Journal of Molecular and Cellular Cardiology Plus 10 (2024) 100092

Contents lists available at ScienceDirect

Journal of Molecular and Cellular Cardiology Plus

journal homepage: www.journals.elsevier.com/journal-of-molecular-andcellular-cardiology-plus

Circulating levels of cadherins are associated with atherosclerosis and cardiovascular outcomes

Cadherins are a large family of cell adhesion molecules, known for their "calcium-dependent adhesion" properties, that play crucial roles in maintaining cell-cell junctions and tissue integrity. There are several types of cadherins, and they are classified into various subfamilies based on their structure, function, and expression patterns.

There are over 100 different types of cadherins identified in humans, including classical cadherins, desmosomal cadherins, protocadherins, and other atypical cadherins (Table 1). Each of these types has distinct roles in tissue development, maintenance, and function [1–3]; moreover, changes in the function and expression of various cadherins are well-documented in different types of cancer.

The role of cadherins in cardiovascular disease progression is not fully understood. Generally, normal tissue development requires dynamic intercellular contacts. These contacts are crucial for forming the coronary artery wall and vascular smooth muscle (VSM) layers. VSM cells are vital for vascular health and disease by influencing vascular tone. Shear stress regulates vessel tone, initiating a myogenic response to ensure optimal blood flow and protect vessels from mechanical injury. In VSM cells, cadherins and integrins interact with mechanosensitive molecules. Cadherin expression changes in VSM during vascular diseases and contributes to the molecular control of VSM phenotype and functions. The transition from differentiated to dedifferentiated VSM phenotypes typically depends on vascular injury and disease progression. Cadherins vary in tissue expression and functions.

The functions and molecular activities of the cadherin superfamily have been studied in experimental models and *in vitro* in the context of cardiovascular diseases. In this issue of *JMCC Plus*, Nadezhda G. Gumanova and colleagues [4] show the associations of three specific cadherins, namely P-, E-, and H-cadherin, with the severity of coronary atherosclerosis and certain cardiovascular outcomes, such as the relative risk of cardiovascular events and unplanned recurrent revascularization. E-cadherin, P-cadherin, and H-cadherin differ in their tissue distribution, function, and structural characteristics.

E-cadherin (Epithelial cadherin) is widely expressed in epithelial tissues, where it is a key component of adherens junctions. It is particularly abundant in the skin, gut, and other epithelial linings. E-cadherin is crucial for maintaining the integrity and polarity of epithelial cell layers. It mediates strong, calcium-dependent cell-cell adhesion, which is essential for tissue architecture and barrier function. E-cadherin also plays a role in signal transduction, influencing cell differentiation, proliferation, and migration. E-cadherin is well-studied in the context of cancer [5] and is recognized as an active suppressor of the growth of many epithelial cancers [3]. Its loss or downregulation is a hallmark of epithelial-to-mesenchymal transition (EMT), a process associated with increased invasiveness and metastasis in epithelial cancers. Germline mutations in the *CDH1* gene encoding E-cadherin are linked to hereditary diffuse gastric cancer and lobular breast cancer. The degradation of E-cadherin due to oxidative stress has been observed in the metastasis of hepatocellular carcinoma [6].

P-cadherin is predominantly found in the placenta, but it is also expressed in other tissues such as the basal layer of the epidermis, mammary gland epithelium, prostate, and some parts of the heart. P-cadherin plays a key role in the development and maintenance of tissues where it is expressed, particularly in areas requiring strong adhesion between cells, such as in the formation of the placenta and in epithelial-mesenchymal interactions during development [7,8]. It is involved in processes such as cell migration and wound healing. Abnormal expression of P-cadherin has been associated with various cancers, including lung, ovarian, breast, skin, and bladder cancers. In some cancers, P-cadherin is upregulated and may contribute to tumor progression and metastasis [9].

H-cadherin (Heart cadherin), also known as cadherin-13 or T-cadherin [10], is primarily expressed in the heart and vascular tissues, but it is also found in the brain, liver, and some epithelial tissues [11–13]. Unlike classical cadherins, H-cadherin lacks the transmembrane and cytoplasmic domains typical of cadherins and is anchored to the cell membrane *via* a glycosylphosphatidylinositol (GPI) anchor. H-cadherin is involved in processes such as cell proliferation, migration, and apoptosis. H-cadherin has been implicated in cardiovascular diseases and various cancers [14,15]. Its expression is often reduced in tumors, and is considered a tumor suppressor. Loss of H-cadherin function may contribute to increased cell motility and invasiveness. Additionally, the specific signaling pathways involving H-cadherin remain to be clarified.

