THE ROLE OF THE MECHANOSENSORY RECEPTOR PIEZO1 IN EPITHELIAL CELLS AND ITS IMPACT ON VOCAL FOLD HOMEOSTASIS: A SYSTEMATIC REVIEW

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SUMMARY

This systematic review examines the role of Piezo1 in epithelial cells, with a focus on vocal folds homeostasis. Understanding the homeostasis recovery process in the vocal fold epithelium is crucial for improving voice treatments, including pharmaceutical and therapeutic interventions. The review was structured based on the PRISMA framework and considered two widely used by the healthcare sciences community electronic databases: PubMed and Scopus. It incorporated MESH terms "Piezo1 protein, mouse", "PIEZO1 protein, human", "Piezo1 protein, rat", and "Epithelial Cells" from 5-year-old papers. The extracted information included sample characterization, analytic techniques, and Piezo1's role in vocal fold homeostasis. Piezo1 is an ion channel responsible of transducing mechanical-sensory stimuli into electrochemical signals, increasing intracellular Ca^{2+} upon activation. However, its role in vocal folds epithelium remains unclear. Understanding Piezo1 regulation and its downstream activation pathway may yield therapies for vocal-fold related disorders (i.e., in developing drugs to modulate Piezo1 action). Thus, it's crucial to examine Piezo1 in epithelial cells, to discuss potential hypotheses about its role in vocal folds to guide future research. This systematic review addresses questions related to the role of Piezo1 in epithelial cells, previous mechanistic models and analytic techniques, to then speculate about its role in vocal fold homeostasis. The reviewed studies indicate that Piezo1's activation leads to the activation of various pathways. Piezo1's roles can be grouped into four categories: vascular system, cancer progression/limitation, inflammatory response, and homeostasis. Given that Piezo1 is expressed in vocal fold epithelium, its potential roles in tissue healing, homeostasis recovery, tumor growth regulation, cell migration, and epithelial cell differentiation and proliferation were discussed. This preliminary knowledge helps prompt further research on Piezo1's role in larynx epithelium healing, tumor growth regulation, and potential activation through therapeutic vibratory exercises.

Introduction

Epithelial cells in the vocal folds

Vocal folds are a multilayered, viscoelastic structure compounded of numerous tissue types (Cannes do Nascimento *et al*., 2020). Vocal folds are made of stratified squamous epithelium covering the flexible and elastic connective tissue of the lamina propria, which are located over the thyroarytenoid muscle (Cannes do Nascimento *et al*., 2020; Gray, 2000; Zhang, 2016). These tissues are susceptible to various type of damage, including harm caused by environmental or systemic-based irritants damage, surgical procedures, and vibratory microtrauma (Gray, 2000). So, as the outer layer, the epithelium has a role in vocal fold defense, working as a physical barrier to both contain the components of the lamina propria and to keep out foreign molecules and organisms (Leydon *et al*., 2014; Rousseau *et al*., 2011). Epithelial cells link by forming protein complexes called cell junctions to seal the paracellular space (Levendoski *et al*., 2014). Different forces that interact during phonation could provoke acute damage due to the disruption of vocal fold epithelial cells or

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junctions, reducing the barrier protective capacity (Branski *et al*., 2006; Levendoski *et al*., 2014; Leydon *et al*., 2014). So, continuous tissue repair and remodeling cycles are required throughout vocal fold lifespan (Branski *et al*., 2006; Leydon *et al*., 2014). In order to preserve the barrier function (retain the epithelial homeostasis), the renewal occurs by a small number of cells in the basal epithelial layer at a time (Leydon *et al*., 2014).

Packed stratified squamous epithelium covers the membranous vocal folds with a structure of 5–10 epithelial cell layers (Gray, 2000; Levendoski *et al*., 2014). Vocal fold stratified squamous epithelium is nonkeratinized, which means that they are nucleated and living differently from skin keratinized stratified squamous epithelium (Levendoski *et al*., 2014). Within the membranous vocal folds, these epithelial cells undergo a transformation into ciliated pseudostratified columnar epithelial cells. This transformation, which includes various cell types such as ciliated columnar cells and mucus-secreting goblet cells, occurs at the anterior and posterior commissures, as well as in the supraglottis (including the upper airway) and subglottis (Gray, 2000; Levendoski *et al*., 2014). In general, these cells are characterized by low proliferation rates until a significant injury occurs, thereafter epithelial cells initiate a quick process for recovery the homeostasis (reparation, proliferation; Foote, Lungova *et al*., 2022). Foote, Tibbetts, *et al*. (2022) reported that Piezo1 is expressed in the vocal fold epithelium to help recovery homeostasis and integrity, which is essential for protection against damage by excessive mechanical vibration in vocal fold tissue. However, the role of Piezo1 in vocal fold epithelium homeostasis and repair remains poorly understood.

Piezo1

Piezo family channels (Piezo1 and Piezo2) were first described in 2010 by Coste *et al*. (2010) in the Neuro2A glial tumor line. This protein, designated as Piezo1, includes approximately 2500 amino acids and did not show similarity with other channels (Coste *et al*., 2010). Piezo family of channels includes both Piezo1 and Piezo2, with the former being found in endothelial, urothelial, and renal epithelial cells (Jaggers *et al*., 2019). It expresses predominantly in non-excitable cell types and participates in some metabolic process of epithelial cells such as inducing insulin release, or macrophage phagocytic activity, among others (Foote *et al*, 2022; Ma *et al*., 202; Deivasikamani *et al*., 2019; Gudipaty *et al*., 2017). In recent years, research has illuminated the important role of Piezo1 in regulating physiological functions of epithelial cells (He *et al*., 2022). However, the role of Piezo1 in the epithelium of the vocal folds, which bear unique characteristics and are essential for voice production, airway protection, and other functions are currently underspecified. Understanding the function and regulation of Piezo1 in the vocal fold epithelium could potentially lead to advanced therapeutic approaches for treating vocal fold-related disorders, including vocal fold nodules, polyps, and scarring. To deepen our knowledge of the role of Piezo1 mechanosensitive channels in the vocal folds, it is first necessary to define the state of the art of Piezo1 function in epithelial cells and discuss potential hypotheses about its role in vocal folds that could guide future research in this area.

