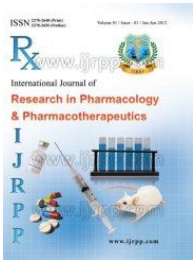
International Journal of Research in Pharmacology & Pharmacotherapeutics



ISSN Print: 2278-2648 ***IJRPP |Vol.9 | Issue 1 | Jan - Mar - 2020***
ISSN Online: 2278-2656 ***Journal Home page: www.ijrpp.com***

Review article ***Open Access***

Several pathways involved in cardiac fibrosis which helps to discover better treatment

Vishwadeep Madhukar Shelke*, Dr. Ghanshyam Balakrishna Jadhav, Govind Radhakrishna Garad

Department of Pharmacology, MVP's College of Pharmacy, MVP Campus, Gangapur Road, Nashik, 422002, Affiliated to S.P. Pune University, (M.S.), and India.

***Corresponding author: Vishwadeep Madhukar Shelke**
Email: vishwadeepshelke@gmail.com

ABSTRACT

Cardiac fibrosis is abnormal accumulation of extracellular matrix and collagen in myocardial tissues. It is major reason of progression of heart failure, so its prevention and treatment is main aim for curing heart failure. The objective of this review is to discuss the pathways and several mechanisms at molecular level which may involve in cardiac fibrosis. Dynamic network of fibrillar collagen, glycoprotein, proteoglycans and other main bio molecules represents ECM, where its regulation controlled by various components synthesis and degradation. The collagen network gives Support and alignment of myocyte blood vessels and lymphatic vessels, relative to one another thereby preserving myocardial thickness and architecture. Some stem cells therapy helps in cardiac fibrosis. Ang II stimulation increases mRNA and protein expression by cardiomyocytes and cardiac fibroblasts. TGF-β with RAS system increases progression of cardiac fibrosis.

Keywords: Cardiac fibrosis, Extracellular matrix, Collagen, Phospholipase-D, TGFβ.

INTRODUCTION

Cardiovascular disease responsible for 31% of all deaths and also main reason of deaths throughout worldwide. Ischemia & IHD, end myocardial fibrosis are primary cause of heart disease. According to American heart association 7.0 million Americans >20 years of age self-report having stroke, where risk of atrial fibrillation recently has been estimated to be 1 in 3 whites & 1 in 5 blacks in United States [1]. Each year CVD cause 3.9 million deaths in European Union. Cardiac fibrosis is the major reason of progression of heart failure, so its prevention and treatment is main aim for curing heart failure [2]. The mechanism of cardiac fibrosis is under investigation because several signaling pathways are involved & still emerging. Where cardiac fibrosis classified in four groups

- Interstitial fibrosis
- Infiltrative fibrosis
- Replacement fibrosis
- Endomyocardial fibrosis

Fibrosis described as several myopathic diseases involving hypertrophy, ischemic, hypertensive, restrictive cardiomyopathy & also radiation induced cardiac myopathy. Cardiac fibrosis described to excess retention of extracellular matrix in cardiac muscles &possesses the structural as well as electrical changes that increase chances of Arrhythmia's, heart failure & ischemia in patients. Due to inappropriate proliferation of fibroblasts there is increase in the thickening of heart valves [3]. Coxsackievirus (B3) (CVB3), Adenoviruses or Parvoviruses B19 or Protozoan, trypanosome, cruzi viral infection cause carditis by autoimmune responses against heart tissue antigens. The dynamic network of fibrillar collagen, glycoprotein, proteoglycans and other main bio molecules represents ECM, where its regulation controlled by various components synthesis and degradation [4]. Zinc dependent matrix metalloproteinase (MMP's) gives degradation of ECM which is a proteolytic enzyme.

According to evidences cardiac fibrosis associated with genetic cardiomyopathy not only in terms of cardiomyocyte injury phenomenon but also involved in pathological cardiac dysfunction [5]. The common cell events in fibrotic conditions are activation of cardiac fibroblasts. Pathophysiological uneasiness can trigger activation of fibrosis that changes ECM compositions and affect the function of cardiomyocyte [6]. All types of fibrosis results 45% all cause of human death and not any proper treatment available yet. The molecular and cellular events and must be light on to develop treatments for cardiac fibrosis. This review will focus on possible mechanisms which contribute cardiac fibrosis [7].

