Přehledový článek | Review article

The caveolin levels ın cardiovascular disease

Lutfu Askin[a], Husna Sengul Askin[b], Okan Tanriverdi[a]

[a] *Department of Cardiology, Adiyaman Education and Research Hospital, Adiyaman, Turkey*
[b] *Department of Infectious Diseases, Adiyaman Education and Research Hospital, Adiyaman, Turkey*

ARTICLE INFO

Article history:
Submitted: 2. 3. 2021
Accepted: 3. 4. 2021
Available online: 6. 10. 2021

Klíčová slova:
Kardiovaskulární onemocnění
Kaveolin
Srdeční selhání

SOUHRN

Kardiovaskulární onemocnění (KVO) jsou celosvětově častým typem postižení vedoucího k úmrtí. Kaveolin je strukturální kaveolární protein se třemi izoformami (caveolin-1 [cav-1], cav-2 a cav-3]. Kaveoly hrají životně důležitou úlohu v přenášení signálů při přežití buněk v rámci kardioprotekce. Zvláště cav-1 ovlivňuje mnoho biologických pochodů (vyvážení buněčné energie, destrukce buněk a fibróza) v rozvoji srdečního selhání. Snížené hodnoty kaveolinu představují cíl léčby; budoucí studie by mohly ozřejmit řadu aspektů působení kaveolinu u starších a obézních pacientů. V tomto přehledu se zabýváme významem kaveol u kardiovaskulárních onemocnění. Zdůrazňujeme i úlohu kaveolinu u řady kardiovaskulárních onemocnění.

Keywords:
Cardiovascular diseases
Caveolin
Heart failure

ABSTRACT

Cardiovascular diseases (CVDs) are common diseases that cause many deaths around the world. Caveolin is a structural caveolae protein with three isoforms (Caveolin-1 [Cav-1], Cav-2, and Cav-3). Caveolae has a vital role in generating survival signals for cardiac protection. In particular, Cav-1 influences many biological processes (cellular energy balance, cellular destruction, and fibrosis) in the development of heart failure (HF). Decreased caveolin levels are a therapeutic target and could shed light on future studies in elderly and obese patients. In this review, we discussed the significance of caveolae in cardiovascular diseases. We have also emphasized the role of caveolin in many cardiovascular diseases.

Introduction

In a rapidly developing world, cardiovascular diseases (CVDs) are common diseases that cause many deaths around the world.[1-2] Cardioprotective mechanisms such as pharmacological and ischemic preconditioning decrease with aging.[3,4] Aged cardiomyocytes remain vulnerable to stress due to abnormal cell signal transduction.[5]

Caveolae is a subset of lipid aggregates with a unique bottle-like structure produced by caveolin and cavin.[6-8] Caveolae and caveolin coordinate cell signal transduction events in many cells.[9] Decreased caveolae cause diseases such as Alzheimer's, atherosclerosis, and diabetes by impairing cellular functions in the elderly.[10] This review focuses on the role of the caveolin in the process and progression of many cardiovascular diseases.

Caveolins

Caveolin is a structural caveolae protein with three isoforms.[7] Caveolin-1 (Cav-1) is required for caveolae formation in the extra-muscular cell type. Cav-2 is important in terms of membrane localization, and Cav-3 serves caveola synthesis in striated (skeletal and cardiac) and smooth muscle cells.[11,12] Caveolins act as a chaperon and scaffold by promoting the temporal and spatial regulation of signal transmission, thus enabling signal transmission.[6] Caveolins not only fix other proteins within the caveolae but also improve the signal transduction ability of this protein. Caveolins also have many other functions such as vesicle transport, cholesterol and calcium homeostasis, and T-tube formation.[13,14]

The research about caveolin deficiency helps us to understand the importance of each caveolin isoform in human

Address: Lutfu Askin, M.D., Adiyaman Education and Research Hospital Cardiology Department, 2230 – Adiyaman, Turkey, e-mail: lutfuaskin23@gmail.com
DOI: 10.33678/cor.2021.045

Please cite this article as: Askin L, Askin HS, Tanriverdi O. The caveolin levels ın cardiovascular disease. Cor Vasa 2021;63:579–582.