Within Piezo family, Piezo1 is a mechanically activated ion channel involved in force sensing in various cell types (also includes Piezo2; Lewis and Grandl, 2021; Li *et al*., 2014; Ridone *et al*., 2019; Zhao *et al*., 2018). This cation channel transduces various forms of mechanical-sensory stimulation, including pinpricks, stretches, and shear stresses into electrochemical signals (Gottlieb and Sachs, 2012; Ridone *et al*., 2019; Z. Wang *et al*., 2021; Zhao *et al*., 2018). These electrochemical signals serve various functions such as proprioception, vascular development, homeostasis, and epithelial growth among others (W. Jiang *et al*., 2021). Importantly, its relevance has been widely demonstrated in sensing shear-stress forces (Li *et al*., 2014) and its function has been associated with stretch-mediated Ca^{2+} and Na^{+} influx in endothelial cells (Wang *et al*., 2021). Piezo1 has a unique molecular architecture (described as bowl shaped) with a central transmembrane pore (cap), surrounded by three peripheral modules (arms) with transmembrane domain and intracellular projections (Choi *et al*., 2022; Jiang *et al*., 2021; Qin *et al*., 2021; Lewis and Grandl, 2021; Zhao *et al*., 2018). This protein has the ability to induce membrane curvature, due to skewing the membrane spatial distribution (Jiang *et al*., 2021; Lewis and Grandl, 2021). The initial convex membrane curvature becomes flatter when the membrane tension increases, opening the channel and allowing nonselective cationic influx (Jiang *et al*., 2021; Qin *et al*., 2021). Even though Piezo1 localization and organization at the plasma membrane are not yet well characterized, it has been described as an ion channel whose interactions with membrane lipids (i.e., phosphatidylinositol 4,5-bisphosphate) are essential for their function (Jiang *et al*., 2021; Ridone *et al*., 2019). That is because Piezo1 works in reconstituted planar bilayers, so the critical role of lipids has been well established (Jiang *et al*., 2021). Furthermore, membrane forces are largely determined by the local arrangement of the cytoskeleton and extracellular matrix. Therefore, the cytoskeleton is also an important structure that synergically works to support Piezo1 activity (Gaub and Müller, 2017; Gottlieb and Sachs, 2012; Li *et al*., 2014). The study by Gaub and Muller (2017) indicates that Piezo1 depends on interactions with the extracellular matrix proteins. Also, Piezo1 is more sensitive when addressing forces pulling the cell membrane than pushing forces. That is because collagen IV proteins interact with Piezo1 specifically, sensitizing it to pulling forces (Gaub and Müller, 2017).

Furthermore, for a holistic understanding of Piezo1's functions in cellular pathways, it is vital to study Piezo1's interactions with associated proteins. Alterations/mutations in Piezo1 and its associated proteins have far-reaching implications for health and disease. Investigating these alterations reveals knowledge gaps, driving further exploration. Additionally, it offers the potential for innovative pharmacological approaches.

Associated proteins

The activation of Piezo channels is reportedly regulated by several associated proteins (i.e., interaction with the endoplasmic reticulum Ca^{2+} pump sarco/ER Ca^{2+} ATPase, regulate Piezo1 mechanogating; Qin *et al*., 2021). One well-known protein that interacts with Piezo1 is its agonist Yoda1 (Qin *et al*., 2021). Yoda1 is a small molecule that delays the kinetic inactivation of Piezo1 responses (Choi *et al*., 2022). Furthermore, Jedi1/2 has been identified to function as specific dose-dependent activators of Piezo1 (Qin *et al*., 2021). Both Yoda1 and Jedi 1/2 are Piezo1 activators that act through different mechanisms. Jedi1/2 activates Piezo1 by interacting with mechanosensory domain, reducing the channel's mechanical threshold for activation. On the other hand, Yoda1 acts once Piezo1 is active, like a wedge that increases tension-induced arm extension, extending the open state of the channel (Choi *et al*., 2022; Qin *et al*., 2021).

Alteration of Piezo

In the study by Zhou *et al*. (2021), they found that natural mutations in Piezo1 (S217L and G2029R) lead to action in the endoplasmic reticulum functions. These mutations cause problems with the movement of the protein to the cell membrane, resulting in reduced stability and an increased level of ubiquitination. This pattern is characteristic of a process called endoplasmic reticulum-associated degradation (Zhou *et al*., 2021).

Regarding morbidity and disease, Piezo1 mutations have been linked to a number of diseases such as xerocytosis, arthrogryposis, loss of proprioception, and lymphedema (Alper, 2017). Gain-of-function (GoF) mutations are linked to autosomal dominant hemolytic anemia, hereditary xerocytosis (dehydrated stomatocytosis; primary red blood cell dehydration), and malaria resistance (Qin *et al*., 2021; Ridone *et al*., 2019; Zhou *et al*., 2021). Changes related to loss of function have been related to autosomal recessive congenital lymphatic dysplasia (characterized by generalized lymphedema that affect the entire body) and bicuspid aortic valve (Alper, 2017; Qin *et al*., 2021; Zhou *et al*., 2021). In addition, Piezo proteins have been linked to various types of cancer. Qin *et al*. (2021) study stated that Piezo1 overexpression was correlated with poor colon cancer prognosis. In vitro studies showed that this protein promoted cancer cell migration and metastasis (Qin *et al*., 2021).

