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Peran Matriks Metalloproteinase dalam Perkembangan Gagal Jantung: Sebuah Tinjauan Naratif

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Abstrak

Gagal jantung merupakan salah satu jenis penyakit kardiovaskular dengan jalur patologis yang kompleks dan dipengaruhi oleh banyak faktor. Mekanisme patologis yang kompleks tersebut akan menyebabkan gangguan pada fungsi jantung dan juga stabilitas struktural. Salah satu yang berperan dalam mempertahankan fungsi dan struktur jantung adalah matriks ekstraseluler (MES), dan disrupsi pada matriks ekstraseluler ini memiliki andil dalam menyebabkan gangguan pada jantung. Pengaturan MES juga dihubungkan dengan matriks metalloproteinase (MMP). Ekspresi berlebih dari matriks metaloproteinase dapat menyebabkan terjadinya proses degradasi MES yang menyebabkan terjadinya proses remodeling jantung. Peran MMP dalam gagal jantung juga berkaitan dengan meningkatnya respon inflamasi yang merupakan salah satu jalur progresi gagal jantung. Kaitan MMP yang erat dengan perkembangan gagal jantung menjadikan MMP sebagai penanda biologis yang potensial. Artikel ini memiliki tujuan untuk memahami peran MMP dan mekanismenya dalam jalur remodeling jantung yang menyebabkan gagal jantung. Tinjauan naratif atau *narrative review* ini menunjukkan bahwa ekspresi MMP yang berlebihan dapat menyebabkan gagal jantung. Inflamasi merupakan salah satu faktor pemicu munculnya MMP. Inflamasi akan meningkatkan pelepasan sitokin pro-inflamasi, sehingga memicu ekspresi MMP. Ketidakseimbangan ekspresi MMP dapat merusak jaringan kolagen melalui degradasi MES dan merusak struktur dan fungsi jantung. MMP juga dapat dijadikan sebagai penanda biologis dalam kasus gagal jantung. Aplikasi MMP sebagai penanda biologis dapat digunakan untuk menilai derajat keparahan penyakit serta menjadi prediktor kejadian gagal jantung. Sebagai kesimpulan, MMP memiliki peran penting dalam proses perkembangan gagal jantung dan dapat menjadi penanda biologis dalam kasus gagal jantung.

Kata Kunci: gagal jantung, matriks ekstraseluler, matriks metalloproteinase, mekanisme

Role of Matrix Metalloproteinase in the Progression of Heart Failure: A Narrative Review

Abstract

Heart failure (HF) is a cardiovascular disease with a complex pathological pathway and influenced by many factors. Such a complex pathological mechanism would impair cardiac function and structural stability. One that plays a role in maintaining the function and structure of the heart is the extracellular matrix (ECM), and disruption in the extracellular matrix has a role

in causing cardiac dysfunction. ECM regulation is associated with matrix metalloproteinase (MMP). Overexpression of matrix metalloproteinases can lead to ECM degradation process which leads to cardiac remodelling. The role of MMP in heart failure is also related to the increased inflammatory response, which is one of the pathways for progression of heart failure. The close association of MMP with the development of heart failure makes MMP a potential biological marker. This article aims was to understand the role of MMP and its mechanisms in cardiac remodelling pathways leading to heart failure. This narrative review suggests that overexpression of MMP can lead to heart failure. Inflammation is one of the factors triggering the expression of MMP. Inflammation will increase the release of pro-inflammatory cytokines, thereby triggering MMP expression. MMP expression imbalance can damage collagen tissue through ECM degradation and damage the structure and function of the heart. MMP can also be used as a biological marker in heart failure cases. The application of MMP as a biological marker can be used to assess the degree of disease severity as well as a predictor of heart failure. In conclusion, MMP has an important role in the development process of heart failure and can be a biological marker in cases of heart failure.

