 8% can result in a burst of Ca2+ sparking [18]. In the Piezo1-KO cardiomyocytes, however, this was not detected [19,20]. According to the research done on human umbilical vein endothelial cells (HUVEC) exposed to shear stress, the constant flow has boosted eNOS synthesis and actin fiber formation in cultured HUVEC

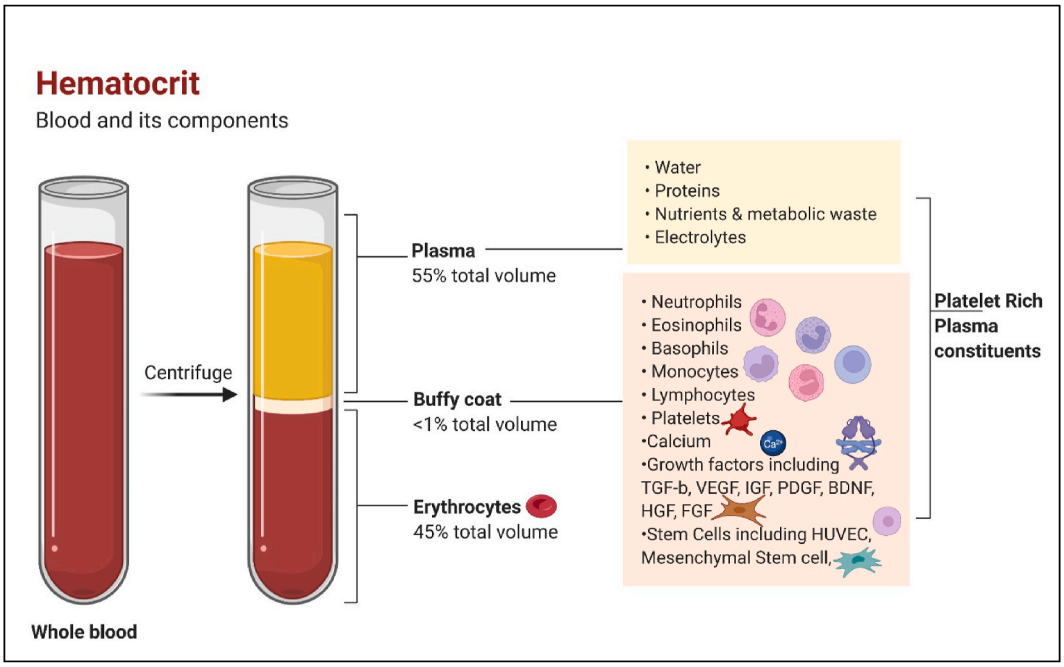

Fig. 1. Exhibiting the platelet rich plasma constituents in whole blood.