Methods

Systematic review

This is a systematic literature review developed following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Prisma) protocol (Page *et al*., 2021). The aim is to address the following questions: What is the role/function of the Piezo1 mechanosensitive protein in epithelial cells? What models and techniques have heretofore been investigated? And finally, to hypothesize how Piezo1 could participate in vocal fold homeostasis.

Search strategies

The search was carried out on February 20th, 2023 by the article author. To answer the research questions, two electronic databases were searched: PubMed and Scopus. Those databases were chosen for being widely used by the healthcare sciences community and for being internationally accessed reference sources. A similar strategy was used in both databases. First, a search in PubMed was conducted. The MESH terms "Piezo1 protein, mouse" [Supplementary Concept] OR "Piezo1 protein, human" [Supplementary Concept] OR "Piezo1 protein, rat" [Supplementary Concept] AND "Epithelial Cells "[Mesh] were combined to form the complete PubMed search strategy. The same keywords and principles were applied in Scopus. Only peer-reviewed journals were considered. The reference lists of all relevant articles, those included in the study, were screened to identify any articles that were not retrieved from the database searches.

Eligibility criteria and data extraction

For the first search filter, the tools available on the PubMed website were used. Articles in English were included from 2018 to 2023 (standard of 5 years old research to ensure quality and updated studies), and full-text available in digital versions. The second selection filter was a title analysis which was employed to exclude duplicate articles, reviews, research in which Piezo1 was not the focus of study, and studies that were not related to the keywords defined in the search strategy. Then a third filter was performed by reading abstracts to ensure that studies considering at least two models or experimental strategies were included. After this, a full-text review was carried out. Studies lacking sufficient information in the abstract were also included in this analysis. In this way, only the articles that answered the research questions were included (whole process in Figure 1). From the full-text reading, the following was extracted:

Sample characterization

Model: This refers to whether the research was carried out in an animal, tissue or cell culture.

Specimen: This refers to the origin of the sample, specifying to which species the animal in the sample belongs and/or to which cell line.

Technique: This refers to what type of instrumentation was used to evaluate the conditions (e.g., intracellular staining, flow cytometry, Western Blot, quantitative RT-PCR, etc.)

Role/function of Piezo1: Describe the findings of each reviewed research regarding the involvement of Piezo1 in the measured processes. sample characterization (model, specimen) technique, role/function of Piezo1.

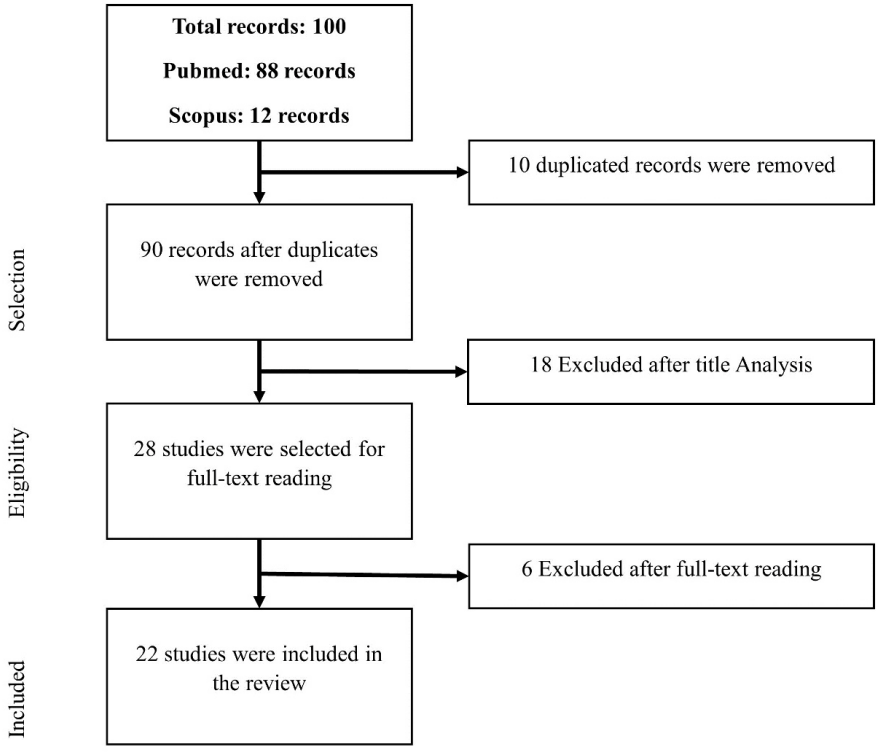

Figure 1. Flow chart showing phases of material identification and selection.

Results

Narrative results

It is possible to establish that Piezo1 is a mechanically activated channel, and its open state allows the increment of Ca^{2+} at intracellular levels. Subsequently, different pathways of action could be triggered. Table I summarizes the findings of this review which can be organized into four groups in which Piezo1 acts: vascular system, cancer proliferation/limitation, inflammatory response, and homeostasis.

In the vascular system, Piezo1 channels are capillary mechanosensors that detect force, stretch, flow, and morphological changes, fulfilling the role of a sensor of the physical activity of the whole body, through the detection of the vascularity (Choi *et al*., 2022). Its activation can cause pulmonary vasoconstriction and regulation of function and maintenance of vascular development (Harraz *et al*., 2022; Choi *et al*., 2022; Z. Wang *et al*., 2021). In addition, Piezo1 activation in endothelial cells plays an important role in the pathogenesis of vascular calcification in high-calcium environments (Liu *et al*., 2021).

