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Molecular mechanisms of myocardial remodeling

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ABSTRACT

Molecular mechanisms of myocardial remodeling involves rearrangement of normally existing structure of heart include size, geometry, shape, composition and function of the myocardium and heart. Myocardial remodeling occurs mainly due to physical, mechanical stimuli like cardiac overload, ischemia and stretch as well as at chemical level includes misbalancing of atrial natriuretic peptide, renin-angiotensin system, aldosterone, endothelin, nitric oxide production, catecholamine and TNF-α. Myocardial infarction, heart failure and other cardiac diseases are major causes of myocardial remodeling. Myocardial infarction at molecular level involves extracellular matrix (ECM) proteins, elevated peripheral blood mononuclear cell counts, muscle LIM(Lin11, Isl-1, Mec-3) protein-calcineurin signaling; late exercise effects on cardiac remodeling following myocardial infarction, influence of AIN-93(American Institute of Nutrition) diet with myocardial infarction are major factors responsible for pathogenesis of myocardial remodeling. Heart failure with adaptive versus maladaptive imbalance processes and neuro-hormonal imbalance activation are major causes of myocardial remodeling. Additional factors influence remodeling includes cardiac myocytes, fibroblast proliferation, collagen degradation and apoptosis. This review mainly focuses on pathophysiology involved in myocardial remodeling after myocardial infarction and heart failure as well as various effects of cardiac autocrines.

Keywords: Myocardial Remodeling, Cardiac Autocrines, Myocardial Infarction, Heart Failure, Cardiac myocytes proliferation.

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INTRODUCTION:

‘‘Remodeling’’ implies changes that result in rearrangement of normally existing structures. Myocardial remodeling concerns the two components of the cardiovascular system. The structure of both the myocardium and the vessels, including the coronary vessels, is indeed able to change under the influence of external factors, such as ischemia and mechanical overload. This review is focused on acquired cardiac remodeling (CR) of the left myocardium. Cardiac remodeling may be defined as changes in the size, geometry, shape, composition and function of the heart. This process occurs in response to several stimuli including pressure and volume overload, myocardial infarction and genetic alterations. Importantly, ventricular remodeling is now recognized as a significant pathological process that results in progressive ventricular dysfunction and cardiovascular death.[1, 2]

This review focuses also on permanent modifications in relation to clinical dysfunction in Myocardial Remodeling (MR) and correlation with various cardiac diseases like myocardial infarction (MI), Arterial hypertension, Heart failure, Cardiac Arrhythmia and senescent heart as well as correlation with various mediators involved in cardiac remodeling (CR).

Myocardial Thickness and Function

The thickness of the myocardium of the four chambers varies according to each chamber’s function. The thin-walled atria deliver blood under less pressure into the adjacent ventricles. Because the ventricles pump blood under higher pressure over greater distances, their walls is thicker (see Figure-1).

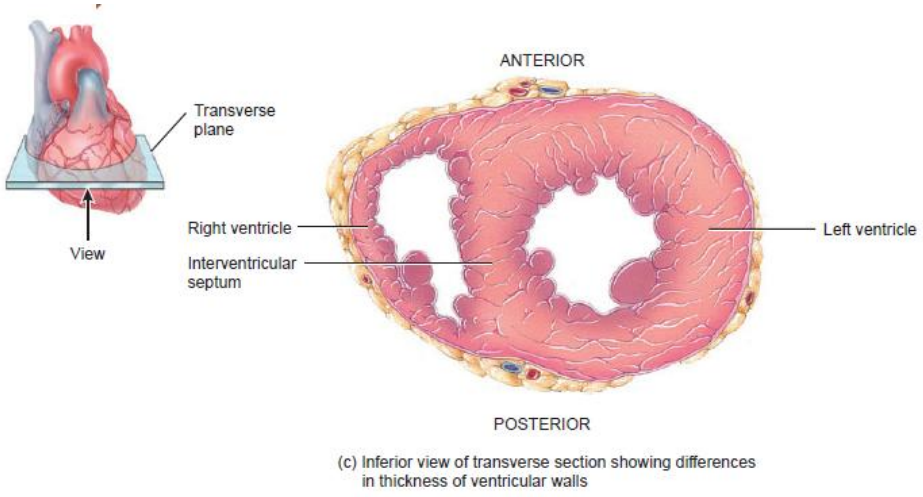

Figure 1: Transverse section of heart showing differences in thickness of heart walls