Gumanova and collaborators measured fasting levels of P-, E-, and H-cadherins, in the serum samples of 214 patients, who were followed up for 3 years in order to evaluate their associations with atherosclerosis [4]. Coronary lesions were evaluated using the Gensini score through coronary angiography. Serum proteomic profiling was carried out with antibody microarrays, and the levels of P-, E-, and H-cadherins in the serum were measured using indirect ELISA. The analysis of the data revealed that high levels of P- and E-cadherins, along with low levels of H-cadherin, were linked to the severity of atherosclerosis. Increased levels of P- and E-cadherins were associated with a higher incidence of nonfatal cardiovascular events, while E-cadherin was correlated with a higher incidence of recurrent revascularization over the three-year follow-up. Spearman rank correlation analysis also revealed various associations of P-, E-, and H-cadherins with lipid, endothelial, and

DOI of original article: https://doi.org/10.1016/j.jmccpl.2024.100091.

https://doi.org/10.1016/j.jmccpl.2024.100092
Received 29 August 2024; Accepted 29 August 2024
Available online 4 September 2024

Table 1
Classification of the main types of cadherins.

Classical cadherins	Atypical cadherins
E-cadherin (Epithelial cadherin)	Desmosomal cadherins: Desmogleins (DSG1–4), Desmocollins (DSC1–3). These cadherins are specialized for cell-cell adhesion in desmosomes, crucial for the integrity of tissues that undergo mechanical stress.
P-cadherin (Placental cadherin)	H-cadherin (Heart) is also known as T-cadherin, (Truncated) or Cadherin-13
N-cadherin (Neural cadherin)	Protocadherins: Clustered Protocadherins (*e.g.,* Pcdhα, Pcdhβ, Pcdhγ) have a large number of isoforms and are primarily involved in the regulation of the nervous system. Non-clustered Protocadherins (*e.g.*, Pcdh7, Pcdh8, Pcdh9) represent a more diverse group with individual genes scattered across the genome.
R-cadherin (Retinal cadherin)	Flamingo cadherins
VE-cadherin (Vascular Endothelial cadherin)	Fat cadherins
M-cadherin (Muscle cadherin)	Dachsous cadherins

Each cadherin subtype plays distinct roles in tissue development, maintenance, and disease, making them essential for various physiological processes and potential targets for therapeutic intervention.

metabolic biomarkers, suggesting that they could serve as potential markers for assessing cardiovascular risk.

This study has several limitations including the small number of cardiovascular deaths observed. Consequently, conclusions regarding the risk of cardiovascular mortality cannot be definitively made. There was also missing information from patients who did not respond to follow-up, potentially introducing bias. Furthermore, the exact timing of cardiovascular events was unavailable because some subjects could not accurately recall the dates, preventing the use of Cox regression analysis. Additionally, previous studies have not measured serum concentrations of cadherins in large groups, resulting in a lack of suitable reference standards for ELISA. To address this issue, the Authors used recombinant cadherin species (specifically P-cadherin) as a standard [4]. However, cadherins are complex transmembrane glycoproteins with multiple antigenic epitopes. Therefore, specific forms of cadherins found in the blood and detected in the serum may come from various unknown sources and have unknown structural and antigenic properties. As a result, the reactivity of the recombinant reference standard with antibodies may differ from that of the cadherin species present in the serum. This aspect suggests that the calibration curve and the measured levels of cadherins (particularly P-cadherin) based on this curve may not accurately reflect the actual serum levels, and should be considered as estimates only.

In conclusion, serum levels of P-, E-, and H-cadherins might represent promising markers for the evaluation of cardiovascular risk.

CRediT authorship contribution statement

Gaetano Santulli: Conceptualization, Supervision, Visualization, Writing – review & editing. **Fahimeh Varzideh:** Methodology, Validation, Visualization. **Yifei Qin:** Methodology, Visualization, Writing – original draft. **Brandon Wang:** Data curation. **Urna Kansakar:** Validation, Visualization. **Stanislovas S. Jankauskas:** Project administration, Validation, Writing – original draft.

Declaration of competing interest

None.

Acknowledgements

G.S. is currently supported in part by the National Institutes of Health (NIH): National Heart, Lung, and Blood Institute (NHLBI: R01-HL164772, R01-HL159062, R01-HL146691, T32-HL144456), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK: R01-DK123259, R01-DK033823), National Center for Advancing Translational Sciences (NCATS: UL1-TR002556-06, UM1-TR004400), by the Diabetes Action Research and Education Foundation, by the American Heart Association (AHA, 24IPA1268813), and by the Monique Weill-Caulier and Irma T. Hirschl Trusts. F.V. is supported in part by the AHA (22-915561 and 24-1195524). U.K. is supported in part by the AHA (23-1026190) and by the NIH (T32-HL172255 PODIUM: Purposeful Outreach for Diversity and Inclusion of Underrepresented Physician-Scientists in Medicine). S.S.J. is supported in part by the AHA (21-836407).