In the presence of cancer cells, Piezo1 regulates tumor growth and cell migration, thus favoring better overall survival in patients with non-small cell lung cancer (Huang *et al*., 2019). The study by Y. Wang *et al*. (2022) found that Piezo1 activation inhibits the growth of dendritic cell tumors. Piezo1 activation by the agonist Yoda1 or shear stress, sensitizes cancer cells to apoptosis in certain cell lines (Hope *et al*., 2019). On the other hand, studies by Li *et al*. (2022) and Liu *et al*. (2021) agree that Piezo1 channel activation is regulated by increased matrix stiffness. Additionally, Piezo1 promotes the expression and secretion of proangiogenic factors in the presence of hepatocellular carcinoma (HCC; Li *et al*., 2022; Liu *et al*., 2021).

Regarding the Piezo1 participation in the inflammatory process, Yang *et al*. (2022) found that it mediates endothelial atherogenic inflammatory responses. The study by Zhang *et al*. (2021) concluded that the expression of Piezo1 is useful in the recovery of high tidal volume Ventilator Induced Lung Injury (VILI) in rats, since it mediates apoptosis in epithelial and endothelial cells and induces inflammatory mediators. Furthermore, it participates in the kinase activation pathway and then KLF2/4 expression, thus suppressing the NK-kB signaling pathway to provide an anti-inflammatory effect and maintain homeostasis and endothelial function (Zheng *et al*., 2022).

Additionally, Piezo1 plays a fundamental role in a number of metabolic processes. For instance, it mediates the development of the lymphatic valve as demonstrated by Choi *et al*. in 2019. Moreover, Piezo1 is involved in regulating the signal transducer during embryo implantation in both humans and mice, as shown by Hennes *et al*. in 2019. It also plays a role in regulating the expression of genes crucial to the remodeling process in cardiac fibroblasts, as indicated by Blythe *et al*. in 2019. Furthermore, Piezo1 is linked to inducing insulin release, as highlighted by Deivasikamani *et al*. in 2019. Lastly, it contributes to inducing macrophage phagocytic activity and subsequent erythrocyte turnover, as described by Ma *et al*. in 2021. Also, Piezo1 action promotes downstream kinase activation, which favors maintaining homeostasis and endothelial function (Zheng *et al*., 2022). Additionally, it facilitates the transendothelial migration of leukocytes (Wang *et al*., 2022). Further, Piezo1 activation promotes Panx1 (a structural component of gap junctions) activation to recover homeostasis, but also, coexpression of Piezo1, Panx1, and P2X4R reconstitutes an ATP-secreting protein complex (Desplat *et al*., 2021). However, the study by Jiang *et al*. (2021) concluded that Piezo1 activation can induce epithelial dysfunction.

Discussion

The present systematic review of the literature followed the Prisma protocol (Page *et al*., 2021) to address the following questions: What is the role/function of the Piezo1 mechanosensitive protein in epithelial cells? What models have been investigated? To finally, deliver some perspectives on how Piezo1 could participate in vocal folds homeostasis. In general terms, the current literature focuses its efforts on deciphering the participation of Piezo1 in the development of human diseases using primary cell culture from human and animal cells. Also, current research utilized cells from transgenic animals (e.g., mice). Qin *et al*. (2021) establishes in a general way the participation of Piezo1 in diverse neural pathologies. For example, upregulation of Piezo1 in astrocytes inhibits the release of cytokines and chemokines, thereby participating in the negative regulation of neuroinflammation. Qin *et al*. (2021) add that Piezo1 could participate in peripheral trigeminal nociception, related to migraine, and that Piezo1 contributes to cell mobility by blocking Abeta peptides in traumatic brain injury. Furthermore, in prostate cancer cells, knockdown of Piezo1 shRNA inhibited cell proliferation and migration and suppressed tumor growth (Qin *et al*., 2021).

Piezo1 is a mechanically activated channel that when open allows the increment of Ca^{2+} at intracellular levels. In the reviewed studies (Table I), it is possible to observe that different pathways of action could be triggered. So, the role of Piezo1 can be organized into four groups: (a) Vascular system, where Piezo1 activation could control the central nervous system blood flow, vascular remodeling and maturation, along join a role in the pathogenesis of vascular calcification in specific environments. (b) Cancer proliferation/limitation, where Piezo1 activation has a role in the regulation and/or formation of tumors in different cell lines and organs. (c) Inflammatory response, where Piezo1 participates in the regulation of some inflammatory mediators such as YAP, TAZ, RhoA/ROCK, and kinase. (d) Homeostasis, where Piezo1 plays a role in maintaining homeostasis and favoring the development, by affecting the expression of genes, insulin release, macrophages actions, transendothelial migration of leukocytes, and reparation processes.

The information collected regarding the role of Piezo1 in epithelial tissue, although it is focused on tissues other than the epithelium of the vocal fold, it is possible to hypothesize about its action on vocal fold epithelium. For example, some studies have been carried out on the epithelium of the respiratory pathway (Zhang *et al*., 2022) which facilitates the extrapolation of their results. In this context, it is possible to hypothesize that Piezo1 could contribute to the health of the vocal fold during the healing process. This is because Piezo1 participates in the activation pathway of anti-inflammatory mediators such as kinases and favors the recovery of homeostasis (Zhang *et al*., 2022; Zheng *et al*., 2022). In addition, Piezo1 contributes another important role during cell healing, favoring the release of macrophages and their phagocytosis action (Ma *et al*., 2021). In response to disruption of the epithelial barrier, Piezo1 could promote the action of structural components of the gap junctions (Panx1) to favor homeostasis in the vocal fold as was demonstrated in the study by Desplat *et al*. (2021) in the bile duct. Furthermore, based on the study by Xu *et al*. (2021) we could hypothesize about the protective role of Piezo1 in epithelium, favoring the release of mucins that could form a protective chemical barrier on the vocal folds. On the other hand,