Although the right and left ventricles act as two separate pumps that simultaneously eject equal volumes of blood, the right side has a much smaller workload. It pumps blood short distance to

the lungs at lower pressure and the resistance to blood flow is small. The left ventricle pumps blood great distances to all other parts of the body at higher pressure, and the resistance to blood flow is larger. Therefore, the left ventricle works much harder than the right ventricle to maintain the same rate of blood flow. The anatomy of the two ventricles confirms this functional difference - the muscular wall of the left ventricle is considerably thicker than the wall of the right ventricle. Note also that the perimeter of the lumen (space) of the left ventricle is roughly circular in contrast to that of the right ventricle, the shape of which is crescent.[3] Clinical manifestations are, in fact, the result of changes to the heart's cellular and molecular components and to mediators that drive homeostatic control. There is general acceptance that as heart disease progresses into heart failure (HF), heart size increases and cardiac function deteriorates and symptoms of HF become evident.[4, 5] Although ''myocardial remodeling'' is now a widely used term, from a historical point of view it was initially used to describe the remodeling that occurs following myocardial infarction (MI). The meaning of the word was subsequently extended and used to qualify a variety of conditions including pure mechanical overload as well as hypertensive, valvular cardiopathy, familial hypertrophic and dilated cardiac myopathy.[6]

ETIOLOGY FOR MYOCARDIAL REMODELING

Transgenic manipulations as well as experimental or clinical hormonal intoxications (due to thyroxine, angiotensin II and aldosterone) are also able to remodel the myocardium. In general, myocardial remodeling is a reversible process provided the cause of the remodeling has been either suppressed or attenuated. This has considerable links to clinical and basic pharmacology and has been extensively reviewed recently. An epidemiological point of view, MI and arterial hypertension are both more frequent in aged persons. In addition, the structural modifications that are observed during senescence in healthy individuals has several points in common with the mechanically over loaded heart.[7] Myocardial remodeling is triggered by mechanical stretch; nevertheless, there are also several different factors including ischemia, hormones and vasoactive peptides, which can modify the effects of the mechanical factor. The most common clinical situation during which remodeling is known to occur is a rather complex mixture of ischemia, stretch due to pressure overload, stress due a myocardial scar and increased plasma levels of hormones or vasoactive peptides. An additional factor has to be listed, namely, the unknown signal that provides to the heart the information concerning the amount of substance that has been lost after MI and that is exactly recovered by the compensatory hypertrophy; such a signal should be similar to that occur after uninephrectomy, unipneumonectomy or partial hepatectomy.[8] The permanent changes in molecular structure and their consequences in terms of

cell physiology can be divided into three principal mechanisms: the deleterious consequences of the general process of adaptation, including cardiac hypertrophy, cell death and fibrosis. [9] Several etiological factors for myocardial remodeling are described below (see table-1).

Table 1: Etiological factors for myocardial remodeling[10]

Acquired Diseased Conditions	**Genetics**
Postmyocardial infarction	Inherited cardiomyopathies
Hypertensive cardiopathy	Familial hypertrophic cardiomyopathy
Myocarditis, Chagas disease	Dilated cardiomyopathy
valve and congenital disease	Marfan disease
Cardiomyocyte lengthening	Hemochromatose
Ventricular wall thins	Transgenic models of cardiac hypertrophy
Infarct expansion rather than extension occurs	Transgenic models of cardiac failure
Continued expansion of infarct zone	
Dilation and reshaping of the left ventricle	
Excessive accumulation of collagen in the cardiac interstitium	
Ongoing myocyte loss	
Myocyte hypertrophy	
Inflammation and reabsorption of necrotic tissue	
Miscellaneous	
Myocardial remodeling during senescence	Diabetes
Cardiac Remdeling owing to the rate	Salt, mineralo and glucocorticoid
Cardiac Remodeling using catecholamines, thyroxine	B6 vitamin deficiency
Atrophy due to heterotopic transplantation	Hypertrophy due to homeotopic transplantation