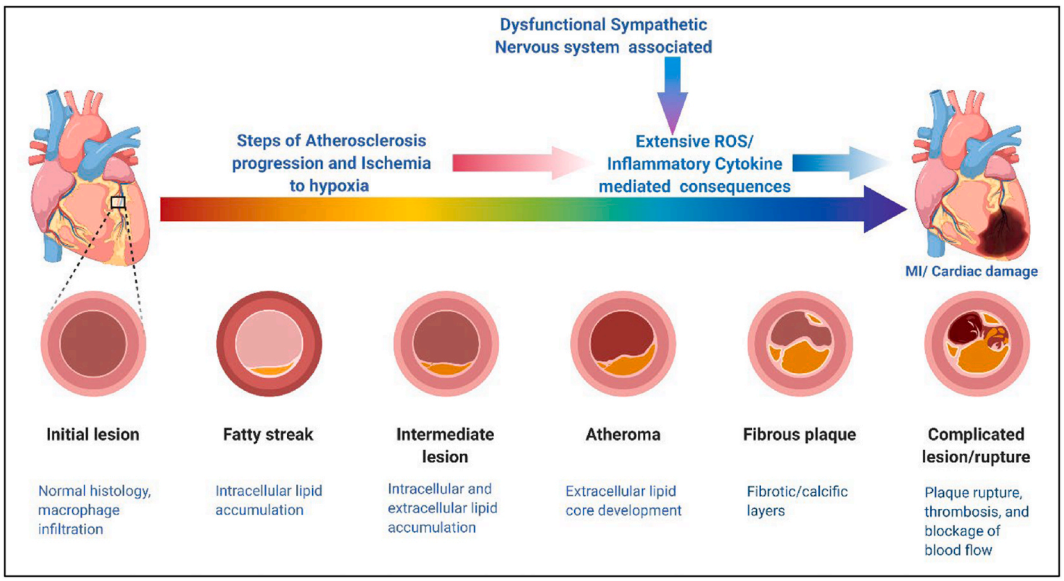

Fig. 2. Exploring the mechanism of cardiac ischemia to hypoxia mediated permanent cardiac cell damage.

cells compared to pulsatile shear stress [21]. It is estimated that Phosphatidylinositol 4,5-bisphosphate (PIP2) and Phosphatidylin ositol-4-phosphate (PI(4)P) contribute to up to one percent of the membrane's lipids, making them the most prevalent phosphoinositides [22]. PIP2 may also influence Piezo1 function, according to certain studies [23]. Phosphoinositides are required for Piezo channel function, and depletion of both Phosphatidylinositol-4-5–phosphate (PI(4,5)P2) and PI(4)P causes a decrease in channel activity [24]. Molecular alterations in membrane structure, such as fatty acids, have been demonstrated to affect Piezo1 activity in recent research [25]. Despite the modest level of Piezo1 expression in platelets, the mRNA transcript and protein levels were both found. According to patch-clamp recordings from human platelets, the lowest density ion channel was completely undetected by qPCR [26,27]. However, during thrombus formation, the activity of the piezo 1 channel was inhibited due to shear stress in arteries [28]. Piezo1 deletion and pharmacological suppression decreased endothelial sprouting and lumen development, while activation of Piezo1 with the specific Piezo1 activator Yoda1 increased sprouting angiogenesis. Substances promoting angiogenesis include growth factors such as basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), sphingosine-1-phosphate, and mechanical stimulation such as wall shear stress on an endothelial cell (EC) lumen [29,30].

As a general rule, mutations in Piezo1 in mice resulted in abnormalities in the yolk sac architecture, which led to embryo mortality. Hence Piezo pathways were first seen as necessary in mechanotransduction [31–34]. Vascular system development at this stage is crucial since primitive vascular plexuses arise in response to shear stress. Vascular growth into larger arteries was impeded in embryos lacking endothelial cells. Even though Piezo1 haploinsufficiency did not result in death, anomalies of the endothelium in mature arteries were discovered. In vitro investigations revealed that early endothelial cells from Piezo 1 mutants could not line in the direction of the fluid flow correctly. This process happens physiologically in blood vessels.

Treatment with GsMTx4, an anti-cationic mechanosensitive channel-inhibiting Spider Venom Peptide, reduced HUVEC alignment by lowering Piezo1. To perform well in physical activity, piezo channels are necessary, but not at the adult stage. They oppose the vasodilatory process of endothelium-derived hyperpolarization, which has a vascular bed-specific influence [35]. Endothelial cell deficit in Piezo1 and Gq/G11 decreases inflammation and atherosclerosis progression [36]. It is thought that Piezo 1 is the mechanoreceptor for uterus vasculature expansion during gestation because it enhances Ca2+ influx mediated endothelial NOS (eNOS) stimulation from endothelium [37,38]. It was later shown that Piezo1 was linked to human vascular development in subsequent human genetic association studies [39]. As a result of these investigations, scientists are beginning to understand the significance of Piezo1 in adult cardiovascular biology [40]. Another essential component, Piezo 2, is not well-studied. In humans, piezo mutations have previously been associated with anemia, lymphedema, and varicose veins (Fig. 3).