TABLE I
STUDY CHARACTERISTICS; RESULTS OF THE SYSTEMATIC REVIEW OF ROLE OF PIEZO1

Article	Sample Characterization		Techniques	Role of Piezo1
	Model	Specimen		
(Liu *et al*., 2021)	Animal	mice C57BL/6J	Automatic biochemical analyzer. The ultrasound analysis, Cell Counting Kit-8 assay. Micro NO Content Assay Kit. qRT-PCR. Western blot analysis. ALP assay kit was used. BCA protein assay kit. Annexin V-FITC Apoptosis Detection Kit and PI Apoptosis Detection Kit. Flow cytometry.	Piezo1 participates in the pathogenesis of vascular calcification since its activation in endothelial cells promotes the transformation of vascular smooth muscle into an osteoblastic phenotype in an environment with high calcium content. This was demonstrated at the animal and cellular levels.
	Cell line	Human umbilical vein endothelial cells (HUVECs); Vascular smooth muscle cells (VSMCs)		
(M. Li *et al*., 2022)	Animal	Sprague Dawley (SD) rat models	Liver elasticity ultrasound, immunohistochemical staining. Microarray, pRT-PCR and Western Blot.	Piezo1 promotes the expression and secretion of proangiogenic factors in Hepatocellular carcinoma (HCC) in the presence of increased matrix stiffness, indicating a poor prognosis. In addition, the findings of this article reveal the existence of positive feedback between matrix stiffness and Piezo 1 (via stiff matrix/integrin β1/miR-625-5p /Piezo1 and COL1/stiffer matrix).
	Cell line	Two human Hepatocellular carcinoma (HCC) cell lines. HUVECs. Buffalo rat HCC cells		
	Clinical database	Clinical data of 372 HCC patients and their tumor gene expression profiles from The Cancer Genome Atlas (TCGA) database.		
(Y. Wang *et al*., n.d.)	Animal	C57BL/6J mice; Piezo1$^{flox/flox}$; Cd11c-Cre; Piezo1$^{-/-}$; Sirt1$^{flox/flox}$; Hif1a$^{flox/flox}$; Cd4-Cre	Intracellular staining, flow cytometry, cell adoptive transfer, The intracellular Ca2+ concentrations ([Ca2+]) were measured fluorometrically.	Piezo1 activated by mechanical stiffness or inflammatory signals mediates Treg and TH1 cell differentiation, which inhibits dendritic cell (DC) tumor growth. This was concluded as the tumor growth rate was significantly faster and higher in Piezo1-/- than in WT in aged mice.
	Cell line	Mouse colon cancer cell line MC-38; mouse melanoma cell line B16.F10; Human DC; Human cord blood CD4+ T cells		
(Zheng *et al*., 2022)	Cell line	HEK293T cells and bEnd.3; HUVECs	Western Blot, quantitative RT-PCR, Ca2+ imaging, immunofluorescence, co-immunoprecipitation.	Piezo1 is activated by the shear stress. When the Piezo1 channel opens, Ca2+ enters the cell, downstream kinases are activated and, subsequently, CaMKII is activated. CaMKII interacts with MEKK3, which promotes MEKK3/MEK5/ERK5 signaling and induces KLF2/4 transcription.
	Animal	Mice Piezo1fl/fl; Tie2Cre; ICR		
(S. Wang *et al*., 2022)	Cell line	HUVECs, bEnd.3	Immunoblot analysis, Ca+2 was determined as fluorescence intensity, permeability assay, flow cytometry, siRNA, shear rate was generated with a multichannel microperfusion system.	Piezo1 favors transendothelial migration of leukocytes in vitro and in vivo. Local hemodynamic forces (fluid shearing) and the grouping of ICAM-1 (Intercellular Adhesion Molecule 1) induce cell membrane tension, which activates the Piezo1 channel (localized opening of the endothelial barrier), increases the concentration of intracellular Ca2+ and leukocyte extravasation is favored.
	Animal	Mice EC-Piezo1-KO (endothelium-specific loss of Piezo1)		
(Harraz *et al*., 2022)	Animal	Mouse C57BL/6J; transgenic mice: B6.Cg-Piezo1$^{tm2.1Apat}$/J, Cdh5(PAC)-CreERT2; Cdh5-GCaMP8; TRPV4 Knockout; inducible brain endothelial $G\alpha_{q/11}$ knockout	Fluorescence, patch-clamp electrophysiology. Piezo1 currents in brain cortical cECs isolated from TRPV4-knockout (TRPV4-KO) mice.	Piezo1 is a mechanosensitive channel that allows the flow of Ca2+ into the cell, which participates in the control of blood flow in the central nervous system. By inhibiting the action of Piezo1 there was no detection of mechanical forces at the level of the capillaries.
(Desplat *et al*., 2021)	Animal	C57BL6 mice	Real-time qPCR, Immunoprecipitation from DIV5 cholangiocytes and NMCs.	Hypotonic stress can activate Piezo1, which increases intracellular Ca2+ levels, and Panx1 activation in cholangiocytes is promoted. Coexpression of Piezo1, Panx1, and P2X4R reconstitutes an ATP-secreting protein complex.
	Cell line	Human embryonic kidney (HEK) cells (293T and P1KO) and normal mouse cholangiocytes		
(Z. Wang *et al*., 2021)	Animal	C57BL/6 mice	RT-PCR. Western Blot.	Piezo1 senses force, stretch, flow, and morphological changes in the vascular system, thereby activating and increasing intracellular Ca2+ concentration in Pulmonary arterial endothelial cells (PAEC). Along with this, pulmonary vasoconstriction, vascular remodeling is generated through the contraction, migration and proliferation of pulmonary arterial smooth muscle cells. In other words, Piezo1 favors vascular remodeling and maturation.
	Cell line	Culture of Human Lung Vascular Endothelial Cells		