Myocardial remodeling is accompanied by an increase in Left Ventricular mass and volume and a change in the shape of the ventricle. If the process is triggered by MI, the remodeling is asymmetric and is associated with infarct expansion.[11] Progression of HF results in a process referred to as cardiac remodeling, characterized by changes in the shape and mass of the ventricles in response to tissue injury. The three primary manifestations of cardiac remodeling are chamber dilation, left ventricular cardiac muscle hypertrophy, and a resulting spherical shape of the left ventricular chamber (Figure) Cardiac remodeling, which starts months to years before the appearance of clinical symptoms, contributes to the progression of the disease despite treatment.[12] (See figure-2)

MOLECULAR MECHANISMS INVOLVED IN PATHOPHYSIOLOGY

Cardiac Autocrines:In Pathogenesis of Myocardail Remodeling: The Heart is an endocrine tissue and is able to produce artial natriuretic peptides, angiotensin II, and even, as recently shown, aldosterone and cathecholamines. Evidences proved that first two are activated during mechanical overloading and that cathecholamines cardiac stores are depleted.

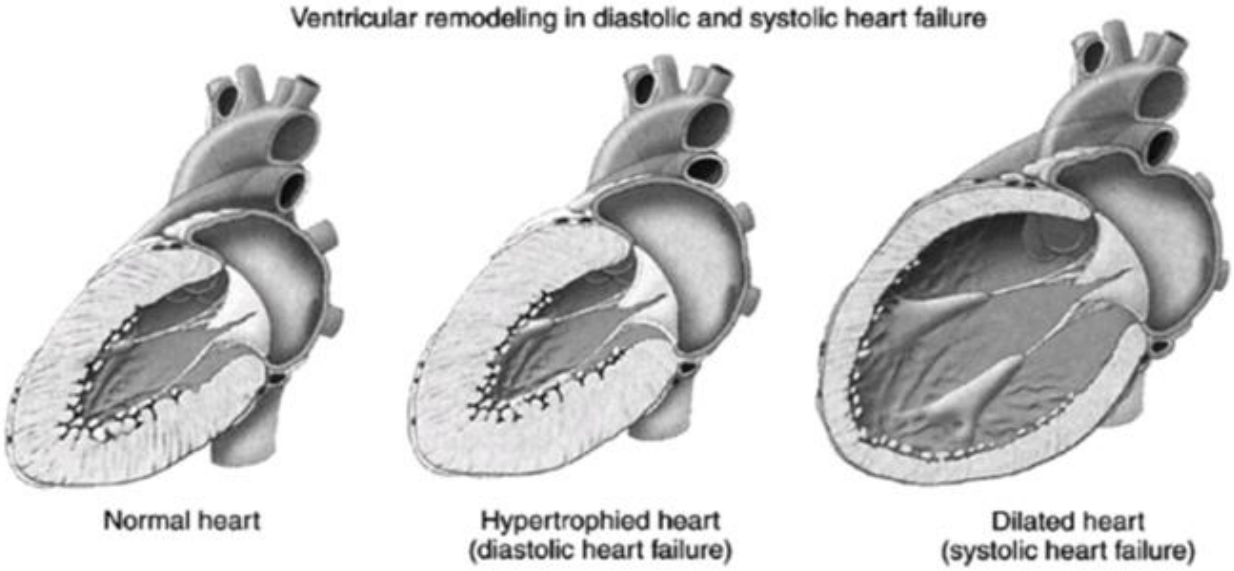

Figure 2: Ventricular remodeling in diastolic and systolic heart failure

1. Atrial natriuretic peptides/factors

Atrial natriuretic peptides/factors (ANP/ANF) mainly involved in overloaded ventricles in various experimental models of cardiac overload are mainly responsible for myocardial remodeling in MI[13] and in CR in humans.[14] The ventricular expression of ANF, and of other natriuretic peptides (brain and C-type natriuretic peptides)[15], is actually considered to be the best biological marker of ventricular overload. It is associated with an increased atrial biosynthesis, with reduced intra-atrial storage and transit time, and increased secretion. The Golgi apparatus is denser, with many secretory granules. Atrial natriuretic factor interacts with particulate guanylate cyclase in target cells to produce cGMP both in vivo and in vitro; as a consequence, urinary cGMP can be considered as an easily measurable humoral second messenger of the ANF system.[13] The plasma levels of ANF and brain natri-uretic peptide were both elevated in patients with hypertrophic obstructive or nonobstructive cardiomyopathy, aortic stenosis, or arterial hypertension; nevertheless, a marked overexpression of the brain form seems a special feature of hypertrophic obstructive cardiomyopathy.[15]