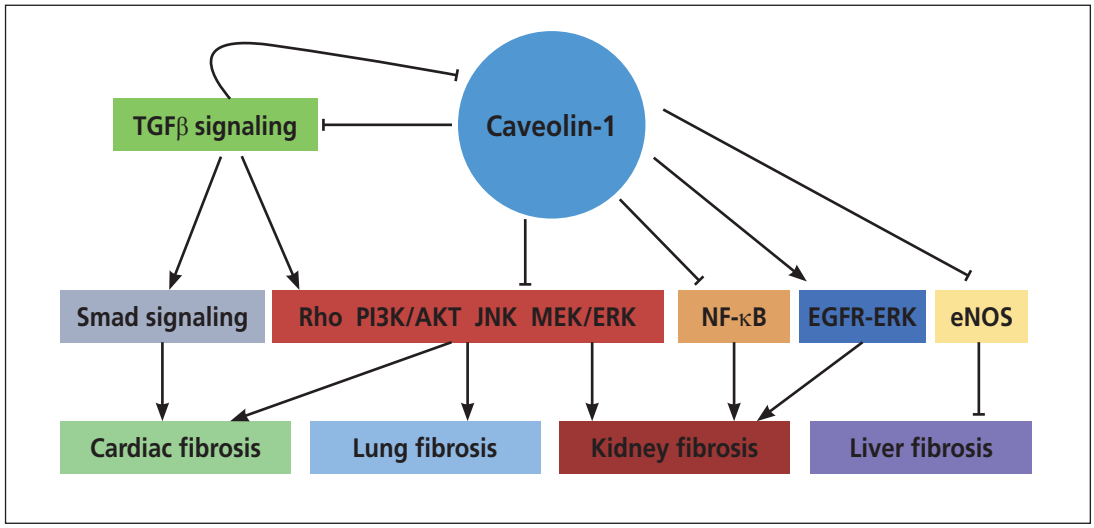

Fig. 1 – The regulation of the fibrotic process in various organs by Cav-1.

disease.The protein expression of caveolin and its relation with caveolin decrease in the elderly. Caveolin loss is thought to cause the aging phenotype.[15,16] For this reason, caveolins are considered as alternative therapeutic agents for the treatment of cardiovascular diseases.

Heart failure (HF)

HF is still one of the most common mortal diseases over the 65 ages.Ventricular dysfunction due to myocardial infarction and/or hypertension is often a major cause of HF.[17] Survival time was reduced by 50% in mice lacking Cav-1.[18] Cav-1 deficiency causes progressive cardiomyopathies over 12 months.[18] Thus, the contraction of the heart is affected and its functions are impaired.

Cav-1 deficiencydamages the signaling pathwayin cardiomyocytes and causing cardiac hypertrophy.[19] In mice lacking Cav-1, overactivity of the p42/44 MAP kinase cascade causes cardiac defects.[20] Hence, the main effect of Cav-1 deficiencymay be due to its function in cardiac support cells (fibroblasts and endothelial cells). Cav-1 deficiency causes impaired contractions due to decreased AMP (cAMP) and ATP levels.[21]

Similar to Cav-1, Cav-3 deficiency may cause cardiac defects.[22] Cav-3 mutations are associated with familial hypertrophic cardiomyopathy.[23] In cardiomyocytes, T-shaped tubules can activate cells quickly and evenly. In HF, the T--tube network undergoes extensive remodeling, and this change may cause abnormal calcium turnover.[24] Cav-3 deficiency causes T tube irregularity in skeletal muscle. It is thought that cardiomyocytes may exhibit a similar phenotype, which may cause HF.Cav-3 deficiency develops progressive cardiomyopathy with cardiac hypertrophy, enlargement, and reduced fractional shortening.[24]

Myocardial infarction (MI)

MI may increase heart damage by causing loss of coronary blood flow and oxygen.[1] There is much evidence that caveolin is the reason for the pathogenesis of ischemic damage. Caveolin expression alters in renal and cerebral ischemia.[25,26] Caveolins prevent ischemic damage. Decreased Cav-1 develops loss of contractility by causing impaired adrenergic signaling.[27] Ischemic preconditioning increases tubulecount in the muscle membrane.[28] The protection of preconditioning in animals and humans decreases with age.

Pulmonary hypertension (PH)

In severe PH, increased pulmonary vascular resistance results in HF and sudden death.Cav-1 is overexpressed in lung endothelial cells.Cav-1 dysfunction in the vascular system may be used as a marker of pulmonary hypertension. Thus, early and advanced treatment strategies may be determined.[29]

Abnormal lungs, reduced alveolar spaces, thickened walls, fibrosis, and hypercellularity are observed in Cav-1deficiency.[30] The anti-fibrotic role of caveolae and caveolin has been proven by animal and pharmacological models. Cav-1 is defined as an anti-fibrotic target in the heart, lungs and kidneys (figure 1).[31] Pulmonary artery catheterization showed that Cav-1 deficiency-induced right ventricular hypertrophy.[32] Decreased Cav-1 expression in the lungs after myocardial infarction triggers the development of PH and remodeling of the lung structure.[33] In severe PH, Cav-1 levels are reduced in lung tissue and pulmonary vascular endothelial cells.[34] ENOS release is reduced in Cav-1 deficiency. Decreased eNOS activity in Cav-1 deficiency may develop cardiopulmonary diseases.