TABLE I (*Cont.*)
STUDY CHARACTERISTICS; RESULTS OF THE SYSTEMATIC REVIEW OF ROLE OF PIEZO1

Article	Sample Characterization		Techniques	Role of Piezo1
	Model	Specimen		
(Yang *et al*., 2022)	Animal	C57BL/6 mice	Oil red O staining. H&E. immunofluorescence staining. Real-time qPCR. Western Blot. Electrophysiology.	Piezo1 activation participates in endothelial atherogenic inflammatory responses. This occurs through the regulation of the Yes-associated protein (YAP)/transcriptional coactivator with activation of the PDZ-binding motif (TAZ) and nuclear localization.
	Cell line	HUVECs		
(Zhang *et al*., 2021)	Animal	Sprague-Dawley rats	Immunohistochemical, flow cytometry, histological examination, ELISA, western blotting, real-time RT-qPCR and survival curves. siRNA transfection. Evans blue dye extravasation method.	In this investigation, a VILI model induced by HVMV in rats was used. Their results indicate that Piezo1 mediates the pathological changes induced by Ventilator Induced Lung Injury (VILI), endothelial and epithelial cell apoptosis, water content, protein loss in the lungs, and induces inflammatory mediators, through the promotion of RhoA/ROCK1 signaling. In other words, Piezo1 could be useful in the treatment of lung lesions.
	Cell line	The human alveolar epithelial cell line (A549) and the human pulmonary microvascular endothelial cell line (HPMEC)		
(Xu *et al*., 2021)	Animal	Piezo1$^{flox/flox}$ and PvilliincreT mouse	Real-time RT-qPCR, ELISA, Western Blot, immunofluorescence, transfection assay. Calcium imaging by fluorescent probe. SEM.	Piezo1 participates in the mechanical detection pathway of goblet cells in the intestinal tract. In addition, the goblet cells respond to these stimuli through the Piezo1-Erk/Ca2+-mucin2 pathway.
	Cell line	LS174T cell line		
(Y. Jiang *et al*., 2021)	Cell line	The human colonic adenocarcinoma cell line Caco-2	Immunochemistry TEER, FITC-D4 (permeability evaluation), real-time RT-qPCR, bicinchoninic acid method.	Piezo1 participates in the regulation of intestinal epithelial function, affecting the regulation of Claudin-1 (negative regulation of epithelial barrier function), through the ROCK1/2 pathway. This was demonstrated by decreasing the amount of Piezo1, which slightly improved the permeability values using TEER. In other words, Piezo1 activation can induce epithelial dysfunction.
	Animal	C57BL/6J mice		
(Liu *et al*., 2021)	Cell line	HepG2 human HCC cells	siRNA and plasmid, Intracellular Ca+2 measurement (Fura-2 fluorescence), MTT assay. Migration assay. Apoptosis assay. Immunofluorescence and immunohitochemical analysis, real-time qPCR, Western blot, BCA Protein Assay Kit.	Piezo1 activation induced by Yoda1 in HepG2 cells participates in the process of Hepatocellular carcinoma (HCC) progression. Piezo1 deletion (or its deficiency) restricted the growth of HepG2-derived tumors.
	Animal	BALC/c nude mice		
(Ma *et al*., 2021)	Animal	Gain-of-function (GOF) Piezo1 mice	Histological analysis, colorimetric procedure. Total Iron-Bind Capacity (TIBC) kit. ELISA. Flow Cytometry, clearance assay (in vivo). Real-time qPCR, in situ hybridization. Electrophysiology.	Piezo1 is a regulator of macrophage phagocytic activity and subsequent erythrocyte turnover. In addition, E756del, a GOF Piezo1 allele (present in one-third of African descent people), was strongly associated with increased plasma iron. Macrophage expression of a GOF Piezo1 allele in mice affects levels of the iron regulator hepcidin and leads to iron overload.
	Human	human blood sample		
(Morozumi *et al*., 2020)	Animal	C57BL/6 and DBA/2J mice	Western blot, immunostaining, immunocytochemistry.	Piezo channel could be involved in retinal ganglion cell damage provoked by high intraocular pressure. Both Piezo1 and Piezo2 were expressed at the corneal epithelium, retina, lens epithelium, and optic nerve head, where Piezo1 was expressed only in the ganglion cell layer in the retina while Piezo2 was expressed extensively in the retina.
	Cell line	Primary cultured Müller glia from Sprague-Dawley rats		
(Andolfo *et al*., 2020)	Human	22 patients with DHS1 (Dehydrated hereditary stomatocytosis with Piezo 1 mutation) diagnosis. 29 patients with a diagnosis of congenital dyserythropoietic type II (CDA II)	Mass spectrometry, ELISA kits. mRNA and PCR of the specific Piezo1 exon and by direct sequencing.	The transcript level of Piezo1 (mRNA) are highly in hepatic carcinoma cell lines (HuH7 and HepG2) and primary hepatic cells (HepaRG). This demostrated the relationship between Piezo1 (as a regulator) and iron metabolism.
	Cell line	The HepG2 and HuH7 hepatic carcinoma cell lines, HepaRG human hepatocytes		

