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Cdh11: Roles in different diseases and potential value in disease diagnosis and treatment

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ABSTRACT

Cadherin is a homophilic, Ca2+-dependent cell adhesion glycoprotein that mediates cell-cell adhesion. Among them, Cadherin-11 (CDH11), as a classical cadherin, participates in and influences many crucial aspects of human growth and development. Furthermore, The involvement of CDH11 has been identified in an increasing number of diseases, primarily including various tumorous diseases, fibrotic diseases, autoimmune diseases, neurodevelopmental disorders, and more. In various tumorous diseases, CDH11 acts not only as a tumor suppressor but can also promote migration and invasion of certain tumors through various mechanisms. Likewise, in non-tumorous diseases, CDH11 remains a pivotal factor in disease progression. In this context, we summarize the specific functionalities and mechanisms of CDH11 in various diseases, aiming to gain a more comprehensive understanding of the potential value of CDH11 in disease diagnosis and treatment. This endeavor seeks to provide more effective diagnostic and therapeutic strategies for clinical management across diverse diseases.

1. Introduction

Cadherin is one of the Calcium-dependent adhesion molecules (CAMs), and it represent a class of homophilic Ca2+-dependent cell adhesion glycoproteins that mediate cell-cell interactions by forming adherens junctions (AJs) [1]. Within the calcium-dependent adhesion molecule superfamily, nearly all members are transmembrane proteins characterized by a distinctive domain known as the EC domain. This EC domain consists of negatively charged DXD, DRE, and DXNDNAPXF sequence motifs, which are tandemly repeated [2]. Calcium ions (Ca2+) bind between these EC domains, conferring rigidity and strength to the CDH11 molecules [3]. Additionally, the cytoplasmic tail of CDH11 often associates with proteins p120-catenin and β-catenin, facilitating linkage to the cell cytoskeleton through the actin-binding protein α-catenin [4]. This linkage is subject to modulation by mechanical forces and the Rho family [5].

Given substantial differences in the number of EC domains, overall domain organization, and other sequence features among various cadherin, this superfamily can be categorized into distinct subfamilies, including classical (Type I and Type II), atypical, desmosomal (desmogleins, desmocollins), protocadherins, and cadherin-related proteins [6, 7]. Among these, classical cadherins have received the most extensive research attention. Furthermore, the functional spectrum of cadherin extends beyond mere facilitation of cell-cell adhesion. Throughout embryonic development and the process of tissue morphogenesis, cadherin emerge as crucial regulators of cell differentiation, adhesion, separation, and migration. Postnatally, these molecules continue to contribute to maintaining cell and tissue structures as well as facilitating cellular motility. In essence, the calcium-dependent adhesion molecule family exerts pivotal roles across an individual's entire developmental trajectory.

CDH11 is a type II classical cadherin, initially discovered in murine osteoblasts, hence referred to as Osteoblast Cadherin (OB -cadherin). The *cdh11* gene is situated on 16q22.1 and spans an approximately 3.8 kb complementary DNA (cDNA), encompassing 16 exons that encode a polypeptide of 796 amino acids. Analogous to the majority of cadherins [8], CDH11 establishes intracellular interactions with proteins such as α -catenin, linking to the cellular cytoskeleton and thereby exerting relevant functional roles (see Fig. 1). Presently, it has come to light that CDH11 is not only expressed in osteoblasts but is also evident in various other cell types including pulmonary alveolar epithelial cells, macrophages, fibroblasts, hepatocytes, smooth muscle cells, hematopoietic stem cells, and eratinocytes [9–11]. Furthermore, at the tissue and organ levels, CDH11 expression extends beyond mesenchymal tissues, being

discernible in diverse other tissues such as the heart, brain, placenta, and lungs [12].

CDH11 orchestrates many cellular processes. Compared to other classical cadherins, the homophilic interactions facilitated by CDH11 exhibit elevated binding strength, enabling comparatively robust cell-cell adhesion [13]. CDH11 is also implicated in focal adhesion, wherein CDH - 11 interacts reciprocally with fibronectin-binding protein syndecan-4, facilitating fibronectin adhesion and contributing to cellular migration [14]. Additionally, a plethora of studies have substantiated the pivotal role of CDH11 in the Epithelial -Mesenchymal Transition (EMT) process [11].

Throughout the entire developmental process of an individual, CDH11 assumes numerous pivotal roles. During gastrulation, the heightened expression of CDH11 enables cells to undergo spatial recognition and segregation in the formation of primitive tissue structures [15,16]. Furthermore, CDH11 is involved in regulating various physiological processes of mesenchymal stem cells, primarily encompassing: (1) CDH11 can modulate the proliferation of mesenchymal stem cells via the Platelet-Derived Growth Factor Receptor Beta-Extracellular Signal-Regulated Kinase 1/2 (PDGFRβ-ERK1/2) signaling pathway [17]; (2) CDH11 can transiently control the Transforming Growth Factor-beta (TGF - β) pathway to regulate the extracellular matrix (ECM), thereby influencing the differentiation process of mesenchymal stem cells [1, 18]. Beyond this, CDH11 also impacts macrophage development and phagocytic functions. In the formation and development of the nervous system, CDH11 exhibits late-stage expression during neural tube formation, contributing to neural system development [19,20], with research suggesting potential involvement in establishing and developing certain neural circuits [21]. In the skeletal system, CDH11 regulates osteoblast differentiation, affecting bone growth [22]. Significantly, emerging research proposes the participation of CDH11 in the formation and development of the visual and auditory systems, including processes such as retinal differentiation and middle ear cavity formation [22,23], although the precise mechanisms require further investigation.

In addition to its engagement in these normal physiological processes, CDH11 also plays diverse roles in various diseases such as cancer, neurological disorders, fibrotic diseases, rheumatoid arthritis, and calcific aortic valve disease. Currently, an increasing body of research is delving into the potential roles and value of CDH11 in therapeutic interventions across a spectrum of diseases (see Table 1).