Keywords: *extracellular matrix, heart failure, matrix metalloproteinase, mechanism*

INTRODUCTION

Extracellular matrix (ECM) is a non-cellular component presents in tissue and organs to maintain the structure and also to connect with other components surrounding the cell to maintain its physiological function. The relation between ECM and other components play an essential role in homeostasis (Bonnans *et al*, 2014). ECM has also had an essential role in pathophysiological changes in tissue, including heart tissue. Any injury mechanism will trigger the ECM to activate the reparative function (Bonnans *et al*, 2014). When an injury occurs, there will be changes in ECM biochemical structure and cause alteration in ECM function. In pathological condition, it may disrupt healthy organ structure and transducing maladaptive signal to the cells (Frangogiannis, 2019). These cellular changes in heart tissue could lead to cardiac remodelling. Role of ECM in cardiac failure is also influenced by matrix metalloproteinase (MMP). A balanced activity of MMP, tissue inhibitors of MMP (TIMP), and pro-inflammatory cytokines such as tumour necrosis factor-α, interleukin-6, and interleukin-1β will maintain the integrity of ECM. These cytokines promote the expression of MMP and can result in decreased matrix deposition and increased matrix degradation (Awad *et al*, 2010; Lu *et al*, 2011). High MMP expression due to pro-inflammatory cytokine can cause the dissolution of collagen. Loss of collagen leads to dilation of the chamber and decreased function (Fan *et al*, 2017). Knowing the role of MMP in the development of cardiac remodelling will

help the physician to manage the patients with heart failure (HF) because MMP could be used as a new biomarker and pharmacological MMP inhibitor might be a future treatment (Spinale and Villarreal, 2014). The purpose of this review was to understand the mechanism of ECM and MMP in the myocardium that leads to cardiac remodelling in HF patients.

METHODS

This review is a narrative review. We searched relevant article from Pubmed for full article in English from 2010. We excluded abstract article and non-English article. We used several keywords such as: matrix metalloproteinase, MMP, and heart failure. We included review article and original study relevant to the topic. All of the included studies were analyzed to discuss about the definition and function of matrix metalloproteinase and also the relation between increased MMP expression in heart failure progression. MMP role is related to inflammation process. We also discussed about the use of MMP as a potential biomarker for heart failure

DISCUSSION

Extracellular Matrix

Extracellular matrix (ECM) is a non-cellular three-dimensional network that is composed of proteoglycans, glycoproteins, and fibrous proteins and has a vital role in linking and protecting the intercellular zone within organs and tissues (Frantz *et al*, 2010). ECM serves as a mechanical scaffold and also as a signal transducer to maintain cellular function and survival. It provides mechanical stability, strength, stiffness, and energy absorption to heart tissue. ECM is also essential in maintaining cardiac function by regulating blood flow during contraction, alignment of myocyte, and compliance (Kwak, 2013). The matrix in myocardial tissue consist of three interconnected levels, which are the endomysium that surrounds individual cardiomyocytes, the perimysium that defines principal bundles, and the epimysium that encases the entire cardiac muscle (Leonard *et al*, 2012). Perimysium and epimysium are formed by type I collagen and become a significant component in the cardiac interstitium. Endomysium is formed by type III collagen (Frangogiannis, 2017). ECM changes play an essential role in heart failure. Different mechanism and duration off injury affect the pattern of ECM disruption in heart failure development. Several mechanisms known to be associated with alteration of cardiac function are myocardial stiffness caused by deposition of cross-linked collagen in the cardiac interstitium,

impaired systolic function caused by disruption of coordination between myocardial excitation and contraction coupling, impairment on perfusion caused by an expansion of ECM in periadventitial, and activation of the pro-inflammatory pathway (Frangogiannis, 2019). Pressure and volume overload also lead to ECM alteration by increasing myocardial stiffness, regulating inflammatory responses, prominent ECM degradation, and induction of MMP (Figure 1) (Hutchinson *et al*, 2010; Zile *et al*, 2014). Several studies showed that ECM expression would increase in cardiomyopathy and heart failure patients (Bayomy *et al*, 2012; Fan *et al*, 2012; Leonard *et al*, 2012). Therefore, ECM has a fundamental role in the mechanism of heart failure because ECM maintains the stability of the structure of the heart, and ECM disruption would lead to changes in the structure.