ASPECTS OF MYOCARDIAL FIBROSIS

Excess deposition of collagen type I and III fibers within myocardium interstitium relative to mass of cardiomyocyte defines myocardial fibrosis. On the basis of measuring purpose, it is characterized as increase in percentage of total myocardial tissue occupied by collagen fibers, denoted as collagen volume fraction (CVF) [8]. For normal systolic and diastolic function requires proper myocardial framework small change can disturb the ratio of synthesis and degradation of myocardial interstitium, where it shows functional abnormalities. Growth in deposition of collagen in perimysal and endomysial space gives rigid ventricles and change in diastolic function. Not only in the diastolic but also in systolic function can changed through several mechanisms.

- Co-ordination of myocardial excitation contraction coupling.
- Triggering micro vascular dysfunction
- Collagen deposition may activate

Protease-dependent pathway that degrade fibrillar collagen thus change balance between matrix and contractile apparatus. According some researchers salt, sex, pressure overload, harmones, vasoactive substance, genetic variation, cytokine and growth factors responsible for increase the collagen in fibrillar tissue can leads to the cardiac fibrosis [9].

POSSIBLE MECHANISM'S INVOLVED IN CARDIAC FIBROSIS

The possibility of producing cardiac fibrosis by mechanisms of inflammatory response, hormonal response any others always kept in considerations. Here some of them are discussed:

Collagen network

The synthesis and degradation of collagen continues cycle. Where the precursor of collagen is synthesized by fibroblast called pro-collagen [10]. This where transported from fibroblast to intercellular space, pro peptides at Amino and Carboxyl terminus of pro-collagen are cleaned and produce mature collagen. The degradation of mature collagen done by Matrix metalloproteinase's [MPP] that can be regulated by Tissue Inhibitors of Metalloproteinase's (TIMP's) [11, 12]. The rate of synthesis is 5% per day where similar amount is degraded daily. In diseased state of myocardium this balance between synthesis and degradation get changes so collagen deposition can occur [12].

The matrix metalloproteinase and myofibroblasts plays key role regarding collagen degradation and synthesis respectively. The matrix metalloproteinases [MPP] decreases degradation of collagen I and II. The degradation is necessary for cardiac myocyte slippage that leads to wall thinning and to muscle fibre alignment in direction [13]. This generally observed in humans dilated cardiomyopathy [14].

Where along with that cardiac fibrosis and myofibroblasts increases the synthesis of collagen I and II [15].

THE FUNCTIONS OF COLLAGEN NETWORK

- Prevention of muscle fibre and cardiac myocyte slippage.
- Support and alignment of myocyte blood vessels and lymphatic vessels, relative to one another thereby preserving myocardial thickness and architecture.
- Protections of myocyte from overstretch.
- Transduction of myocyte generated forces to ventricular chamber.
- Relengthaning of myocytes.
- Basis for diastolic myocardial stiffness [16].

This overall synergism gives stiffness into myocardial muscle and possesses hardness to left ventricle.

Due to the decrease in collagenase activity the pressure overload occur on left ventricle. These hemodynamic loads on left ventricle further leads to ventricular fibrosis. Type III collagen expression increase in patient suffers from cardiomyopathy [15].

Role of proginator cells in cardiac fibrosis

Some cells fighter recruited or residual to the myocardium is characterized as phenotypes, where others represented as progenitors. Some reports provides in vivo evidence CD116+ monocytes, CD133+ progenitor cells reveal strong immunosuppressive power and effectively attenuates EAM [17].

In mouse model of myocarditis, heart in filtering CD133+ progenitors for macrophages and myocarditis, fibroblasts [17]. Identification of bone marrow derived fibroblasts in fibrotic hearts further suggests the recruitment of progenitor cells with fibrogenic potential [18]. Thus, current evidence supports the view that progenitor cells differ into macrophages and fibroblasts but not cardiomyocytes in affected hearts. Also some stem cells therapy helps in cardiac fibrosis [19].