TABLE I (*Cont.*)
STUDY CHARACTERISTICS; RESULTS OF THE SYSTEMATIC REVIEW OF ROLE OF PIEZO1

Article	Sample Characterization		Techniques	Role of Piezo1
	Model	Specimen		
(Deivasikamani *et al*., 2019)	Cell line	INS-1 832/13 cells derived from rat insulinoma	RT-PCR and siRNA, ELISA, BCA assay (Pierce).	Piezo1 agonists have a role as insulin release enhancers due to our data shows Piezo1 agonists trigger insulin release from pancreatic islets and β-cell lines of mouse.
	Animal	Piezo1 knockout line mice		
(Hope *et al*., 2019)	Cell line	Prostate (PC3 and DU145), breast (MDA-MB-231), and colorectal (COLO 205) adenocarcinoma cell lines	Annexin-V assay (FITC-conjugated Annexin-V), flow cytometry, western blot, apoptosis modeling was carried out in MATLAB (computational model)	The activation on Piezo1 by Yoda1 or shear stress in PC3, MDA-MB-231 and COLO 205 cells sensitizes cancer cells to TRAIL by calcium influx.
(Blyde *et al*., 2019)	Cell Line	HUVECs; Primary culture from human biopsies of atrial appendages and long saphenous veins from coronary artery bypass patients; CD146+ pulmonary endothelial cells; HEK T-REx-293 cells	qRT-PCR, Western blot, Intracellular Ca+ measurements, gene silencing by siRNA, electrophysiology, Cell viability assay, stretch experiments, ELISA, Multiplex kinase activity profiling (serine-threonine kinase (STK).	The activation of Piezo1 triggers the expression and secretion of an important cytokine pro-hypertrophic IL-6, which has an important role in regulating cardiac remodeling after cardiac injury.
	Animal	Mice C57JBL/6		
(Huang *et al*., 2019)	Human	Gene alteration of Piezo's channels in Non-small cell lung cancer (NSCLC) patients from TCGA database	Real-time qPCR, western blot analysis, shRNA transfection, scratch assay.	Piezo1 and Piezo2 are related to better overall survival for all NSCLC patients, through the gene regulation related to both tumor growth and cell migration. This made an impression that Piezo's channel could be a target for drug development for NSCLC patients.
	Cell line	Human LC (lung cancer) cell (A549, CCL-185)		
	Animal	Nude mice (female, 6 weeks old)		
(Hennes *et al*., 2019)	Human	Human endometrial organoids (EMO) were generated from endometrial biopsies of fertility treatment patients at reproductive age.	immunocytochemistry, RNAscope in situ hydridization assay, RT-qPCR, functional measurements (pharmacology, calcium imaging, mechanical stimulation of cells, whole-cell patch clamp), fluorescence microscope.	Piezo1 has a significant role as a signal transducer in embryo implantation in the endometrial epithelial cell of mouse and human, which might be critical in embryo-uterine crosstalk.
	Cell line	HEC-1A and HEK-293T cells (human). Isolation of primary mouse endometrial epithelial cells.		
(Choi *et al*., 2019)	Animal	Mice Prox1-EGFP, Prox1-tdTomato, Prox1-CreER, $Piezo1^{fl/fl}$, $Piezo1^{P1\text{-}tdT}$ and $Cdh5(PAC)\text{-}CreER^{T2}$	qPCR, western blot, fluorescence microscopy.	Piezo1 regulates key genes of the lymphatic valve (like FOXC2 and GATA2). Its activation accelerated the lymphatic valve formation, on the other hand, Piezo1 deletion provokes substantial valve degeneration.
	Cell line	Human primary lymphatic endothelial cells (LECs)		

in pathologies such as cancer, there is evidence that Piezo1 regulates tumor growth and cell migration, so it is possible to hypothesize that it would also play a role in stopping tumor growth in the vocal folds. However, it is important to bear in mind that previous words are purely hypothetical thinking, and it is necessary to depth in the knowledge through scientific research in the vocal fold tissue.

Although the role of Piezo1 mechanosensitive channel has not been investigated extensively in depth in the vocal folds, there are some studies that did focus on this tissue. Moreover, chronic exposure to environmental factors, such as smoke inhalation, acid reflux, and vocal abuse, can lead to damage to the vocal folds and the knowledge of how this tissue recovers at the cellular and molecular levels is still uncertain. Piezo1 has been shown to be expressed in the vocal fold epithelium (Foote, Tibbetts, *et al*., 2022) where it helps maintain tissue homeostasis and integrity. The study by Foote, Tibbetts, *et al*. (2022) found that Piezo1 is essential for protection against damage caused by mechanical vibration in vocal fold tissue. The researchers observed that the loss of function of Piezo1 in mouse vocal fold epithelial cells caused increased susceptibility to mechanical vibration and tissue injury, suggesting that Piezo1 is necessary to protect the vocal fold epithelium from injury caused by vibration. Although in other tissues, this is verified by the results of some of the articles included in this review (Desplat *et al*., 2021). Additionally, Foote, Lungova, *et al*. (2022) have shown that Piezo1 also regulates the differentiation and proliferation of epithelial cells in the vocal folds, which is essential for the maintenance of vocal function. The researchers found that activation of Piezo1 promoted epithelial cell proliferation and the expression of genes involved in the differentiation of the vocal fold epithelium. In summary, the Piezo1 membrane channel contributes to vocal fold health by protecting against damage caused by mechanical vibration and by regulating epithelial cell differentiation and proliferation.

Finally, the projections for the study of the Piezo1 mechanosensitive channel in the epithelium of the vocal folds are oriented towards deepening the participation of Piezo1 in the different stages of healing of the larynx epithelium (differentiating its role in the vocal fold, ventricular bands, epiglottis, and subglottis), determining its location and function by using transgenic mice with Gain of Function and knock out the Piezo1. Furthermore, understanding its role in regulating tumor growth in the vocal folds is crucial. This could involve inducing a tumor in an animal model and subsequently manipulating Piezo1 activation and inhibition to study its effects. Ultimately, focus on the task of seeking Piezo activation through therapeutic stimulation. For this, it could be possible hypothesize about the potential benefits of vibratory exercises trying to correlate Piezo1 quantification before and after external stimulation.