Other situations

Cav-1 may be a predictor of coronary artery lesions in Kawasaki disease.[35] Caveolae and CD36 play a role in LDL endocytosis and affect the early stages of atherosclerosis.[36] Caveolin-1 deficit increases ADAM17 and TNF release in adipose tissues of obese elderly patients.[37]

In contrast, Frank et al.[38] suggested that caveolin-1 may contribute to the development of atherosclerosis by the

regulation of lipoprotein metabolism. Malinska et al.[39] suggested that CAV-2 overexpression may increase graft failure in the usage of an autologous internal thoracic artery.In vascular smooth muscle and endothelium, Cav-1 has a critical effect on vascular remodeling by the regulation of blood pressure.[40]

Conclusions

Caveolins may be therapeutically valuable proteins for age-related cardiovascular diseases. In caveolin therapy, targeting a specific cell type is important because of its wide expression range. Decreased levels of caveolin are a therapeutic target and could shed light on future studies in elderly and obese patients.

In particular, Cav-1 affects many biological processes (cellular energy balance, cellular destruction, and fibrosis) that cause HF.Therefore, therapeutic approaches especially towards CAV-1 can provide significant improvements in the field of HF. Based on the above evidence, larger observational studies are needed to make caveolins an even more valuable marker in cardiovascular disease.

Conflict of interest
The authors declare that there is no conflict of interest regarding the publication of this paper.