Phospholipase –D

According to some researchers role of PLD is important concern in cardiac fibrosis as PLD present in the synthesis of collagen and collagenase was tested in cultured fibroblasts by use of primary and secondary alcohols [20]. The presence of primary alcohol inhibits production of phosphatidic acid by PLD, progression of left ventricle fibrosis, consists collagen synthesis stimulation in fibroblasts by growth factors agonist binding G-protein receptor, where PLD is important component in that signalling platelet derived growth factor, epidermal growth factor oxidation stress also help to activation of PLD [21, 22]. A positive feedback provided by protein kinas C to PLD also increase chances of ventricular fibrosis [23, 24]. Phosphatidic acid is converted in 1, 2-diacylglycerol results activation of protein kinas-C, where, Phosphatidic acid involved in inducing signalling pathways present in inflammatory response [25, 26]. During congestive heart failure and myocardial infarction in scar tissue PLD, mRNA, protein activity level decreases. Where, inhibition of PLD activity shows reduction in left ventricular fibrosis which results improvement in cardiac function. Some agonists that activate PLD also stimulate the hydrolysis of PIP2 by PI-Phospholipase with subsequent production of diacylglycerol and activation of PLC [27].

So, PLD may contribute to pathogenesis of heart failure with ventricular fibrosis.

TGF-β

It is a pleotropic peptide. Its signalling pathways activation regulated by active TGF-β from complex present in most of the tissues [27]. Its dimeric complex consist C terminal mature TGF-β and N-terminal pro-domain LAP [TGF-β latency associated peptide] [28]. Following steps shows activation of complex.

TGF-β release which is bioactive requires proteolytic cleavage and separation of LAP from TGF-β

↓

Furin involved in processing of pro- TGF-β complex

↓

Now the complex can be activated. [29]

Separation of TGF-β from active LAP

Complex poorly known process TGF-β that involved Thrombospondin (TSP) 1 matricellular protein, where it's binding to LAP alters the conformation of TGF-β makes it component to receptor site. TGF-β regulate function of cell involved tissue injury, repair and remodelling depend on cytokine milieu effect of TGF-β on inflammatory leukocyte can be inhibitory or stimulatory [30]. It also modulates fibroblast phenotype and function [31]. Myofibroblast differentiation also induces by its stimulation and increase extracellular matrix protein synthesis [32]. Where, it also shows potent matrix-preserving action by suppressing the activity of metalloproteinases [MPP] and increase synthesis of protease inhibitors like TIMP's and PAI-1 [33, 34]. In concern of lymphocyte mainly possess proliferation and differentiation of lymphocytes.

RAS and TGF-β

Many reports of clinical trial show AT1 receptor blockade and ACE inhibition effects in patients having myocardial infarction and heart failure [35]. Evidence shows TGF-β1 acts downstream of Ang II [36]. Results from several clinical trials and animal studies on ACE inhibitors shows that Ang II has important role in regulation of growth of cardiac fibroblast and synthesis of extracellular matrix [37-39]. Ang II stimulation increases mRNA and protein expression by cardiomyocytes and cardiac fibroblasts. There are some evidence shows that Ang II contributes in cardiac fibrosis some of them are following

- Cardiac myocyte necrosis induced by exogenous or endogenous Ang II was accompanied by enhanced DNA synthesis and microscopic scarring [40].
- Rat model of myocardial infarction, ACE inhibitor provide collagen accumulation and DNA synthesis [41].
- In some model, early treatment with Losartan on AT1- Receptor blocker shows completely inhibited collagen deposition [42].

ACE inhibitors and AT1 blockers shows decrease levels of TGF-β1 in infarcted hearts. Schultz and co-workers shows that TGF-β1-/- mice breed in immune compromised RagI background protected from development of cardiac hypertrophy related to doses of Ang II [43]. That shows TGF-β1 acts on processing of Ang II to support cardiac growth. Sun et.al found that marked ACE binding within adventitia of intramyocardial coronary arteries and matrix of heart vehicle by using in vitro quantitative autoradiography together with iodinated derivative of Lisinopril (125I-351A) [44].