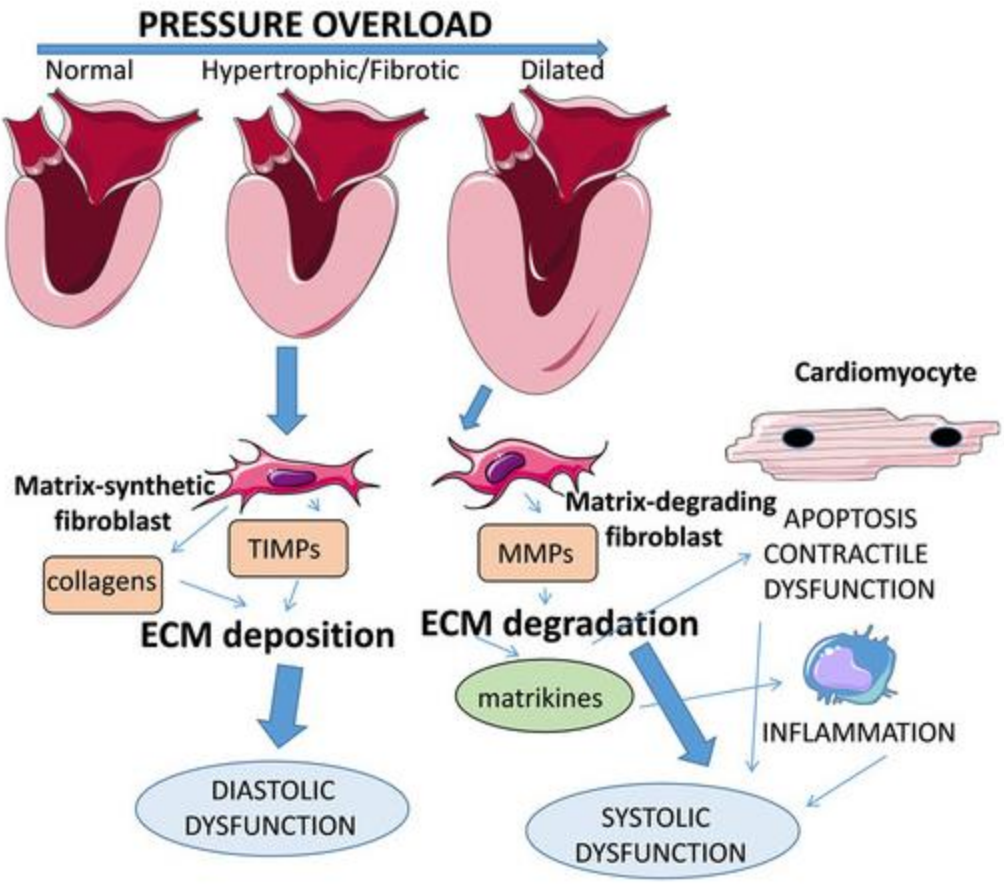

Figure 1. Pressure overload cause imbalanced between protease and antiprotease levels causing cardiac dysfunction (Frangogiannis, 2019).

MMP: Definition and Function

Matrix metalloproteinase (MMPs) are Ca^{2+} and Zn^{2+} -dependent proteases and have a role in degrading extracellular matrix. This role of MMP is found in human cardiac tissue and associated with progression of heart failure (Lindsey *et al*, 2016). MMPs are mainly expressed from the cardiomyocytes and fibroblast in the myocardium. MMP is expressed in proMMP form, which is inactive and activated by tissue or plasma proteinase. Activation of MMPs requires removal of amino-terminal propeptide domain by autoproteolysis, another MMP, or serine protease. MMPs play an essential role in physiological function such as angiogenesis, bone remodelling, immunity, and wound healing although it is expressed in low levels.

Several subtypes of MMP had been discovered and associated with cardiac remodelling such as MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, and MMP-13 (DeLeon-Pennell *et al*, 2017; Morishita *et al*, 2017). Each of the MMPs has specific functions. MMP-1 and MMP-13 function for cleaving the triple-helical collagen fibrils into gelatine fragments. MMP-3 expression related to degradation of type I and II collagen, and proteoglycan. In general, MMPs in cardiac remodelling is associated with the degradation of collagen. The pathological process occurs when there is over-expression of MMP (Doxakis *et al*, 2019; Toba *et al*, 2017). To balance the expression of MMP, there is an inhibitor called tissue inhibitors of matrix metalloproteinase (TIMP) and alteration of TIMP levels can contribute in left ventricular remodelling. There are 4 TIMPs. Growth factors and cytokines induce expression of TIMP-1 and -3. TIMP-2 and -4 are expressed constitutively. TIMP-3, via heparin sulphate proteoglycans, binds to the ECM and other TIMPs in soluble form (Moore *et al*, 2012).