2. Tumor

2.1. Breast cancer

Breast cancer (BC) is the most prevalent malignancy in women worldwide and a leading cause of cancer-related death in females. Remarkably, BC has a pronounced propensity for bone metastasis (BM). Approximately 5–6% of BC patients are diagnosed with bone metastases at presentation, and a striking 65–75 % of advanced hormone receptor-positive breast tumors demonstrate skeletal dissemination [24,25]. Pertinent studies suggest that infiltrating BC exhibits a notable elevation in cdh11 mRNA levels compared to normal breast tissue, underscoring the pivotal role of CDH11 in BC pathogenesis [26]. Elucidating its mechanistic role, researchers like Li et al. unveiled a novel Homeobox C8-Cadherin-11-Trio-Rac(HOXC8-CDH11-Trio-Rac) signaling axis impacting breast cancer cell migration. Homeobox C8 (HOXC8), acting as a CDH11-specific transcription factor, binds to the -196 to -191 nucleotide site on the cdh11 promoter, enhancing cdh11 expression. CDH11 subsequently recruits Trio to the plasma membrane of Rac, culminating in robust Rac activation and ultimately promoting breast cancer cell invasion and migration [27,28]. Subsequent immunoprecipitation and mass spectrometry analysis reveal that Interleukin enhancer-binding factor 3 (ILF3) binds to the *cdh11* promoter and interacts with HOXC8, jointly activating *cdh11* transcription to facilitate BC cell proliferation and migration [29]. Moreover, in the context of bone metastasis, BC cells with elevated Runt-related transcription factor 2 (RUNX2) expression release extracellular vesicles (EVs) that induce pre-metastatic niches in osteoblasts, EVs with high CDH11 expression are avidly internalized by osteoblasts exhibiting similar CDH11 expression, indicating that CDH11 fosters pre-metastatic niche formation by recognizing tumor cell-derived EVs and resident osteoblasts, thereby influencing BC tumor cell bone metastasis [30]. Collectively, CDH11 holds promise as a novel avenue for future BC therapy. Recent research utilizing murine tumor xenograft models has demonstrated that anti-cdh11 antibodies significantly reduce tumor cell metastasis and cancer stem cell (CSC)-like phenotypes [26], providing further grounds for the clinical application of monospecific anti-cdh11 antibodies as therapeutic modalities for metastatic breast cancer patients.
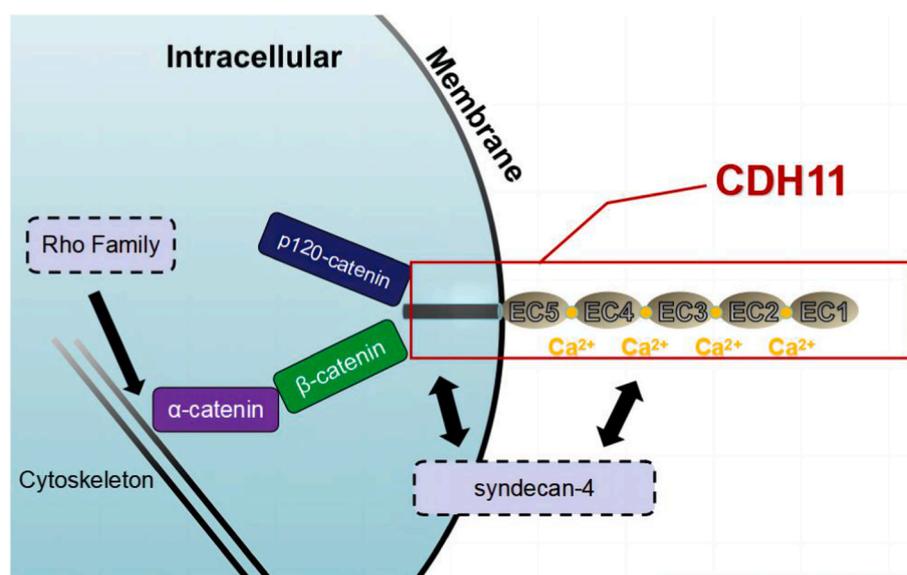
Fig. 1. The basic features of CDH11. CDH11 features multiple consecutive extracellular (EC) domains with Ca2+ binding occurring between the EC domains. Its cytoplasmic tail associates with p120-catenin and β-catenin, mediating linkage to the cellular cytoskeleton through α-catenin, a connection subject to mechanical force and regulation by the Rho GTPase family. Additionally, CDH11 interacts with syndecan-4, participating in focal adhesion processes and playing a role in cell migration.

Table 1

xCDH11 in various diseases.

Diseases	Roles	Related molecular mechanisms and signaling pathways	Targeted therapy	Reference
Breast cancer	Promote tumor development and bone metastasis	HOXC8-CDH11-Trio-Rac Induce pre-metastatic niches	✓	[26–30]
		Triple-negative breast cancer : CDH11/β-catenin , WNT	√ (23C6)	[31,32]
Gastric cancer	Unclear (tumor suppressor/tumor promotion)	Promoter methylation Influence immune milieu formation		[33,34,36, 37]
Head and neck squamous cell carcinomas	Inhibit tumor development			[41,43–45]
Colorectal cancer	Unclear (tumor suppressor/tumor promotion)	Promoter methylation , PI3K-AKT		[46–48]
Bladder cancer	Unclear (tumor suppressor/tumor promotion)	Promoter methylation		[50–52]
Prostate cancer	Promote tumor development and bone metastasis	Regulates PCa cell migration and invasion through endocytosis mediated by cadherin -related proteins.	√ (mAb 2C7)	[53,55,56]
Pancreatic cancer	Promote tumor development and metastasis.		√ (23C6)	[32,62,63]
Retinoblastoma	Tumor suppressor			[64]
Pulmonary fibrosis	Promote the fibrotic process of various organs.	Regulate the production of TGF-β and the process of EMT. Foster the formation of a fibrotic niche.		[9,11]
Liver fibrosis		The activation of hepatic stellate cells. TGFβ/Smad		[68–70]
Cardiac fibrosis		MAPKs CaMKII-STAT3	√ (SYN0012)	[71–75]
Rheumatoid Arthritis	Regulate cell-cell contacts and in vitro invasive abilities of FLS	TNF-α , IL-1β , MAPK , NF-κB , IL-6 , MMPs		[78,80–82]
Systemic sclerosis	Promotes the process of skin fibrosis	TGF-β		[83,84]
Calcific aortic valve disease	Involved in the calcification of the aortic valve	RhoA/Sox9	✓	[71,86–89]
Autism Spectrum Disorder	Participate in disease development			[21,90,91]
ElsahyWaters syndrome	One of its causal factors is attributed to loss-of-function variants in CDH11.			[91–94]
Melasma	Participate in disease development	Induce N-cadherin during EMT process. Induce basal membrane disruption and cutaneous alterations.		[95,96]

Triple-negative breast cancer (TNBC) accounts for 10–20 % of all breast cancer cases. In comparison to hormone receptor-positive and *HER2* -positive breast cancers, TNBC demonstrates heightened invasive characteristics and poorer patient prognosis. Currently, TNBC lacks available targeted therapeutic approaches. Within the TNBC subtype, CDH11 regulates the expression levels of β -catenin, while the CDH11/β -catenin signaling axis exerts regulatory effects on the canonical Wingless-related integration site (WNT) signaling pathway in TNBC. Studies have shown that targeting β -catenin and CDH11 can modulate the WNT signaling pathway, inhibiting the csc-like and metastatic phenotypes of TNBC cells, underscoring the crucial role of CDH11 in TNBC [31]. Moreover, a recent study by Douglas et al. has identified an antibody (23C6) targeting cadherins, which can concurrently recognize CDH1 and CDH11 on circulating tumor cells (CTCs), effectively suppressing hematogenous metastasis in genetically engineered mouse models and xenografts of TNBC [32]. This study proposes the potential of antibody-based targeting of intravascular CTCs to inhibit hematogenous metastasis in TNBC, presenting a novel direction for TNBC treatment.

2.2. Gastric cancer

Gastric cancer (GC) is one of the most common malignancies globally and ranks as the third leading cause of cancer-related deaths. The expression of CDH11 in GC is associated with its clinical characteristics, though its correlation remains debated in the academic community. Certain studies indicate that *cdh11*, as a tumor suppressor gene, exhibits significant promoter CpG island methylation in gastric adenocarcinoma patients, suggesting a potential link between *cdh11* inactivation and promoter methylation [33,34]. Interestingly, other research demonstrates that CDH11 expression in gastric cancer tissue is markedly higher than in normal tissue, with higher expression in advanced stages, suggesting a potential association between CDH11 overexpression and gastric cancer progression and poor prognosis. They also propose that

insufficient *cdh11* promoter methylation in GC might not reverse the upregulation caused by other factors [35]. Furthermore, CDH11 can interact with certain cytokines, inducing macrophages to enter the tumor microenvironment (TME), promoting M1 to M2 transition, ultimately influencing immune milieu formation [36]. Current research increasingly supports the promotional role of CDH11 overexpression in GC progression, although further studies are necessary for conclusive validation. Recently, a research review has addressed the conflicting conclusions regarding the correlation between CDH11 expression and clinical characteristics of gastric cancer (GC). Upon analyzing the reasons for this disparity, a targeted assessment of CDH11 expression on the cell membrane in GC was conducted, leading to the conclusion that aberrant CDH11 expression in primary GC serves as a clinical biomarker for predicting distant metastasis in gastric cancer [37].