High density ACE binding was found in per vascular fibrosis which is present in scars tissue around the intramural coronary arterioles in both ventricles within 2 weeks of AngII administration [45, 46]. This scars tissue which appeared with high circulating levels of ACE and ALDO that also associate with ACE binding.

End MT

It represents the most important contributor to the generation of fibrotic tissue. Abnormal activation of EndMT in adults and its differentiation of fibroblast like cells to collagen producing myofibroblast play significant role in development and progression of fibrosis in heart and lungs [47, 48]. Endothelial cell disaggregation, morphologic change related to myofibroblast differentiation and gradual loss of endothelial markers like VE cadherin, VWF, CD31 helps to characterize EndMT. However, the molecular basis of TGF-β induced EndMT is poorly understood. To confirm transition of cardiac

endothelial cells to fibroblast like cells, Ghosh and co-workers exposes MCEC's to TGF-β2 for 7 days labelled with Dil-AC-LDL. There results shows that in absence of TGF-β2 cells were labelled with Dil-AC-LDL which shows MCEC's loss the endothelial property [47].

REFERENCES

[1]. Benjamin EJ, Muntner P, Bittencourt MS. Heart disease and stroke statistics update: a report from the American Heart Association. Circulation. 139(10), 2009, e56-28.

[2]. Gyöngyösi M, Winkler J, Ramos I, Do QT, Firat H, McDonald K, González A, Thum T, Díez J, Jaisser F, Pizard A. Myocardial fibrosis: biomedical research from bench to bedside. European journal of heart failure. 19(2), 2017, 177-91.

[3]. Hinderer S, Schenke-Layland K. Cardiac fibrosis–A short review of causes and therapeutic strategies. Advanced drug delivery reviews. 146, 2019, 77-82.

[4]. Kania G, Blyszczuk P, Eriksson U. Mechanisms of cardiac fibrosis in inflammatory heart disease. Trends in cardiovascular medicine. 19(8), 2009, 247-52.

[5]. Ho CY, Day SM, Ashley EA, Michels M, Pereira AC, Jacoby D, Cirino AL, Fox JC, Lakdawala NK, Ware JS, Caleshu CA. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). Circulation. 138(14), 2008, 1387-98.

[6]. Russo I, Frangogiannis NG. Diabetes-associated cardiac fibrosis: cellular effectors, molecular mechanisms and therapeutic opportunities. Journal of molecular and cellular cardiology. 90, 2016, 84-93.

[7]. Murtha LA, Schuliga MJ, Mabotuwana NS, Hardy SA, Waters DW, Burgess JK, Knight DA, Boyle AJ. The processes and mechanisms of cardiac and pulmonary fibrosis. Frontiers in physiology. 8, 2017, 777.

[8]. González A, Schelbert EB, Díez J, Butler J. Myocardial interstitial fibrosis in heart failure: biological and translational perspectives. Journal of the American College of Cardiology. 71(15), 2018, 1696-706.

[9]. Inagaki K, Iwanaga Y, Sarai N, Onozawa Y, Takenaka H, Mochly-Rosen D, Kihara Y. Tissue angiotensin II during progression or ventricular hypertrophy to heart failure in hypertensive rats; differential effects on PKCε and PKCβ. Journal of molecular and cellular cardiology. 34(10), 2002, 1377-85.

[10]. De Jong S, van Veen TA, de Bakker JM, Van Rijen HV. Monitoring cardiac fibrosis: a technical challenge. Netherlands Heart Journal. 20(1), 2012, 44-8.

[11]. van der Rest M, Garrone R. Collagen family of proteins. FASEB J. 5(13), 1991, 2814–23.

[12]. Weber KT, Sun Y, Katwa LC, Cleutjens JP, Zhou G. Connective Tissue and Repair in the Heart: Potential Regulatory Mechanisms a. Annals of the New York Academy of Sciences. 752(1), 1995, 286-99.