According to a new zebrafish study, improper development of the OFT and aortic valves is caused by disruption of Piezo1 signaling. A significant regulator of cellular responses to hemodynamic stressors, Piezo1 plays a vital role in creating zebrafish valves [41,42]. Furthermore, cardiomyopathies caused by doxorubicin boost Piezo1 expression in CM, and clinical studies show elevated Piezo1 expression in heart biopsies from people with hypertrophic cardiomyopathy. Piezo1 [19].

4. Biology of platelet rich plasma

Platelet concentrates are made from centrifuged whole blood and are divided into four essential groups largely dependent on their leukocyte and platelet content and fibrin construction: pure platelet-rich fibrin (P-PRF), leukocyte and platelet-rich plasma (L-PRP), platelet-rich fibrin (L-PRF), pure platelet-rich plasma (P-PRP), leukocyte and P-PRP preparations contain plasma containing growth factors (GFs) as well as activated GFs. In addition to their high concentrations of platelets and growth factors, these substances have been shown to aid in osteogenesis, angiogenesis, and tissue regeneration. These growth factors are fibroblast growth factor (FGF), transforming growth factor β (TGF-β), vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF), platelet-derived growth factor (PDGF), and brain-derived neurotrophic factor (BDNF). Neovascularization and angiogenesis of infarcted cardiac tissues may contribute to speeding up the regenerative mechanism. Nowadays, stem cell therapy and GFs administration, including different PDGF, FGF, and VEGF, and respective combinations, have been used to accelerate angiogenesis mechanisms. Indeed, platelets exhibit dense granules in addition to GF-rich alpha granules, which release chemicals that may positively affect cardiac muscle repair, including Calcium, serotonin, Histamine, ATP, and polyphosphate. Myocardial pathology amplifies the stress on the spared heart muscle, whereas mechanical stretch augments ATP exocytosis from cardiomyocytes [43–45]. Myocardial infarction is linked with cardiac progenitor cell