Paclitaxel (PTX) intraperitoneal chemotherapy emerges as a promising therapeutic approach for advanced gastric cancer, yet susceptibility to drug resistance remains a drawback. Recent years have seen studies indicating a downregulation of CDH11 expression in PTX -resistant patients' ascites, tissues, and cell lines. Diminished CDH11 expression has been linked to the promotion of PTX resistance, invasion, and migration of gastric cancer cells. As such, CDH11 holds potential as a predictive marker for the development of PTX resistance in gastric cancer peritoneal metastasis patients [38]. Currently, further research is warranted to elucidate the impact of CDH11 on clinical features of gastric cancer and its underlying mechanisms, in order to offer more efficacious treatment strategies for gastric cancer patients [39].

2.3. Head and neck squamous cell carcinomas

Head and neck squamous cell carcinomas (HNSCCs), including oral squamous cell carcinoma (OSCC), nasopharyngeal carcinoma, and thyroid cancer, among others [40], have shown elevated levels of CDH11 expression in HNSCC tissues compared to normal tissues. Downregulation of CDH11 has been linked to enhanced proliferation and

invasion of HNSCC cells, suggesting a tumor-suppressive role for CDH11 in HNSCCs [41]. OSCC, a common subtype of HNSCCs, has exhibited an overall five-year survival rate of less than 50 % over the past three decades, lower than many other malignancies [42]. Overexpression of CDH11 has been confirmed in OSCC and correlated with clinical progression. Additionally, *cdh11* mutations have been observed across various stages of OSCC, suggesting its potential as a valuable biomarker in OSCC diagnosis and treatment [43,44]. Tongue squamous cell carcinoma (TSCC), a prevalent subtype within OSCC, is characterized by frequent mobility and rich lymphatic, neural, and vascular structures, making it prone to invading surrounding organs such as regional lymph nodes, neck, and pharynx. In TSCC, CDH11 has exhibited tumor-suppressive effects by inhibiting invasion and migration of TSCC cells. Pending further research validation, CDH11 could emerge as a promising new therapeutic target for treating TSCC [45].

2.4. Colorectal cancer

Colorectal cancer (CRC), the second most lethal cancer globally, suffers from a lack of meaningful biomarkers, resulting in challenging early diagnosis and late-stage detection for most patients. Current research on CDH11 in CRC yields inconsistent findings, with some studies even presenting contradictory perspectives. One study suggests CDH11 is downregulated in CRC cell lines and tissues due to promoter methylation. CDH11 induces cell cycle arrest at the G0/G1 phase and apoptosis, thereby inhibiting CRC cell proliferation, migration, and invasion. This indicates *cdh11* might function as a functional tumor suppressor gene in CRC [46]. In contrast, another viewpoint gaining more traction suggests CDH11 is overexpressed in CRC and can be activated by microcystin, enhancing tumor cell migration and invasion. Consequently, CDH11 holds promise as a biomarker for CRC, and silencing CDH11 expression might be a prospective therapeutic strategy for certain CRC patients [47,48]. Moreover, CDH11 facilitates CRC bone metastasis, including promoting adhesion between osteoclast precursors and enhancing specific collagen production, which contributes to fibrotic changes in the tumor microenvironment. Additionally, CDH11 expression is regulated by lactate (LA) through the Phosphatidylinositol 3-kinase - Protein kinase B (PI3K -AKT) pathway. In summary, current research on CDH11 in CRC underscores its potential therapeutic value [49]. However, its reliability and specific molecular mechanisms require further investigation to offer novel treatment strategies for CRC.

2.5. Bladder cancer

Bladder cancer (BCA) refers to malignant tumors that develop on the bladder mucosa and is relatively common among malignancies in the genitourinary system. Clinically, BCA can be categorized into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). BCA lacks reliable therapeutic targets in clinical treatment. Current research on CDH11 in BCA still yields contradictory conclusions. In one strand of research, CDH11 expression is found to be significantly downregulated in BCA tissues, and abnormal promoter methylation of *cdh11* is identified in BCA tissues [50]. This group suggests a close association between *cdh11* methylation and the malignant behavior of bladder cancer, but the precise mechanism remains unclear [51]. On the other hand, another set of research proposes elevated CDH11 expression in BCA. Chen et al. reported through qPCR and western blotting that: (1) CDH11 is upregulated in BCA cell lines and tissues; (2) CDH11 expression in MIBC tissues is higher than in NMIBC; (3) CDH11 expression correlates closely with histological grade, pT status, tumor size, tumor recurrence, and progression; (4) High CDH11 expression predicts adverse prognosis in NMIBC patients. They concluded that CDH11 is a reliable therapeutic target in BCA and a useable indicator for predicting the likelihood of recurrence and progression in NMIBC patients [52]. In conclusion, although recent years have seen increased research interest in the significance of CDH11 in

BCA diagnosis and treatment, the conclusions remain divergent, and the specific mechanisms are not yet well -defined, necessitating further investigation.

2.6. Prostate cancer

Prostate cancer (PCa) is the most prevalent malignancy in the male genitourinary system, characterized by a relatively slow progression, difficult detection, and a high likelihood of bone metastasis in advanced stages. CDH11 has been identified as playing a crucial role in the migration and invasion of PCa. Atypical expression of CDH11 enhances the interaction between prostate cancer cells and osteoblasts, thereby promoting the colonization of prostate cancer cells within the bone microenvironment [53].

Regarding its specific mechanisms, CDH11 potentially regulates PCa cell migration and invasion through endocytosis mediated by cadherin -related proteins, breaking down adhesion complexes or modulating its own surface trafficking [54]. Given CDH11's significant role in PCa bone metastasis, researchers have begun exploring the possibility of targeting CDH11 to prevent such metastasis. Lee et al. developed a monoclonal antibody (mAb) targeting CDH11 and found that mAb 2C7 could recognize a unique motif within the extracellular domain of CDH11, aa 343–348. Through experiments in a murine model, they verified its efficacy in inhibiting bone metastasis. This further underscores the potential of targeting CDH11 in future PCa treatments [55].

Furthermore, the expression of CDH11 in PCa is similarly regulated by certain factors. Firstly, *cdh11* mRNA and protein levels are under the control of Glycogen Synthase Kinase-3 Beta (GSK3β) activity [56]. Secondly, studies have indicated that Prostate-Specific Antigen (PSA) can enhance CDH11 expression in mesenchymal stem cells (MSCs) through activation of the Akt signaling pathway, thereby affecting the migration and invasion of PCa cells [57]. It's noteworthy that androgen depletion has been found to upregulate CDH11 expression, thereby increasing the risk of PCa bone metastasis. Consequently, it has been proposed that in advanced PCa patients during androgen deprivation therapy, consideration should be given to inhibiting CDH11 expression. However, specific strategies for CDH11 inhibition require further exploration [58].