[13]. Weber KT. Shape and structure of the normal and failing human heart. Myocardial Hypertrophy and Failure. 7, 1983, 85-102.

[14]. Weber KT, Pick R, Janicki JS, Gadodia G, Lakier JB. Inadequate collagen tethers in dilated cardiopathy. The American heart journal. 116(6), 1988, 1641-6.

[15]. Kong P, Christia P, Frangogiannis NG. The pathogenesis of cardiac fibrosis. Cellular and molecular life sciences. 71(4), 2014, 549-74.

[16]. Weber KT, Sun Y, Tyagi SC, Cleutjens JP. Collagen network of the myocardium: function, structural remodeling and regulatory mechanisms. Journal of molecular and cellular cardiology. 26(3), 1994, 279-92.

[17]. Kania G, Blyszczuk P, Stein S, Valaperti A, Germano D, Dirnhofer S, Hunziker L, Matter CM, Eriksson U. Heart-Infiltrating Prominin-1+/CD133+ Progenitor cells represent the cellular source of transforming growth factor β–mediated cardiac fibrosis in experimental autoimmune myocarditis. Circulation research. 105(5), 2009, 462-70.

[18]. Möllmann H, Nef HM, Kostin S, von Kalle C, Pilz I, Weber M, Schaper J, Hamm CW, Elsässer A. Bone marrow-derived cells contribute to infarct remodelling. Cardiovascular research. 71(4), 2006, 661-71.

[19]. Segers VF, Lee RT. Stem-cell therapy for cardiac disease. Nature. 451(7181), 2008, 937-42.

[20]. Yamamoto K, Takahashi Y, Mano T, Sakata Y, Nishikawa N, Yoshida J, Oishi Y, Hori M, Miwa T, Inoue S, Masuyama T. N-Methylethanolamine attenuates cardiac fibrosis and improves diastolic function: inhibition of phospholipase D as a possible mechanism. European heart journal. 25(14), 2004, 1221-9.
[21]. Exton JH. Regulation of phospholipase D. Biochim Biophys Acta 1439, 1999, 121–33.
[22]. Corl CM, Cao YZ, Cohen ZS et al. Oxidant stress enhances Lyso-PAFAcT activity by modifying phospholipase D and phosphatidic acid in aortic endothelial cells. Biochem Biophys Res Commun 302, 2003, 610–4
[23]. Nishizuka Y. Intracellular signalling by hydrolysis of phospholipids and activation of protein kinase C. Science 258, 1992, 607–14
[24]. Eskildsen-Helmond YEG, Van Heugten HAA, Lamers JMJ. Regulation and functional significance of phospholipase D in myocardium. Mol Cell Biochem 157, 1996, 39–48.
[25]. Exton JH. New developments in phospholipase D. Journal of Biological Chemistry. 272(25), 1997, 15579-82.
[26]. Exton JH. Phospholipase D—structure, regulation and function. In Reviews of physiology, biochemistry and pharmacology. Springer, Berlin, Heidelberg. 2002, 1-94.
[27]. Dobaczewski M, Chen W, Frangogiannis NG. Transforming growth factor (TGF)-β signalling in cardiac remodeling. Journal of molecular and cellular cardiology. 51(4), 2011, 600-6.
[28]. Koli K, Saharinen J, Hyytiainen M, Penttinen C, Keski-Oja J. Latency, activation, and binding proteins of TGF-beta. Microsc Res Tech 52, 2001, 354–62.
[29]. Lyons RM, Keski-Oja J, Moses HL. Proteolytic activation of latent transforming growth factor-beta from fibroblast-conditioned medium. J Cell Biol 106, 1998, 1659–65.
[30]. Fan K, Ruan Q, Sensenbrenner L, Chen B. Transforming growth factor-beta 1 bifunctionally regulates murine macrophage proliferation. Blood 79, 1992, 1679–85.
[31]. Mauviel A. Transforming growth factor-beta: a key mediator of fibrosis. Meth Mol Med 117, 2005, 69–80.
[32]. Desmouliere A, Geinoz A, Gabbiani F, Gabbiani G. Transforming growth factor-beta 1 induces alpha-smooth muscle actin expression in granulation tissue myofibroblasts and in quiescent and growing cultured fibroblasts. J Cell Biol 122, 1993, 103–11.
[33]. Schiller M, Javelaud D, Mauviel A. TGF-beta-induced SMAD signaling and gene regulation: consequences for extracellular matrix remodeling and wound healing. J Dermatol Sci 35, 2004, 83–92.
[34]. Parker TG, Packer SE, Schneider MD. Peptide growth factors can provoke "fetal" contractile protein gene expression in rat cardiac myocytes. J Clin Invest 85, 1990, 507–14.
[35]. Pfeffer JM, Fischer TA, Pfeffer MA. Angiotensin-converting enzyme inhibition and ventricular remodeling after myocardial infarction. Annu Rev Physiol 57, 1995, 805–26.
[36]. Gray MO, Long CS, Kalinyak JE, Li HT, Karliner JS. Angiotensin II stimulates cardiac myocyte hypertrophy via paracrine release of TGF-beta 1 and endothelin-1 from fibroblasts. Cardiovasc Res 40, 1998, 352–63.
[37]. Brilla CC, Maisch B, Weber KT. Myocardial collagen matrix remodelling in arterial hypertension. Eur Heart J 13, 1992, 24-32.
[38]. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium: fibrosis and renin-angiotensin-aldosterone system. Circulation 83, 1991, 1849-65.
[39]. Lindpaintner K, Niedennaier N, Drexler H, Ganten D. Left ventricular remodelling after myocardial infarction: does the renin-angiotensin system play a role? J Cardiovasc Pharmacol 20(1), 1992, S41-s47.
[40]. Tan L-B, Jalil JE, Pick R, Janicki JS, Weber KT. Cardiac myocyte necrosis induced by angiotensin II. Circ Res 69, 1991, I185-95.
[41]. Van Krimpen C, Smits JFM, Cleutjens JPM, et al. DNA synthesis in the non-infarcted cardiac interstitium after coronary artery ligation in the mt: effects of captopril. J Mol Cell Cardiol 23, 1991, 1245-53.
[42]. Smits JFM, van Krimpen C, Shoemaker RG, Cleutjens JPM, Daemen MJAP. Angiotensin II receptor blockade after myocardial infarction in rats: effects on hemodynamics, myocardial DNA synthesis, and interstitial collagen content. J Cardiovasc Pharmacol 20, 1992, 772-8.