References

[1] Burg N, Malpass R, Alex L, Tran M, Englebrecht E, Kuo A, et al. Endothelial cell sphingosine 1-phosphate receptor 1 restrains VE-cadherin cleavage and attenuates experimental inflammatory arthritis. JCI Insight 2024;9(11).
[2] Yakovlev S, Tjandra N, Strickland DD, Medved L. Identification of neural (N)-cadherin as a novel endothelial cell receptor for fibrin and localization of the complementary binding sites. Biochemistry 2024;63(2):202–11.
[3] Lu G, Cai Z, Jiang R, Tong F, Tu J, Chen Y, et al. Reduced expression of E-cadherin correlates with poor prognosis and unfavorable clinicopathological features in gastric carcinoma: a meta-analysis. Aging (Albany NY) 2024;16(12):10271–98.
[4] Gumanova NG, Vasilyev DK, Bogdanova NL, Havrichenko YI, Drapkina OM. P-, E-, and H-cadherins differ in their relationships with coronary stenosis, cardiovascular outcomes, and unplanned recurrent revascularization. JMCC Plus 2024 [In press].
[5] Zou G, Huang Y, Zhang S, Ko KP, Kim B, Zhang J, et al. E-cadherin loss drives diffuse-type gastric tumorigenesis via EZH2-mediated reprogramming. J Exp Med 2024;221(4).
[6] Huang Z, Zhou L, Duan J, Qin S, Jiang J, Chen H, et al. Oxidative stress promotes liver cancer metastasis via RNF25-mediated E-cadherin protein degradation. Adv. Sci. (Weinh.) 2024;11(13):e2306929.
[7] Ravizzini G, Erwin W, De Palatis L, Martiniova L, Subbiah V, Paolillo V, et al. Dosimetry of a novel (111)indium-labeled anti-P-cadherin monoclonal antibody (FF-21101) in non-human primates. Cancers (Basel) 2023;15(18).
[8] Sao Jose C, Pereira C, Ferreira M, Andre A, Osorio H, Gullo I, et al. 3D chromatin architecture re-wiring at the CDH3/CDH1 loci contributes to E-cadherin to P-cadherin expression switch in gastric cancer. Biology (Basel) 2023;12(6).
[9] Gronewold M, Grote I, Bartels S, Christgen H, Kandt LD, Brito MJ, et al. Micro-environment-induced restoration of cohesive growth associated with focal activation of P-cadherin expression in lobular breast carcinoma metastatic to the colon. J Pathol Clin Res 2024;10(2):e12361.
[10] Okita T, Kita S, Fukuda S, Kondo Y, Sakaue TA, Iioka M, et al. Soluble T-cadherin secretion from endothelial cells is regulated via insulin/PI3K/Akt signalling. Biochem Biophys Res Commun 2024;732:150403.
[11] Lee SW. H-cadherin, a novel cadherin with growth inhibitory functions and diminished expression in human breast cancer. Nat Med 1996;2(7):776–82.
[12] Staebler S, Hoechst S, Thongmao A, Schneider N, Bosserhoff AK, Kuphal S. The role of T-cadherin (CDH13) in treatment options with garcinol in melanoma. Cancers (Basel) 2024;16(10).
[13] Takeuchi T, Misaki A, Fujita J, Sonobe H, Ohtsuki Y. T-cadherin (CDH13, H-cadherin) expression downregulated surfactant protein D in bronchioloalveolar cells. Virchows Arch 2001;438(4):370–5.
[14] Sato M, Mori Y, Sakurada A, Fujimura S, Horii A. A GT dinucleotide repeat polymorphism in intron 1 of the H-cadherin (CDH13) gene. J Hum Genet 1998;43(4):285–6.
[15] Toyooka KO, Toyooka S, Virmani AK, Sathyanarayana UG, Euhus DM, Gilcrease M, et al. Loss of expression and aberrant methylation of the CDH13 (H-cadherin) gene in breast and lung carcinomas. Cancer Res 2001;61(11):4556–60.

Gaetano Santulli[a,b,*], Fahimeh Varzideh[a], Yifei Qin[b], Brandon Wang[a], Urna Kansakar[b], Stanislovas S. Jankauskas[a]

[a] *Department of Medicine, Division of Cardiology, Wilf Family Cardiovascular Research Institute, Einstein Institute for Neuroimmunology and Inflammation (INI), Albert Einstein College of Medicine, Montefiore University Hospital, New York, NY 10461, USA*

[b] *Department of Molecular Pharmacology, Einstein-Mount Sinai Diabetes Research Center (ES-DRC), Fleischer Institute for Diabetes and Metabolism (FIDAM), Einstein Institute for Aging Research, Albert Einstein College of Medicine, Montefiore University Hospital, New York, NY 10461, USA*

[*] Corresponding author at: 1300 Morris Park Avenue, 10461 New York, NY, USA.
E-mail address: gsantulli001@gmail.com (G. Santulli).