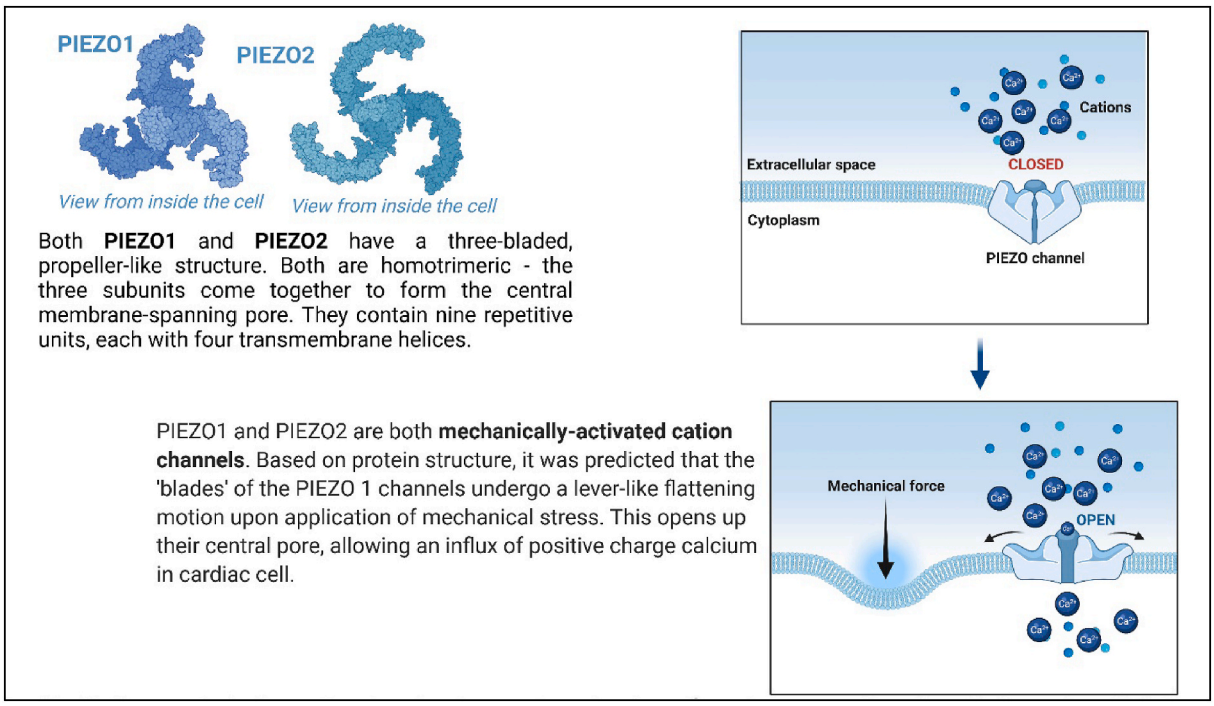

Fig. 3. Demonstrate the molecular structure and mechanism of mechanosensitive piezo 1 channel mediated calcium cation movement in cardiac cell.

division and the formation of physiologically viable heart cells in animals and people, corroborating the hypothesis that ATP-mediated cardiac progenitor cell proliferation is required for heart regeneration.

Growth factors function as signaling polypeptides that can elicit various physiological actions in a biological setting. These can participate in the production of the matrix, cell proliferation, chemotaxis, differentiation of cells, and cell regeneration, among so many other things [46]. Tissue repair and regeneration are enabled by intracellular changes in DNA synthesis and expression brought about by growth factors released by platelets, polymorphonuclear leukocytes, and macrophages at the site of damage [47,48]. Several growth factors must be in a well-balanced ensemble in regenerating tissues. The EGF restricts communication to a small distance [49], but IGF-1 may function at enormous distances [50] together with VEGF-driven angiogenesis [51]. Furthermore, the b-FGF, IGF, and their variants play an essential part in tissue repair & regeneration by increasing cellular proliferation, protein production, collagen formation, and other biological responses [52–55]. Many researchers have been intrigued by the anabolic properties of IGF [56]. There are several growth factors in wound healing and scar formation, one of which is TGF-b. Cells that generate TGF-b during wound healing include smooth muscle cells, epithelium and fibroblasts as well as lymphocytes and endothelial cells [57]. The post-infarction healing process is regulated by PDGF signaling. There are two types of growth factors that PDGF stimulates macrophages to produce: mitogens and chemotactic agents for fibroblasts and smooth muscle cells. PDGF receptors also induce the creation of various ECM components, including collagen and fibronectin (PDGFR-alpha and PDGFR-beta) [58,59]. Prior research had showed that BMSC proliferation was best achieved with 10% PRP as the ideal concentration [60–62].

Recent investigations have demonstrated that a complete regeneration response requires full revascularization of the wounded tissue via the coronary arteries. When the heart of a zebrafish is damaged, cECs quickly enter the cell cycle and revascularize the injured area. Pre-existing coronary arteries regenerate both superficially and intraventricularly, creating a scaffold for the repopulation of the injured tissue with cardiomyocytes. Blocking this mechanism has two side effects: the decreased proliferation of cardiomyocytes and decreased repopulation of wounded tissue; the other is increased scarring [63]. VEGFC controls lymphangiogenesis in the developing mouse and zebrafish [64,65] and the heart of an adult zebrafish [66,67].