[43]. Schultz Jel J, Witt SA, Glascock BJ, Nieman ML, Reiser PJ, Nix SL, et al. TGF-beta1 mediates the hypertrophic cardiomyocyte growth induced by angiotensin II. J Clin Invest 109, 2002, 787–96.

[44]. Sun Y, Weber KT. Angiotensin II and aldosterone receptor binding in rat heart and kidney: response to chronic angiotensin II or aldosterone administration. The Journal of laboratory and clinical medicine. 122(4), 1993, 404-11.

[45]. Sun Y, Ratajska A, Zhou G, Weber KT. Angiotensin-converting enzyme and myocardial fibrosis in the rat receiving angiotensin II or aldosterone. The Journal of laboratory and clinical medicine. 122(4), 1993, 395-403.

[46]. Johnston CI, Mooser V, Sun Y, Fabris B. Changes in cardiac angiotensin converting enzyme after myocardial infarction and hypertrophy in rats. Clinical and experimental pharmacology and physiology. 18(2), 1991, 107-10.

[47]. Ghosh AK, Nagpal V, Covington JW, Michaels MA, Vaughan DE. Molecular basis of cardiac endothelial-to-mesenchymal transition (EndMT): differential expression of micro RNAs during EndMT. Cellular signalling. 24(5), 2012, 1031-6.

[48]. Arciniegas E, Frid MG, Douglas IS, Stenmark KR. Perspectives on endothelial-to-mesenchymal transition: potential contribution to vascular remodelling in chronic pulmonary hypertension. American Journal of Physiology-Lung Cellular and Molecular Physiology. 293(1), 2007, L1-8.