Inflammation is one of various mechanism that is associated with MMP expression. MMP expression is related to both good and bad effects regarding the inflammation. In inflammatory process, MMP could modulate the cytokines to promote the inflammatory response in various conditions. However, there was also an evidence that MMP could supress and inactivate the inflammatory cascade by proteolytic modification of chemokines (DeLeon-Pennell *et al*, 2015). A Study by Iyer *et al* also showed that early inhibition of the MMP-9 actually worsen the function in animal models with myocardial infarction due to disruption in resolution of inflammation (Iyer *et al*, 2016a). Understanding the role and function of MMPs in various conditions is important to further find out the relationship between

the dysregulation and the disease progression.

Role of MMP in Heart Failure

MMP play essential roles in cell development and migration due to its ECM-degrading activities that are triggered by growth factors and cytokines. Inflammation process in cardiovascular disease can occur in myocardial infarction and heart failure. Inflammation in myocardial tissue will increase the expression of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α). TNF-α is associated with increased MMP expression and disrupt the ECM structure leading to left ventricular dysfunction and dilatation. TNF-α inhibition by specific antibody can downregulate the MMP expression. These showed that MMP expression is associated with cardiac remodelling and the development of heart failure (figure 2). After myocardial infarction, there will be a significant increasing of MMP that marks the process of left ventricular remodelling and also a decreased of TIMP (Iyer *et al*, 2016b; Ma *et al*, 2014). Impairment in MMP and TIMP levels will also affect the collagen network thus causing structural and functional impairment. Ageing process may also contribute to ECM degradation in relation to MMP.

An Association between MMP and cardiac dysfunction was also studied in another animal study. This study stated that increased expression of MMP-2 in the heart of transgenic mice was related to significant cardiac remodelling, hypertrophy, proliferation of the cardiac fibroblast, and disruption of sarcomere and myofilament. Chronic expression of MMP in the heart also caused a degenerative process in the heart valves. These changes mark a notable MMP influence in cardiac structure and function (Azevedo *et al*, 2014).

There are already several established biomarkers for heart failure. However, a multi-marker approach might be more reliable than the use of one biomarker due to the large variation. Several types of MMP have been studied for their usefulness as predictors in heart failure patient. MMP-9 is one of those MMPs that has been proposed to be a potential biomarker for cardiac remodelling. A study by Morishita *et al* on patients with chronic heart failure showed that patients with heart failure events had a higher MMP-9 plasma levels that the patients without heart failure events. This study found that MMP-9 was related to disease severity and useful as a predictor of heart failure events (Morishita *et al*, 2017). Increased MMP-9 expression could be used as an indicator of the occurrence of ventricular remodelling. MMP could also

identify a damage in cardiac myocyte before a deteriorated function occur (Morishita *et al*, 2017). MMP-9 plays a role in activating chemokines and releasing pro-inflammatory receptors that make MMP-9 responsive to inflammatory stimuli. In post-myocardial infarct heart, neutrophil contributed to cardiac remodelling. The early rise of MMP-9 expression is related to high neutrophil levels and indicating that MMP-9 from the neutrophil has a role in disruption in degradation process (Halade *et al*, 2013). Therefore, strong association between MMP and heart failure suggests that MMP might be useful for further assessment in patients with heart failure.