Additionally, VEGFC modulates blood vessel angiogenesis in various developmental contexts [68,69]. VEGFC, for example, promotes angiogenic sprouting in chick embryos and mice corneas. In zebrafish, morpholino-mediated Vegfc knockdown inhibits intersegmental vascular sprouting [70–72]. Human VEGFC was shown to cause intersegmental vascular hypersprouting when overexpressed in the zebrafish embryo [73,74], indicating the significance of VEGFC in blood vessel angiogenesis regulation. Recent research has also revealed that VEGFC plays a critical function in controlling coronary development [75]. The coverage and branching of subepicardial coronaries are significantly reduced in the cardiac ventricles of Vegfc mutant mice. emilin2a was also shown to be an effector of the Vegfc signaling pathway, and it was found that emilin2a expression might affect coronary revascularization and cardiomyocyte proliferation. Cardiovascular endothelial cells have high levels of the CXCL8A receptor gene; however, cells originating from the epicardium do not. Therefore, we looked into the possibility that the proliferation of coronary endothelial cells during cardiac regeneration depends on CXCL8A-CXCR1 signaling [76]. As discussed before, platelet plasma membranes may offer lipid substrates such as phosphatidylinositol bisphosphate [77–79], assisting in activating the piezo 1 ion channel in the cardiovascular system [24].

Cardiovascular fibroblasts are critical to the heart's regular functioning and its ability to respond to injury or stress. Ca2+-permeable ion channel Piezo1 is connected to gene expression alterations that impact remodeling in cardiac fibroblasts. In addition, fibroblasts can become myofibroblasts through Piezo 1 channel-mediated Ca2+ signaling, which has been demonstrated to be involved in mechanosensation [16,80]. We conclude that the stretch-activated Piezo1 is irrelevant since the softer matrix (collagen-1) created an effect, while plastic culture dishes were not. In future investigations, researchers should evaluate the stiffness of the extracellular matrix in cardiac fibroblasts to see whether stiffer substrates have a biomechanical effect on Piezo activation.

5. Role of calcium and growth factors in cardiac cell generation

Ca++ excess in postinfarcted heart muscle is often managed by administering calcium-channel antagonists either alone or parallel with -beta-blockers. Calcium channel blockers (CCBs) inhibit the L-type ca2 + channels in heart cells and myocardial nodal tissue (sinoatrial and atrioventricular nodes). The L-type Ca++ channel influences the pacing currents in myocardial nodular cells. By preventing Ca++ from entering the cell, CCBs inhibit velocity of conduction (negative dromotropy), heart rate (negative chronotropic), and force of contraction (negative inotropy) inside the Myocardium. Cardiovascular calcium channel blockers treat high blood pressure, myocardial infarction, and dysrhythmias. However, Ca++ levels, on the other hand, are strongly connected to cardiomyocyte mechanical behavior and are also reported to increase the number of physiological activities, such as cell division, growth, proliferation & differentiation (Fig. 4).

The research studies revealed that human cardiac stem cells oscillate their Ca+2 concentration spontaneously, cell division, with the highest values showing. ATP, histamine, and IGF 1 were all involved in regulating these oscillations. Intriguingly, the fraction of cells with fluctuating calcium levels, frequency of these oscillations, and the number of cells dividing increased significantly when cardiac stem cells were cultured in any of these substances [81]. CXCL8 increases PLC signaling, which causes protein kinase C phosphorylation (PKC). CXCL8 stimulates human cancer cell motility by activating the PLC-dependent PKC signaling pathway, which modulates the actin cytoskeleton when combined with increased calcium concentration [82]. PKC-delta, p38-MAPK, and AKT are all related to increased SERCA and MHC [83]. CXCL8 has been demonstrated to serve as a proangiogenic factor in various contexts by activating the G-protein–coupled receptors CXCR1/2 [84–86]. Our findings of decreased cEC proliferation in cxcl8a and cxcr1 mutants imply that Cxcl8a mediates its angiogenic role in cardiac regeneration via activating CXCR1 produced by cECs. The proliferation of HUVECs and ECs in chick embryos has been connected to the activation of Rho, Rac, and MAPK signaling pathways by CXCR1 [87]. Notably, all these pathways are calcium-dependent, and cell proliferation and angiogenesis were necessary to recover myocardial cells [88]. The results clearly show that Piezo1 promotes sprouting angiogenesis induced by wall shear stress (WSS) and sphingosine 1-phosphate (S1P) therapy. Angiogenesis is stimulated by Piezo1-mediated Ca2+ influx and membrane translocation, which results from mechanical and pharmacological inputs and other associated signaling pathways [89].