Funding body
The funding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

References

1. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics – 2010 update: A report from the American Heart Association. Circulation 2010;121:E46–E215.
2. Askin L, Tanriverdi O, Tibilli H, et al. Associations between Vaspin Levels and Coronary Artery Disease. Cardiovasc Innov Appl 2020;4:211–216.
3. Mio Y, Bienengraeber MW, Marinovic J, et al. Age-related attenuation of isoflurane preconditioning in human atrial cardiomyocytes: Roles for mitochondrial respiration and sarcolemmal adenosine triphosphate-sensitive potassium channel activity. Anesthesiology 2008;108:612–620.
4. Boengler K, Konietzka I, Buechert A, et al. Loss of ischemic preconditioning's cardioprotection in aged mouse hearts is associated with reduced gap junctional and mitochondrial levels of connexin 43. Am J Physiol Heart Circ Physiol 2007;292:H1764–H1769.
5. Boengler K, Schulz R, Heusch G. Loss of cardioprotection with ageing. Cardiovasc Res 2009;83:247–261.
6. Williams TM, Lisanti MP. The caveolin proteins. Genome Biol 2004;5:214.
7. Vinten J, Johnsen AH, Roepstorff P, et al. Identification of a major protein on the cytosolic face of caveolae. Biochim Biophys Acta 2005;1717:34–40.
8. Liu L, Pilch PF. A critical role of cavin (polymerase i and transcript release factor) in caveolae formation and organization. J Biol Chem 2008;283:4314–4322.
9. Insel PA, Patel HH. Membrane rafts and caveolae in cardiovascular signaling. Curr Opin Nephrol Hypertens 2009;18:50–56.
10. Simons K, Ehehalt R. Cholesterol, lipid rafts, and disease. J Clin Invest 2002;110:597–603.
11. Cho WJ, Chow AK, Schulz R, et al. Caveolin-1 exists and may function in cardiomyocytes. Can J Physiol Pharmacol 2010;88:73–76.
12. Pradhan BS, Prószyński TJ. A Role for Caveolin-3 in the Pathogenesis of Muscular Dystrophies. Int J Mol Sci 2020;21:8736.
13. Hardin CD, Vallejo J. Caveolins in vascular smooth muscle: Form organizing function. Cardiovasc Res 2006;69:808–815.
14. Kawabe JI, Grant BS, Yamamoto M, et al. Changes in caveolin subtype protein expression in aging rat organs. Mol Cell Endocrinol 2001;176:91–95.
15. McMurray JJ, Pfeffer MA. Heart failure. Lancet 2005;365:1877–1889.
16. Park DS, Cohen AW, Frank PG, et al. Caveolin-1 null (-/-) mice show dramatic reductions in life span. Biochemistry 2003;42:1512–1531.
18. Patel HH, Murray F, Insel PA. Caveolae as organizers of pharmacologically relevant signal transduction molecules. Annu Rev Pharmacol Toxicol 2008;48:359–391.
19. Nonami A, Taketomi T, Kimura A, et al. The Sprouty-related protein, Spred-1, localizes in a lipid raft/caveola and inhibits ERK activation in collaboration with caveolin-1. Genes Cells 2005;10:887–895.
20. Wunderlich C, Schober K, Lange SA, et al. Disruption of caveolin-1 leads to enhanced nitrosative stress and severe systolic and diastolic heart failure. Biochem Biophys Res Commun 2006;340:702–708.
21. Woodman SE, Park DS, Cohen AW, et al. Caveolin-3 knockout mice develop a progressive cardiomyopathy and show hyperactivation of the p42/44 mapk cascade. J Biol Chem 2002;277:38988–38997.
22. Hayashi T, Arimura T, Ueda K, et al. Identification and functional analysis of a caveolin-3 mutation associated with familial hypertrophic cardiomyopathy. Biochem Biophys Res Commun 2004;313:178–184.
23. Crossman DJ, Ruygrok PN, Soeller C, et al. Changes in the organization of excitation-contraction coupling structures in failing human heart. PLoS One 2011;6:e17901.
24. Zager RA, Johnson A, Hanson S, et al. Altered cholesterol localization and caveolin expression during the evolution of acute renal failure. Kidney Int 2002;61:1674–1683.
25. Head BP, Patel HH, Tsutsumi YM, et al. Caveolin-1 expression is essential for n-methyl-d-aspartate receptor-mediated src and extracellular signal-regulated kinase ½ activation and protection of primary neurons from ischemic cell death. FASEB J 2008;22:828–840.
26. Jasmin JF, Rengo G, Lymperopoulos A, et al. Caveolin-1 deficiency exacerbates cardiac dysfunction and reduces survival in mice with myocardial infarction. Am J Physiol Heart Circ Physiol 2011;300:H1274–H81.
27. Tsutsumi YM, Horikawa YT, Jennings MM, et al. Cardiacspecific overexpression of caveolin-3 induces endogenous cardiac protection by mimicking ischemic preconditioning. Circulation 2008;118:1979–1988.
28. Fridolfsson HN, Patel HH. Caveolin and caveolae in age associated cardiovascular disease. J Geriatr Cardiol 2013;10:66–74.
29. Razani B, Engelman JA, Wang XB, et al. Caveolin-1 null mice are viable but show evidence of hyperproliferative and vascular abnormalities. J Biol Chem 2001;276:38121–38138.
30. Shihata WA, Putra MRA, Chin-Dusting JPF. Is There a Potential Therapeutic Role for Caveolin-1 in Fibrosis? Front Pharmacol 2017;8:567.
31. Zhao YY, Liu Y, Stan RV, et al. Defects in caveolin-1 cause dilated cardiomyopathy and pulmonary hypertension in knockout mice. Proc Natl Acad Sci USA 2002;99:11375–11380.
32. Jasmin JF, Mercier I, Hnasko R, et al. Lung remodeling and pulmonary hypertension after myocardial infarction: Pathogenic role of reduced caveolin expression. Cardiovasc Res 2004;63:747–755.

33. Patel HH, Tsutsumi YM, Head BP, et al. Mechanisms of cardiac protection from ischemia/reperfusion injury: A role for caveolae and caveolin-1. FASEB J 2007;21:1565–1574.
34. Zhu F, Huang J, Wang X, et al. The expression and significance of serum caveolin-1 in patients with Kawasaki disease. Chin J Physiol 2020;63:90–94.
35. Gerbod-Giannone MC, Dallet L, Naudin G, et al. Involvement of caveolin-1 and CD36 in native LDL endocytosis by endothelial cells. Biochim Biophys Acta Gen Subj 2019;1863:830–838.
36. Dou H, Feher A, Davila AC, et al. Role of Adipose Tissue Endothelial ADAM17 in Age-Related Coronary Microvascular Dysfunction. Arterioscler Thromb Vasc Biol 2017;37:1180–1193.
37. Frank PG, Pavlides S, Cheung MW, et al. Role of caveolin-1 in the regulation of lipoprotein metabolism. Am J Physiol Cell Physiol 2008;295:C242–C248.
38. Malinska A, Podemska Z, Sujka-Kordowska P, et al. Caveolin 2: a facultative marker of unfavourable prognosis in long-term patency rate of internal thoracic artery grafts used in coronary artery bypass grafting. Preliminary report. Interact Cardiovasc Thorac Surg 2017;24:714–720.
39. Forrester SJ, Elliott KJ, Kawai T, et al. Caveolin-1 Deletion Prevents Hypertensive Vascular Remodeling Induced by Angiotensin II. Hypertension 2017;69:79–86.