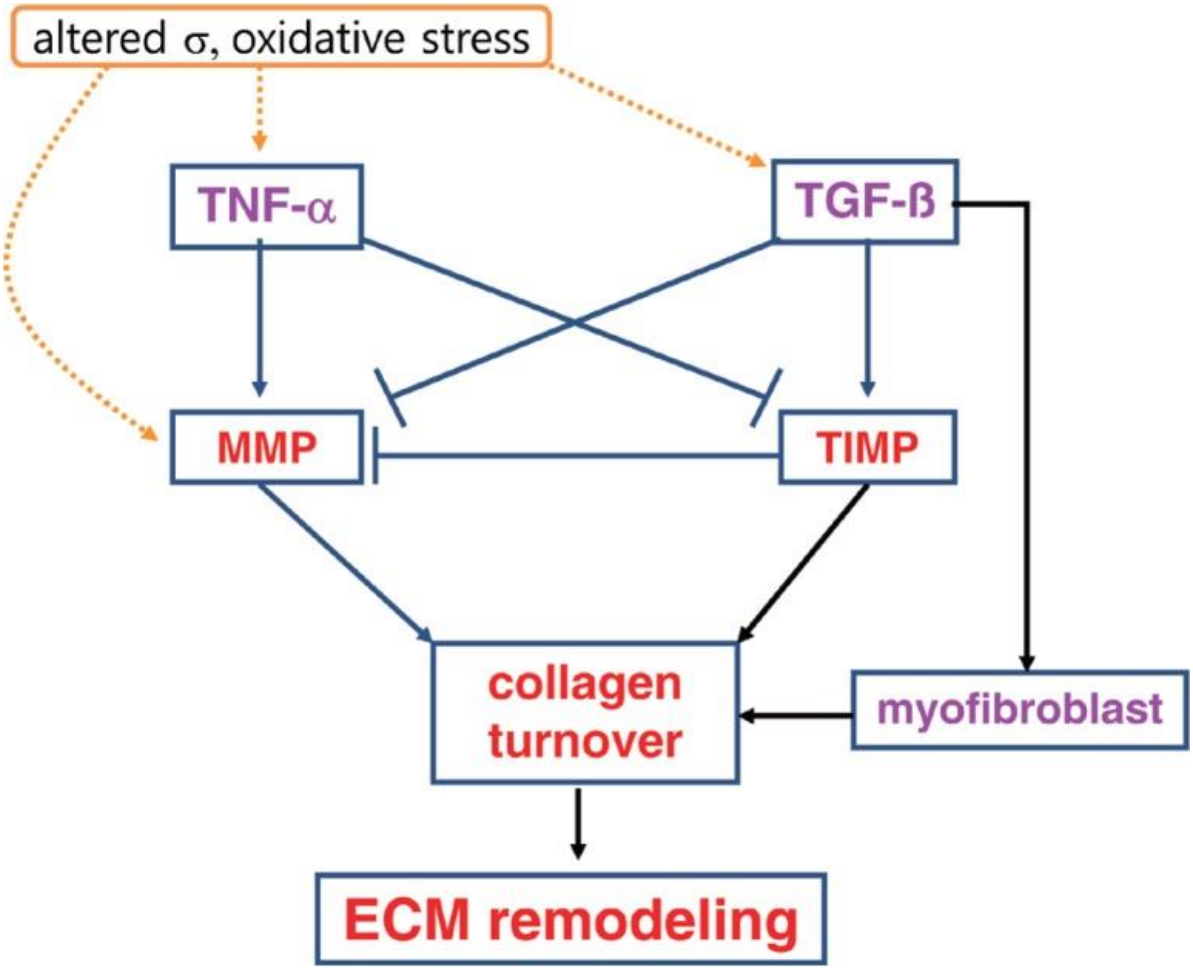

Figure 2. Mechanism of ECM remodelling in cardiac tissue by MMP activation (Kwak, 2013).

CONCLUSION

Myocardial cells are enmeshed within a network of ECM that is important to maintain cardiac structural integrity and function by providing a delicate scaffold. Following cardiac injury, there will be changes in cardiac pro-inflammatory cytokines profile due to inflammation.

These may cause higher expression in MMP. Higher MMP with decreased levels of TIMP will contribute to collagen degradation in ECM. It is essential to understand the pathological pathway related to MMP-related degradation of ECM.

CONFLICT OF INTEREST

The authors declare there is no competing interests

FUNDING

None to declare

AUTHOR CONTRIBUTION

SL and BS designed the article and contributed in the revision, supervision, and approval of the manuscript. RHS performed the literature research and drafted the manuscript. All authors approved the final manuscript.

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