The caveolin levels in cardiovascular disease

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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.

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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

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 deficiency damages the signaling pathway in 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 deficiency may 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 caveo-

lin 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 tubule count 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-1 deficiency.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.

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