2.7. Other tumors

Osteosarcoma is a malignant bone tumor that commonly occurs in children and adolescents. Numerous studies have shown a significant downregulation of CDH11 expression in osteosarcoma tissues, and its expression level is notably correlated with patient survival rate. This suggests that CDH11 is likely an independent prognostic factor associated with poorer overall survival in osteosarcoma patients [59–61].

Pancreatic cancer is a frequently encountered malignant tumor within the digestive system, characterized by its high malignancy, challenging early diagnosis, rapid progression, and relatively poor prognosis. Relevant research has revealed a significant increase in CDH11 expression in pancreatic cancer cells, indicating its involvement in pancreatic cancer development and metastasis. CDH11 might serve as a potential therapeutic target in pancreatic cancer [62]. Murine models have shown that loss or inhibition of CDH11 significantly prolongs the survival of pancreatic tumor-bearing mice and restores sensitivity to gemcitabine, further highlighting the potential role of CDH11 [63]. Presently, Micalizzi et al. have identified a calcium-binding antibody (23C6) capable of concurrently recognizing CDH1 and CDH11, targeting circulating tumor cells within blood vessels, thereby inhibiting hematogenous metastasis in pancreatic cancer [32].

In the context of retinoblastoma, a deficiency in CDH11 expression has been identified in late-stage tumor tissues, suggesting its role as a potential tumor suppressor gene in retinoblastoma [64]. Subsequent mouse experiments have demonstrated that CDH11 can facilitate tumor cell death both in vivo and in vitro, affirming its tumor-suppressive

function in retinoblastoma [65].

Concerning Acute Lymphoblastic Leukemia (ALL), studies have found a connection between chemoresistance in B -ALL and high methylation of *cdh11* [66]. Gliomas are one of the most common primary intracranial tumors. It has been observed that CDH11 is expressed in infiltrative glioma cells in situ and can modulate glioma cell invasion in vitro [67].

3. Fibrotic disease

Fibrosis commonly arises from chronic inflammation and injury, characterized by an excessive accumulation of fibrous connective tissue within organ structures accompanied by a reduction in parenchymal cells. If it progresses unabated, fibrosis can lead to structural organ damage and functional impairment. A thorough understanding of the pathogenic mechanisms underlying fibrosis, and the identification of novel therapeutic targets from these mechanisms, is of paramount importance. Presently, it is established that CDH11 is upregulated in fibrotic tissues of various organs including the lungs, liver, heart, skin, kidneys, and intestines. Moreover, CDH11 is implicated in the fibrotic processes occurring in these diverse anatomical sites.

3.1. Pulmonary fibrosis

In pulmonary fibrosis, CDH11 is implicated in regulating the production of TGF- β and the process of epithelial to mesenchymal transition, thereby facilitating the progression of pulmonary fibrosis [11]. Additionally, CDH11 can modulate the development of monocyte-derived macrophages, their polarization toward the pro -fibrotic M2 phenotype, and their phagocytic function [9]. Furthermore, it promotes specific binding and sustained activation between macrophages and resident fibroblasts, fostering the formation of a fibrotic niche and maintaining the stability of this fibrotic microenvironment [10].

3.2. Liver fibrosis

As is widely recognized, the activation of hepatic stellate cells (HSCs) constitutes a pivotal step in the process of liver fibrosis. It has now been demonstrated that CDH11 participates in the activation of HSCs, thereby facilitating the progression of liver fibrosis [68,69]. Furthermore, under conditions of bile stasis, CDH11 may play a significant role in cholestatic liver fibrosis by modulating the TGF β/Smad signaling pathway under conditions of cholesterol accumulation [70]. Consequently, CDH11 holds substantial potential to offer more effective therapeutic approaches for patients with liver fibrosis in the future.

3.3. Cardiac fibrosis

Cardiac fibrosis can occur in various conditions such as coronary artery disease, valvular heart disease, and myocarditis. It is characterized by excessive proliferation and activation of cardiac fibroblasts (CFs), excessive extracellular matrix deposition, and cardiac tissue remodeling. In severe cases, it can lead to arrhythmias, heart failure, and significantly increase the risk of mortality. CDH11 expression has been identified in human cardiac fibroblasts and cardiomyocytes, and it plays a role in the cardiac fibrosis process [71,72].

At the molecular level, CDH11 promotes CF activation, inducing the secretion of interleukin-6 (IL- 6) by CFs, thereby regulating pathological processes in cardiac myocytes, promoting cardiac fibrosis and tissue remodeling. This process may also involve the Mitogen-Activated Protein Kinases (MAPKs) and Ca2+/Calmodulin-Dependent Protein Kinase II- Signal Transducer and Activator of Transcription 3 (CaMKII -STAT3) pathways [73,74]. Consequently, CDH11 presents itself as a potential novel therapeutic target for cardiac fibrosis-related diseases. Schroer et al. treated a subset of myocardial infarction mice with a functional

blocking antibody against CDH11 (SYN0012) and observed significant improvements in heart function and reduced cardiac tissue remodeling compared to other mice [75]. This observation further underscores the potential value of CDH11 in the treatment of cardiac fibrosis -related diseases.

3.4. Fibrosis in other organs

In renal fibrosis and intestinal fibrosis tissues, the expression of CDH11 has also been identified, and its expression level positively correlates with the severity of the respective diseases. Additionally, CDH11 is involved in the process of skin fibrosis in certain conditions [76,77]. In summary, CDH11 holds the potential to serve as a novel biomarker and therapeutic target for various fibrotic diseases.

4. Autoimmune disease

4.1. Rheumatoid arthritis\

Rheumatoid Arthritis (RA) is an autoimmune disease characterized primarily by erosive arthritis, with synovitis as its pathological hallmark. Normal synovium consists of fibroblast-like synoviocytes (FLS) and macrophages. In RA patients, there is extensive infiltration of immune cells in the synovium, leading to destruction of surrounding cartilage and bone tissue. CDH11 overexpression in the synovial tissue of RA patients was observed several years ago, and its expression has also been detected in the peripheral blood of some patients [78]. Research suggests that CDH11 plays a role in regulating cell -cell contacts and in vitro invasive abilities of FLS [79]. CDH11 induces the secretion of various inflammatory factors such as IL- 6 and matrix metalloproteinases (MMPs) in synovial fibroblasts, thereby promoting disease progression and cartilage destruction. This process can be achieved through at least two distinct mechanisms: 1. Synergistic effects mediated by tumor necrosis factor -alpha (TNF- α) and Interleukin-1 beta (IL- 1β); 2. Activation of mitogen-activated protein kinases (MAPK) and nuclear factor kappa-B (NF- κB) [80,81]. Given its specific roles, CDH11 holds potential as a new biomarker or therapeutic target in the diagnosis and treatment of RA. Additionally, it's worth noting that umbilical cord -derived mesenchymal stem cells in RA can suppress CDH11 expression in FLS through interleukin- 10 (IL- 10) mediation, a mechanism that could potentially be targeted for RA treatment in the future [82].

4.2. Systemic sclerosis

Systemic sclerosis (SSc) is a systemic autoimmune disease characterized by progressive fibrosis of the skin and internal organs. CDH11 plays a crucial role in SSc, manifesting as follows: (1) CDH11 expression is increased in damaged skin of SSc patients, predominantly localized within dermal fibroblasts and macrophages; (2) Examination of diffuse SSc patients with a disease duration of 40 years revealed a correlation between CDH11 levels and skin fibrosis severity defined by modified Rodnan Skin Score; (3) Inhibition of CDH11 expression led to significant attenuation of skin fibrosis [83,84]. Furthermore, in early diffuse SSc skin samples, CDH11 expression was closely associated with cartilage oligomeric matrix protein and platelet-derived growth factor- 1 expression (Spearman's r ≥ 0.9), indicating an interplay between CDH11 and the TGF- β pathway in SSc [83]. In conclusion, CDH11 holds potential as a predictive biomarker, exerting its role in SSc diagnosis and treatment.