2. Renin-angiotensin system

A major peripheral factor of adaptation to changes in hemodynamic conditions occurring during CF is the activation of the circulating renin-angiotensin system (RAS) and aldosterone production which both contribute to maintain a normal arterial pressure by increasing the peripheral resistance and plasma volume.[16] Tissue RAS has been demonstrated in both vessels[17] and myocardium.[18] In the heart, positive immuno-reactivity for angiotensinogen has been found predominantly in atria. The angiotensin converting enzyme (ACE), which is a membrane bound

protein, and renin have also been successfully evidenced in the myocardium, although renin is rare or even absent, in the ventricles. As a final result, isolated hearts produce angiotensinogen and angiotensin II. Isolated cardiocytes from rats express genes encoding the three components of RAS.[19] The myocardial RAS, including angiotensinogen and ACE, is activated by mechanical stretch due to aortic stenosisin rats, in the cardiomyopathic Syrian hamster, by volume overload in the dog, and also in the senescent left ventricle.[20] The activity of the ACE is increased by almost fourfold after thoracic aortic stenosis in rats.[21] Hypertrophied cardiocytes have been isolated from the failing myocardium 7 days after coronary artery narrowing and have been found to contain more renin, angiotensinogen, ACE, as well as angiotensin I and II than controls. Direct assessment of angiotensin I and II levels in canine myocardial interstitial fluid were obtained by using microdialysis probes and showed levels 100-fold higher than plasma levels that are not affected by intravenous injection of angiotensin II, suggesting that angiotensin II production or degradation in the heart is compartmentalized and medicated by different mechanism than in intravascular spaces.[20]

3. Aldosterone

Aldosterone is mainly secreted by the adrenal cortex, but there is now evidence that aldosterone can also be synthesized and regulated in the myocardium. It is as yet not known if the myocardial aldosterone system is modified during CR.[22]

4. Endothelin

Endothelin-1 is a potent vasoconstrictor and mitogenic peptide whose plasma level is elevated in CF. Selective and nonselective endothelin receptor antagonist compounds are currently being evaluated and may be therapeutically useful in CF. Endothelin-1 and preproendothelin-1 mRNA were detectable in normal heart and lungs and were significantly increased in several experimental models of CF, including a canine model with a low cardiac output[23] and the rat model of MI.[24] In humans, the elevation of plasma endothelin-1 became significant in patients with moderate Cardiac Failure (New York Heart Association class III and IV); nevertheless, as yet, there is no clear evidence of a stimulation of the myocardial production of the peptide in the failing human heart.[25]

5. Nitric oxide production:

In normal conditions, optimal circulatory homeostasis ventricle sis is achieved by a delicate balance of vasodilator and vasoconstrictor mechanisms that is modified in congestive CF. It has recently been shown that nitric oxide (NO) plays an important role in this type of regulation. The cardiac autocrine function undoubtedly plays a role in this delicate peripheral adaptation

procedure. Basal circulating NO levels nearly double in idiopathic dilated cardiomyopathy;[26] in contrast, the capacity of the endothelium to release NO on stimulation is reduced.[27, 28] Nitric oxide can be generated by three different isoforms of NO synthase (NOS): brain NOS, endothelial constitutive NOS (ecNOS), and inducible NOS (iNOS). The iNOS mRNA and protein are not present in the normal human heart, but they are co-expressed with ANF in the myocardium of patients with both mild and severe CF, independent of the cause, which raises the possibility that autocrine and paracrine actions of iNOS may be of physiopathological importance.[29]