Taken together, we have outlined the various roles of Piezo1, delving deeper into its functions within vocal fold tissues. Furthermore, we have highlighted the existing knowledge gap regarding the involvement of Piezo1 in vocal fold processes. The hypotheses we have put forth could potentially serve as guiding principles for forthcoming research focused on addressing pathologies associated with vocal folds.

Strengths and Limitations

The present study looked to ensure that the review process is methodical, transparent, and replicable. This review was realized under a well-structured approach to minimize bias and enhance the overall quality of the review. A comprehensive search strategy was utilized to include all relevant studies, minimizing the risk of selection bias along with including the totality of available evidence. The rigor used in the several articles selection, and its full-text analysis summarized in an organized chart allows the readers to make more informed judgments about the role of Piezo1 in epithelial cells and its participation in vocal fold homeostasis. However, every review has some limitations such as, negative or inconclusive results are less likely to be published (so, these research are not available for reviews). Also, variability in study designs, populations, and interventions among included studies can make it challenging the ability to draw clear conclusions.

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EL ROL DEL RECEPTOR MECANOSENSORIAL PIEZO1 EN LAS CÉLULAS EPITELIALES Y SU IMPACTO EN LA HOMEOSTASIS DE LAS CUERDAS VOCALES: UNA REVISIÓN SISTEMÁTICA

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RESUMEN

Esta revisión sistemática examina el papel de Piezo1 en las células epiteliales, centrándose en la homeostasis de los pliegues vocales. La revisión se estructuró en base al marco PRISMA y consideró dos bases de datos electrónicas ampliamente utilizadas por la comunidad de ciencias de la salud: PubMed y Scopus. Incorporó los términos MESH "Piezo1 protein, mouse", "PIEZO1 protein, human", "Piezo1 protein, rat", and "Epithelial Cells" de artículos de hace 5 años. La información extraída incluyó la caracterización de la muestra, la técnica y el rol de Piezo1. Piezo1 es un canal que transduce estímulos mecánico-sensoriales en señales electroquímicas, aumentando el Ca^{2+} intracelular tras su activación. Sin embargo, su papel en el epitelio de las cuerdas vocales sigue sin estar claro. Comprender esto puede contribuir a generar terapias para los trastornos relacionados con los pliegues vocales. Por lo tanto, es crucial examinar Piezo1 en las células epiteliales, para discutir posibles hipótesis sobre su rol en los pliegues vocales para guiar futuras investigaciones. Este estudio aborda preguntas relacionadas con el papel de Piezo1 en células epiteliales y modelos y técnicas anteriores, para luego especular sobre su papel en la homeostasis de los pliegues vocales. Los estudios revisados indican que la activación de Piezo1 conduce a varias vías. Las funciones de Piezo1 se pueden agrupar en cuatro categorías: sistema vascular, progresión/limitación del cáncer, respuesta inflamatoria y homeostasis. Dado que Piezo1 se expresa en el epitelio de los pliegues vocales, se discutieron sus funciones potenciales en la cicatrización de tejidos, la recuperación de la homeostasis, la regulación del crecimiento tumoral, la migración celular y la diferenciación y proliferación de células epiteliales. Este conocimiento preliminar ayuda a impulsar más investigaciones sobre el rol de Piezo1 en la curación del epitelio de la laringe, la regulación del crecimiento tumoral y la activación potencial a través de ejercicios vibratorios terapéuticos.

O PAPEL DO RECEPTOR MECANOSSENSORIAL PIEZO1 NAS CÉLULAS EPITELIAIS E SEU IMPACTO NA HOMEOSTASE DAS PREGAS VOCAIS: UMA REVISÃO SISTEMÁTICA

Mauricio Alfaro-Calfullan

RESUMO

Esta revisão sistemática examina o papel do Piezo1 nas células epiteliais, com foco na homeostase das pregas vocais. A revisão foi estruturada com base no framework PRISMA e considerou duas bases de dados eletrônicas amplamente utilizadas pela comunidade de ciências da saúde: PubMed e Scopus. Ele incorporou os termos MESH "Piezo1 protein, mouse", "PIEZO1 protein, human", "Piezo1 protein, rat" e "Epithelial Cells" de artigos de 5 anos atrás. As informações extraídas incluíam caracterização de amostra, técnica e função de Piezo1. Piezo1 é um canal que transduz estímulos mecânico-sensoriais em sinais eletroquímicos, aumentando o Ca2+ intracelular quando ativado. No entanto, seu papel no epitélio das pregas vocais permanece obscuro. Entender isso pode render terapias para distúrbios relacionados às pregas vocais. Assim, é crucial examinar Piezo1 em células epiteliais, para discutir possíveis hipóteses sobre seu papel nas pregas vocais para orientar pesquisas futuras. Este estudo aborda questões relacionadas ao papel do Piezo1 em células epiteliais e modelos e técnicas anteriores, para então especular sobre seu papel na homeostase das pregas vocais. Estudos revisados indicam que a ativação de Piezo1 leva a vários caminhos. As funções de Piezo1 podem ser agrupadas em quatro categorias: sistema vascular, progressão/limitação do câncer, resposta inflamatória e homeostase. Dado que Piezo1 é expresso no epitélio da prega vocal, foram discutidos seus papéis potenciais na cicatrização de tecidos, recuperação da homeostase, regulação do crescimento tumoral, migração celular e diferenciação e proliferação de células epiteliais. Esse conhecimento preliminar ajuda a promover pesquisas adicionais sobre o papel do Piezo1 na cicatrização do epitélio da laringe, regulação do crescimento tumoral e ativação potencial por meio de exercícios vibratórios terapêuticos.