5. Calcific aortic valve disease

Calcific aortic valve disease (CAVD), an increasingly prevalent condition, has emerged as the second leading cause of adult cardiac disease. CAVD is not merely a simple degenerative change, but a complex and

active pathological process characterized by various pathological alterations. Current treatment options for CAVD primarily involve the replacement of valves with biological or mechanical prosthetics. Due to the lack of effective therapeutic targets, there are no drugs available to prevent or reverse the occurrence and progression of CAVD. CDH11 has been confirmed to play a pivotal role in proper embryonic cushion formation and aortic valve maturation [85]. However, research has revealed its involvement in aortic valve calcification as well. CDH11 is highly expressed in calcified leaflets of human aortic valves, promoting the formation of calcific nodules on aortic valves [71].

Regarding its specific molecular mechanisms, two regulatory pathways of CDH11 expression have been identified: (1) Enhanced Akt activity in aortic valve interstitial cells with *notch1* mutations leads to upregulation of CDH11 expression [86]. (2)microRNA- 101 -3p also regulates CDH11 expression [87]. Furthermore, overexpression of CDH11 upregulates downstream targets Ras Homolog Family Member A (RhoA) and SRY-Box Transcription Factor 9 (Sox9), inducing extracellular matrix remodeling and calcification of aortic valve cells [88]. While these discovered mechanisms are not yet fully comprehensive, the potential role of CDH11 in CAVD treatment is evident. Studies have already confirmed that humanized mouse CDH11 antibodies can prevent valve stenosis, leaflet thickening and stiffness, as well as inflammatory gene expression [89]. Targeting CDH11 stands as a novel therapeutic strategy for CAVD.

6. Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by primary clinical features of social communication deficits and the presence of restricted, repetitive behaviors or interests. The most consistent neuropathological changes in the brains of individuals with ASD occur in the cerebellum, including underdevelopment of the cerebellum and reduced numbers of Purkinje cells. Numerous studies have proposed the involvement of CDH11 in regulating the development of neural circuitry, which may be relevant to ASD. This is evidenced by two key points: (1) Elevated expression of CDH11 in the central region of the VI/VII lobules of the cerebellum is correlated with reduced expression of Purkinje cell marker calbindin during normal cerebellar development, consistent with delayed maturation of Purkinje cells in the same region [90]; (2) In mice with *cdh11* knockout, alterations in levels of synaptic proteins such as postsynaptic density (PSD) - 95, neuroligin- 1, and cadherin- 8 lead to changes in the morphology and activity of excitatory neurons, indicating a significant role of CDH11 in regulating dendritic morphology and synaptic function of excitatory neurons [21]. Subsequent research discovered altered CDH11 expression in individuals with ASD, further suggesting that changes in its expression may partially contribute to the pathological process of ASD. In line with this, behavioral studies conducted on mice with CDH11 deficiency revealed a range of autism-like behavioral changes [91], providing further confirmation of the significance of CDH11 in ASD.

7. ElsahyWaters syndrome

ElsahyWaters syndrome (EWS) was initially described in three sons of first-cousin parents, displaying a constellation of distinctive features including brachycephaly, maxillary hypoplasia, mandibular prognathism, strabismus, nystagmus, cleft palate, dental cysts, dental malocclusion, facial characteristics (proptosis, hypertelorism, broad and flat nasal root, wide nasal tip, and high arched palate), pectus excavatum, cervical vertebrae fusion, hypospadias, and intellectual disability. Over the course of nearly 50 years, the etiology of EWS remained uncertain due to its rarity. It wasn't until recent years that studies employing genetic sequencing in EWS patients revealed a definitive association with *cdh11*. To date, a total of 7 molecularly confirmed *cdh11*-related cases of EWS have been reported, originating from 5 families, including two

sisters from a consanguineous couple, a male child, an Indian female, a sibling pair, and a male individual from Japan. Homozygous variants in *cdh11* were identified in these patients, confirming EWS as an autosomal recessive disorder, wherein one of its causal factors is attributed to loss-of-function variants in *cdh11* [91–94]. However, it is important to emphasize that the current understanding of *cdh11* in relation to this syndrome remains limited, necessitating further validation of its reliability.

8. Other diseases

Melasma is a pigmentation disorder affecting the skin of the upper lip, cheeks, forehead, and chin, characterized by increased melanin deposition in the epidermal and dermal layers. In certain melasma patients, elevated CDH11 expression has been identified and implicated in disease progression, manifesting as follows: 1. CDH11 participates in melanogenesis by inducing N-cadherin during EMT process [95]. 2. CDH11 induces basal membrane disruption and cutaneous alterations seen in melasma (collagen dissolution, accumulation of elastic material, and vascular dilation), which is independent of ultraviolet radiation exposure [96].

In the context of airway remodeling in asthma patients, the involvement of CDH11 has been observed. In this setting, CDH11-induced EMT was associated with β-catenin signaling activation. Aberrant activation of the β-catenin pathway may influence the onset and progression of asthma [97].

Additionally, in studies related to head and neck venous malformations, CDH11 mutations have been found to potentially inhibit the migration and contractility of vascular smooth muscle cells, which could contribute to or enhance the formation of VM (venous malformations) [98]. Furthermore, CDH11 may exert a certain degree of influence on the process of atherosclerosis, although it remains poorly understood and requires further investigation [99].

9. Summary

Currently, an expanding body of research has revealed CDH11's involvement in a wide spectrum of diseases. Its roles in disease pathogenesis are notably diverse. In various tumorigenic conditions, cdh11 can function as either a tumor suppressor gene or a promoter of tumor progression. As a tumor suppressor, inactivation of cdh11 due to promoter methylation can contribute to the genesis of specific malignancies. Conversely, in certain tumors, CDH11 may facilitate invasion and migration through known or unknown signaling pathways. Additionally, in non-neoplastic disorders including fibrotic diseases, CAVD, RA, ASD, and EWS, CDH11 plays distinct roles influencing disease initiation and progression. Regarding the divergent or opposing effects of CDH11 in certain diseases, it is our belief that this may be associated with the heterogeneity of disease subtypes, stages, and the diversity in CDH11's modes of action. The precise mechanisms by which CDH11 operates in specific diseases require further elucidation through comprehensive research. In conclusion, CDH11's multifaceted roles across various diseases, with often similar or divergent outcomes, underscore its significant potential value in the treatment of the aforementioned conditions. Given the frequent overexpression of CDH11 in the tissues and cells of diverse diseases, CDH11 can be regarded as a novel biomarker or a target for innovative therapeutic strategies. Experimental approaches targeting CDH11 have already been explored in various studies. Examples include utilizing antibodies recognizing CDH1 and CDH11 on intravascular CTCs in TNBC and pancreatic cancer [32], monoclonal antibodies specific to extracellular domain motifs of CDH11 in PCa [55], functional-blocking CDH11 antibodies (SYN00 12) in murine models of myocardial fibrosis [74], and corresponding CDH11 antibodies in BC and CAVD mice [26,88]. These studies have demonstrated the efficacy of targeting CDH11 for therapeutic purposes. However, most CDH11 -targeted therapies are still in the experimental phase,

requiring extensive research to validate their reliability. In conclusion, the concerted aspiration is to comprehensively elucidate the specific mechanistic roles and molecular processes of CDH11 in various diseases, subsequently translating this knowledge into the diagnosis and treatment of respective conditions. By doing so, we aim to enhance therapeutic efficacy and prognostication for clinical patients, aligning with our collective objective.