6. Conclusion

Our understanding of mechanical sensing in physiological systems is emerging, and cardiovascular function depends on MS channels. As a result, the discovery of novel MS channels (such as Piezo) has emphasized the significance of further research into the biological processes that underlie mechano transduction. As a result, mechanosensation can be better understood, and therapeutic targets for various disorders may be discovered by examining specific ion channels' roles in translating mechanical forces into physiological responses. According to current studies, many MS channels are needed to integrate cellular and physiological responses to mechanical stress. These results show that a particular system requires many mechanotransducers to function effectively. Additionally, the application of PRP-induced stress response activates piezo 1 mediated calcium influx, which, in combination with IGF-1, VEGF-A and VEGF-C, PDGF-AA, PDGF -AB, and PDGF -BB, and EGF from PRP, can enhance differentiation & proliferation, cell migration, stem cell homeostasis, and local angiogenesis. In conjunction with the accumulation of proteins such as collagen, these substances are critical in restoring typical tissue structure and function and their ability to regenerate damaged heart tissue.

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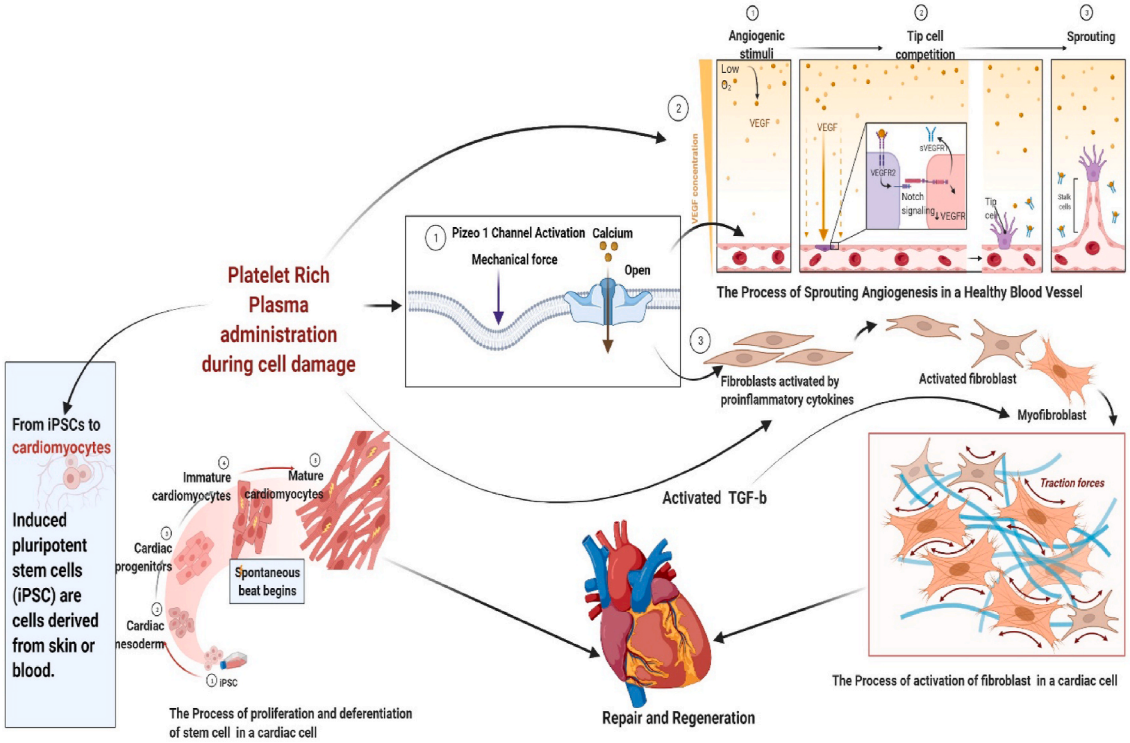

Fig. 4. Exploring the role of Piezo-1 and platelet rich plasma in cardiac repair and regeneration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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