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Declaration of competing interest

The authors have declared that no competing interest exists.

Data availability

Data will be made available on request.

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Abbreviations

CAMs	Calcium-dependent adhesion molecules
AJs	adherens junctions
ECM	extracellular matrix
BC	breast cancer
BM	bone metastasis
RUNX2	Runt-related Transcription factor 2
EVs	extracellular vesicles; CSC: cancer stem cell
LA	lactate
TNBC	Triple-negative breast cancer
CTCs	circulating tumor cells
GC	Gastric cancer
TME	tumor microenvironment
PTX	Paclitaxel
HNSCCs	Head and neck squamous cell carcinomas
OSCC	oral squamous cell carcinoma
TSCC	Tongue squamous cell carcinoma
CRC	Colorectal cancer; BCA:Bladder cancer
NMIBC	non-muscle-invasive bladder cancer
MIBC	muscle-invasive bladder cancer
PCa	Prostate cancer
PSA	Prostate-Specific Antigen
GSK3β	Glycogen Synthase Kinase-3 Beta
TNF- α	tumor necrosis factor-alpha
IL- 1β	Interleukin-1 beta
MSCs	mesenchymal stem cells
ALL	Acute Lymphoblastic Leukemia
HSCs	hepatic stellate cells
CFs	cardiac fibroblasts
IL-6	interleukin-6
RA	Rheumatoid Arthritis
FLS	fibroblast-like synoviocytes
MMPs	matrix metalloproteinases
IL- 10	interleukin- 10
SSc	Systemic sclerosis
CAVD	Calcific aortic valve disease
ASD	Autism Spectrum Disorder
EWS	ElsahyWaters syndrome
EMT	epithelial-mesenchymal transition

References

[1] S. Alimperti, S.T. Andreadis, CDH2 and CDH11 act as regulators of stem cell fate decisions, Stem Cell Res. 14 (3) (2015) 270–282.

[2] M. Takeichi, Cadherins: a molecular family important in selective cell-cell adhesion, Annu. Rev. Biochem. 59 (1990) 237–252.

[3] T. Yagi, M. Takeichi, Cadherin superfamily genes: functions, genomic organization, and neurologic diversity, Genes Dev. 14 (10) (2000) 1169–1180.

[4] M. Peifer, A.S. Yap, Traffic control: p120-catenin acts as a gatekeeper to control the fate of classical cadherins in mammalian cells, J. Cell Biol. 163 (3) (2003) 437–440.

[5] S. Yamada, W.J. Nelson, Localized zones of Rho and Rac activities drive initiation and expansion of epithelial cell-cell adhesion, J. Cell Biol. 178 (3) (2007) 517–527.

[6] M. Goodwin, A.S. Yap, Classical cadherin adhesion molecules: coordinating cell adhesion, signaling and the cytoskeleton, J. Mol. Histol. 35 (8–9) (2004) 839–844.

[7] M.D. Kottke, E. Delva, A.P. Kowalczyk, The desmosome: cell science lessons from human diseases, J. Cell Sci. 119 (Pt 5) (2006) 797–806.

[8] C. Dou, Y. Yan, S. Dong, Role of cadherin- 11 in synovial joint formation and rheumatoid arthritis pathology, Mod. Rheumatol. 23 (6) (2013) 1037–1044.

[9] S. To, et al., Cadherin- 11 regulates macrophage development and function, Front. Immunol. 13 (2022), 795337.

[10] M. Lodyga, et al., Cadherin- 11-mediated adhesion of macrophages to myofibroblasts establishes a profibrotic niche of active TGF-beta, Sci. Signal. 12 (564) (2019).

[11] D.J. Schneider, et al., Cadherin- 11 contributes to pulmonary fibrosis: potential role in TGF-beta production and epithelial tomesenchymal transition, Faseb. J. 26 (2) (2012) 503–512.

[12] Chavula, T.S. To, S.K. Agarwal, Cadherin- 11 and its role in tissue fibrosis, Cells Tissues Organs 212 (4) (2023) 293–303.

[13] P. Pittet, et al., Fibrogenic fibroblasts increase intercellular adhesion strength by reinforcing individual OB-cadherin bonds, J. Cell Sci. 121 (Pt 6) (2008) 877–886.

[14] R.P. Langhe, et al., Cadherin- 11 localizes to focal adhesions and promotes cell-substrate adhesion, Nat. Commun. 7 (2016), 10909.

[15] B.M. Gumbiner, Cell adhesion: the molecular basis of tissue architecture and morphogenesis, Cell 84 (3) (1996) 345–357.

[16] C. Guillot, T. Lecuit, Mechanics of epithelial tissue homeostasis and morphogenesis, Science 340 (6137) (2013) 1185–1189.

[17] F.R. Passanha, M.L. Divinagracia, V. LaPointe, Cadherin- 11 regulates cell proliferation via the PDGFRbeta-ERK1/2 signaling pathway in human mesenchymal stem cells, Stem Cell. 40 (2) (2022) 165–174.

[18] F.R. Passanha, T. Geuens, V. LaPointe, Cadherin- 11 influences differentiation in human mesenchymal stem cells by regulating the extracellular matrix via the TGFbeta1 pathway, Stem Cell. 40 (7) (2022) 669–677.

[19] S.C. Suzuki, et al., Neuronal circuits are subdivided by differential expression of type-II classic cadherins in postnatal mouse brains, Mol. Cell. Neurosci. 9 (5–6) (1997) 433–447.

[20] V. Marthiens, et al., Cadherin-based cell adhesion in neuromuscular development, Biol. Cell. 94 (6) (2002) 315–326.

[21] J.A. Frei, et al., Regulation of neural circuit development by cadherin- 11 provides implications for autism, eNeuro 8 (4) (2021).

[22] A. Di Benedetto, et al., N-cadherin and cadherin 11 modulate postnatal bone growth and osteoblast differentiation by distinct mechanisms, J. Cell Sci. 123 (Pt 15) (2010) 2640–2648.

[23] Y. Kiyama, et al., The adhesion molecule cadherin 11 is essential for acquisition of normal hearing ability through middle ear development in the mouse, Lab. Invest. 98 (11) (2018) 1364–1374.

[24] F. Macedo, et al., Bone metastases: an overview, Onco Rev. 11 (1) (2017) 321.

[25] S. D'Oronzo, et al., Metastatic bone disease: pathogenesis and therapeutic options: up-date on bone metastasis management, J. Bone Oncol. 15 (2019) 4.

[26] J.H. Chen, et al., Monospecific antibody targeting of CDH11 inhibits epithelial-to-mesenchymal transition and represses cancer stem cell-like phenotype by up-regulating miR-335 in metastatic breast cancer, in vitro and in vivo, BMC Cancer 19 (1) (2019) 634.

[27] Y. Li, et al., HOXC8-Dependent cadherin 11 expression facilitates breast cancer cell migration through Trio and rac, Genes Cancer 2 (9) (2011) 880–888.

[28] Y. Li, et al., HOXC8 promotes breast tumorigenesis by transcriptionally facilitating cadherin- 11 expression, Oncotarget 5 (9) (2014) 2596–2607.

[29] Y. Zhang, et al., Interleukin enhancer-binding factor 3 and HOXC8 co-active cadherin 11 transcription to promote breast cancer cells proliferation and migration, Oncotarget 8 (64) (2017) 107477–107491.

[30] X.Q. Li, et al., Extracellular vesicle-packaged CDH11 and ITGA5 induce the premetastatic niche for bone colonization of breast cancer cells, Cancer Res. 82 (8) (2022) 1560–1574.

[31] P.B. Satriyo, et al., Cadherin 11 inhibition downregulates beta-catenin, deactivates the canonical WNT signalling pathway and suppresses the cancer stem cell-like phenotype of triple negative breast cancer, J. Clin. Med. 8 (2) (2019).

[32] D.S. Micalizzi, et al., Targeting breast and pancreatic cancer metastasis using a dual-cadherin antibody, Proc. Natl. Acad. Sci. USA 119 (43) (2022), e2209563119.

[33] S. Eyvazi, et al., CpG islands methylation analysis of CDH11, EphA5, and HS3ST2 genes in gastric adenocarcinoma patients, J. Gastrointest. Cancer 51 (2) (2020) 579–583.

[34] J.L. Sepulveda, et al., High-definition CpG methylation of novel genes in gastric carcinogenesis identified by next-generation sequencing, Mod. Pathol. 29 (2) (2016) 182–193.

[35] Q. Wang, et al., Clinical and prognostic association of oncogene cadherin 11 in gastric cancer, Oncol. Lett. 19 (6) (2020) 4011–4023.

[36] Z. Feng, et al., Prognostic and predictive value of cadherin 11 for patients with gastric cancer and its correlation with tumor microenvironment: results from microarray analysis, BioMed Res. Int. 2020 (2020), 8107478.

[37] H. Mita, et al., Aberrant Cadherin11 expression predicts distant metastasis of gastric cancer, Pathol. Res. Pract. 242 (2023), 154294.

[38] Z. Yang, et al., Downregulation of CDH11 promotes metastasis and resistance to paclitaxel in gastric cancer cells, J. Cancer 12 (1) (2021) 65–75.

[39] J. Ni, et al., Cadherin 11-mediated juxtacrine interaction of gastric cancer cells and fibroblasts promotes metastasis via YAP/tenascin-C signaling, Sci. Bull. (Beijing) 67 (10) (2022) 1026–1030.

[40] N. Cirillo, Merging experimental data and in silico analysis: a systems-level approach to autoimmune disease and cancer, Expet Rev. Clin. Immunol. 8 (4) (2012) 361–372.

[41] S. Piao, et al., CDH11 inhibits proliferation and invasion in head and neck cancer, J. Oral Pathol. Med. 46 (2) (2017) 89–97.

[42] J.W. Kim, et al., Prognostic value of glucosylceramide synthase and P-glycoprotein expression in oral cavity cancer, Int. J. Clin. Oncol. 21 (5) (2016) 883–889.

[43] Y. Wei, et al., Expression signature and molecular basis of CDH11 in OSCC detected by a combination of multiple methods, BMC Med. Genom. 16 (1) (2023) 70.

[44] C. Ma, et al., Combined overexpression of cadherin 6, cadherin 11 and cluster of differentiation 44 is associated with lymph node metastasis and poor prognosis in oral squamous cell carcinoma, Oncol. Lett. 15 (6) (2018) 9498–9506.

[45] B.T. Zheng, et al., CDH11 regulates adhesion and transcellular migration of tongue squamous cell carcinoma, OncoTargets Ther. 14 (2021) 4211–4222.

[46] S. Yuan, et al., Cadherin 11 is inactivated due to promoter methylation and functions in colorectal cancer as a tumour suppressor, Cancer Manag. Res. 11 (2019) 2517–2529.

[47] Q. Zhu, et al., The role of cadherin 11 in microcystin-LR-induced migration and invasion in colorectal carcinoma cells, Oncol. Lett. 15 (2) (2018) 1417–1422.

[48] Z. He, et al., Identification of BGN and THBS2 as metastasis-specific biomarkers and poor survival key regulators in human colon cancer by integrated analysis, Clin. Transl. Med. 12 (11) (2022) e973.

[49] J. Qian, et al., Lactic acid promotes metastatic niche formation in bone metastasis of colorectal cancer, Cell Commun. Signal. 19 (1) (2021) 9.

[50] F. Feng, et al., Identifying stage-associated hub genes in bladder cancer via weighted gene co-expression network and robust rank aggregation analyses, Medicine (Baltim.) 101 (51) (2022), e32318.

[51] Y.L. Lin, S.L. Gui, J.G. Ma, Aberrant methylation of CDH11 predicts a poor outcome for patients with bladder cancer, Oncol. Lett. 10 (2) (2015) 647–652.

[52] M.K. Chen, et al., Predictive value of cadherin 11 for subsequent recurrence and progression in non-muscle invasive bladder cancer, Jpn. J. Clin. Oncol. 50 (4) (2020) 456–464.

[53] C.F. Huang, et al., Cadherin 11 increases migration and invasion of prostate cancer cells and enhances their interaction with osteoblasts, Cancer Res. 70 (11) (2010) 4580–4589.

[54] R.L. Satcher, et al., Cadherin 11 endocytosis through binding to clathrin promotes cadherin 11-mediated migration in prostate cancer cells, J. Cell Sci. 128 (24) (2015) 4629–4641.

[55] Y.C. Lee, et al., Inhibition of cell adhesion by acadherin 11 antibody thwarts bone metastasis, Mol. Cancer Res. 11 (11) (2013) 1401–1411.

[56] A.K. Farina, et al., Post-transcriptional regulation of cadherin 11 expression by GSK-3 and beta-catenin in prostate and breast cancer cells, PLoS One 4 (3) (2009) e4797.

[57] L. Wu, et al., Prostate-specific antigen modulates the osteogenic differentiation of MSCs via the cadherin 11-Akt axis, Clin. Transl. Med. 10 (1) (2020) 363–373.

[58] Y.C. Lee, et al., Androgen depletion up-regulates cadherin 11 expression in prostate cancer, J. Pathol. 221 (1) (2010) 68–76.

[59] G. Nakajima, et al., CDH11 expression is associated with survival in patients with osteosarcoma, Cancer Genomics Proteomics 5 (1) (2008) 37–42.

[60] S. Azarsina, et al., Diagnostic investigations of PLA2G16 and CDH11 expression levels as independent prognostic markers of human osteosarcoma, Arch. Med. Sci. 13 (6) (2017) 1347–1351.

[61] Z. Deng, et al., The prognostic significance of CD44V6, CDH11, and beta-catenin expression in patients with osteosarcoma, BioMed Res. Int. 2013 (2013), 496193.

[62] C. Birtolo, et al., Cadherin 11 is a cell surface marker up-regulated in activated pancreatic stellate cells and is involved in pancreatic cancer cell migration, Am. J. Pathol. 187 (1) (2017) 146–155.

[63] I. Peran, et al., Cadherin 11 promotes immunosuppression and extracellular matrix deposition to support growth of pancreatic tumors and resistance to gemcitabine in mice, Gastroenterology 160 (4) (2021) 1359–1372.e13.

[64] M.N. Marchong, et al., Minimal 16q genomic loss implicates cadherin 11 in retinoblastoma, Mol. Cancer Res. 2 (9) (2004) 495–503.

[65] M.N. Marchong, et al., Cdh11 acts as a tumor suppressor in a murine retinoblastoma model by facilitating tumor cell death, PLoS Genet. 6 (4) (2010), e1000923.

[66] M. Abdullah, et al., ADAMTSL5 and CDH11: putative epigenetic markers for therapeutic resistance in acute lymphoblastic leukemia, Hematology 22 (7) (2017) 386–391.

[67] S. Delic, et al., Identification and functional validation of CDH11, PCSK6 and SH3GL3 as novel glioma invasion-associated candidate genes, Neuropathol. Appl. Neurobiol. 38 (2) (2012) 201–212.

[68] W. Ruan, et al., CDH11 promotes liver fibrosis via activation of hepatic stellate cells, Biochem. Biophys. Res. Commun. 508 (2) (2019) 543–549.

[69] M. Pedroza, et al., Cadherin 11 contributes to liver fibrosis induced by carbon tetrachloride, PLoS One 14 (7) (2019), e0218971.

[70] B. Wu, et al., Upregulation of cadherin 11 contributes to cholestatic liver fibrosis, Pediatr. Investig. 6 (2) (2022) 100–110.

[71] J.D. Hutcheson, et al., Cadherin 11 regulates cell-cell tension necessary for calcific nodule formation by valvularmyofibroblasts, Arterioscler. Thromb. Vasc. Biol. 33 (1) (2013) 114–120.

[72] B. Hinz, et al., Myofibroblast development is characterized by specific cell-cell adherens junctions, Mol. Biol. Cell 15 (9) (2004) 4310–4320.

[73] G. Fang, et al., Cadherin 11 deficiency mitigates high-fat diet-induced inflammatory atrial remodeling and vulnerability to atrial fibrillation, J. Cell. Physiol. 236 (8) (2021) 5725–5741.

[74] W. Cao, et al., Cadherin 11 deficiency attenuates Ang-II-induced atrial fibrosis and susceptibility to atrial fibrillation, J. Inflamm. Res. 14 (2021) 2897–2911.

[75] A.K. Schroer, et al., Cadherin 11 blockade reduces inflammation-driven fibrotic remodeling and improves outcomes after myocardial infarction, JCI Insight 4 (18) (2019).

[76] I.M. Schmidt, et al., Cadherin 11, Sparc-related modular calcium binding protein-2, and Pigment epithelium-derived factor are promising non-invasive biomarkers of kidney fibrosis, Kidney Int. 100 (3) (2021) 672–683.

[77] E. Franze, et al., Cadherin 11 is a regulator of intestinal fibrosis, J. Crohns Colitis 14 (3) (2020) 406–417.

[78] P.P. Sfikakis, et al., Cadherin 11 mRNA transcripts are frequently found in rheumatoid arthritis peripheral blood and correlate with established polyarthritis, Clin. Immunol. 155 (1) (2014) 33–41.

[79] P.P. Sfikakis, N.I. Vlachogiannis, P.F. Christopoulos, Cadherin 11 as a therapeutic target in chronic, inflammatory rheumatic diseases, Clin. Immunol. 176 (2017) 107–113.

[80] E.H. Noss, et al., Modulation of matrix metalloproteinase production by rheumatoid arthritis synovial fibroblasts after cadherin 11 engagement, Arthritis Rheum. 63 (12) (2011) 3768–3778.

[81] S.K. Chang, et al., Cadherin 11 regulates fibroblast inflammation, Proc. Natl. Acad. Sci. USA 108 (20) (2011) 8402–8407.

[82] C. Zhao, et al., Umbilical cord-derived mesenchymal stem cells inhibit cadherin 11 expression by fibroblast-like synoviocytes in rheumatoid arthritis, J. Immunol. Res. 2015 (2015), 137695.

[83] M. Wu, et al., Identification of cadherin 11 as a mediator of dermal fibrosis and possible role in systemic sclerosis, Arthritis Rheumatol. 66 (4) (2014) 1010–1021.

[84] M. Pedroza, R.L. Welschhans, S.K. Agarwal, Targeting of cadherin 11 decreases skin fibrosis in the tight skin 1 mouse model, PLoS One 12 (11) (2017), e0187109.

[85] C.J. Bowen, et al., Cadherin 11 coordinates cellular migration and extracellular matrix remodeling during aortic valve maturation, Dev. Biol. 407 (1) (2015) 145–157.

[86] J. Chen, et al., Notch1 mutation leads to valvular calcification through enhanced myofibroblast mechanotransduction, Arterioscler. Thromb. Vasc. Biol. 35 (7) (2015) 1597–1605.

[87] J. Chen, Y. Lin, Z. Sun, Inhibition of miR 101-3p prevents human aortic valve interstitial cell calcification through regulation of CDH11/SOX9 expression, Mol. Med. 29 (1) (2023) 24.

[88] D.C. Sung, et al., Cadherin 11 overexpression induces extracellular matrix remodeling and calcification in mature aortic valves, Arterioscler. Thromb. Vasc. Biol. 36 (8) (2016) 1627–1637.

[89] C.R. Clark, et al., Targeting cadherin 11 prevents notch1-mediated calcific aortic valve disease, Circulation 135 (24) (2017) 2448–2450.

[90] C. Wang, et al., Segregated expressions of autism risk genes Cdh11 and Cdh9 in autism-relevant regions of developing cerebellum, Mol. Brain 12 (1) (2019) 40.

[91] N. Wu, et al., Association of CDH11 with autism spectrum disorder revealed by matched-gene Co-expression analysis and mouse behavioral studies, Neurosci. Bull. 38 (1) (2022) 29–46.

[92] M. Castori, et al., A novel mutation in CDH11, encoding cadherin 11, cause Branchioskeletogenital (Elsahy-Waters) syndrome, Am. J. Med. Genet. 176 (9) (2018) 2028–2033.

[93] E.Z. Taskiran, et al., Homozygous indel mutation in CDH11 as the probable cause of Elsahy-Waters syndrome, Am. J. Med. Genet. 173 (12) (2017) 3143–3152.

[94] M. Minatogawa, et al., Detailed clinical and radiological features of the first patient with Elsahy-Waters syndrome in East Asia, Am. J. Med. Genet. 185 (12) (2021) 3909–3915.

[95] N.H. Kim, et al., Cadherin 11, a miR-675 target, induces N-cadherin expression and epithelial-mesenchymal transition in melasma, J. Invest. Dermatol. 134 (12) (2014) 2967–2976.

[96] N.H. Kim, et al., Cadherin 11 involved in basement membrane damage and dermal changes in melasma, Acta Derm. Venereol. 96 (5) (2016) 635–640.

[97] T. Wang, Q. Zhou, Y. Shang, MiRNA-451a inhibits airway remodeling by targeting Cadherin 11 in an allergic asthma model of neonatal mice, Int. Immunopharm. 83 (2020), 106440.

[98] Z. Du, et al., Genetic landscape of common venous malformations in the head and neck, J. Vasc. Surg. Venous Lymphat Disord. 9 (4) (2021) 1007–1016.e7.

[99] C.L. Johnson, et al., Impaired macrophage trafficking and increased helper T-cell recruitment with loss of cadherin-11 in atherosclerotic immune response, Am. J. Physiol. Heart Circ. Physiol. 321 (4) (2021) H756–H769.