6. Catecholamines

Both plasma and urinary catecholamines increase in proportion to the severity of CF as a consequence of the hemodynamic deficit. [30] Norepinephrine stores are depleted in every kind of decompensated cardiac hypertrophy.[31] Comparable results were obtained in models of CCH which cardiac hypertrophy was obtained acutely in such models, myocardial catecholamines were depleted, and this was associated with reduction in the activity of tyrosine hydroxylase, the rate-limiting enzyme in the synthetic pathway for catecholamines, and with a defect in the reuptake mechanism.[32]

7. TNF-α

Tumor necrosis factor-α (TNF-α) is a pro-inflammatory cytokine that has cytolytic effect and produces negative inotropic effects by binding to TNF receptors types 1 and 2. The TNF-α mRNA and protein are present in the heart, and their level increases in CF. Two TNF receptors subtypes are present both in the heart and plasma. Cardiac receptors are down regulated in dilated and ischemic cardiomyopathy; in contrast, soluble receptors of the plasma increase.[33, 34] The plasma level of both TNF-α and interleukin-6 is normal in patients with compensated hypertrophy and enhanced in advanced congestive CF.[35] In such patients, the elevated plasma TNF-α is not directly related to the degree of cachexia, since high circulating TNF-α was also found in noncachectic(Having not cachexia) patients and had no real prognostic significance.[36] Cardiac cachexia is more likely to be the result of the overall neurohormonal activation than from one specific factor.[37] Overexpression of TNF-α in the heart using transgenic technology leads to severe myocarditis and cardiomegaly, strongly suggesting that such a cytokine actively participates in end-terminal myocardial deterioration.[38]

Myocardial remodeling after myocardial infarction

With the growth of the elderly population and westernization of eating habits, the number of patients with ischemic heart disease continues to increase in the developed world. In the Unites

States alone, about 8 million people have myocardial infarction (MI) every year and almost 30% of those are reported to die.[39] After onset of MI, the left ventricle (LV) undergoes a continuum of molecular, cellular and extracellular responses that result in LV wall thinning, dilatation and dysfunction.[40] If the cardiac healing does not proceed properly after MI, it could lead to cardiac rupture or maladaptive cardiac remodeling, such as further LV dilatation and dysfunction, and ultimately death.[41] In general, the cardiac healing process after MI can be divided into four phases: (a) Death of cardiomyocytes; (b) Inflammatory phase, which features monocyte and lymphocyte migration into the necrotic myocardium for the removal of dead cardiomyocytes; (c) Formation of granulation tissue, which is characterized by the presence of fibroblasts, macrophages, myofibroblasts, new blood vessels, and extracellular matrix (ECM) proteins; and (d) scar formation, which is characterized by a cellular and cross-linked collagen rich regions.[42]

1. Extracellular matrix (ECM) proteins

The ECM is now proven to be a dynamic structure that is continually remodelingin response to various stimuli. Alterations in the composition of the ECM provide signals to adjacent cells via cell surface receptors. Thus, interaction of ECM with cells via cell surface receptors such as integrin regulates cellshape, proliferation, intracellular signaling and differentiation, which are critical for maintaining normal tissue function and wound healing.[43] The components of ECM include basic structural proteins such as collagen, elastin and specialized proteins such as fibronectin, proteoglycans and matricellular proteins. Matricellular proteins are a class of non-structural and secreted proteins that probably exert regulatory functions through direct binding to cell surface receptors, other matrix proteins and soluble extracellular factors such as growth factors and cytokines.[44] Matricellular proteins include osteopontin (OPN), thrombospondin-1/2 (TSP-1/2), tenascin-C/X (TNC/TNX), periostin and secreted protein, rich in cysteine; also known as osteonectin (SPARC), and are abundantly expressed during development, while in adults, their production is mainly restricted to wound healing and tissue remodeling[45] (see figure-3). Many studies have been done to investigate the role of matricellular proteins during MI, utilizing matricellular protein gene-deficient mice.[46]

2. Elevated peripheral blood mononuclear cell counts

Peripheral blood mononuclear cells (PBMCs), defined as monocytes plus lymphocytes, are prevalent within the necrotic myocardium after the onset of AMI. Monocytes and macrophages are thought to be major sources of proinflammatory cytokines [47] and matrix metalloproteinases.[48] The expression of these cytokines and matrix metalloproteinases by monocytes are enhanced by

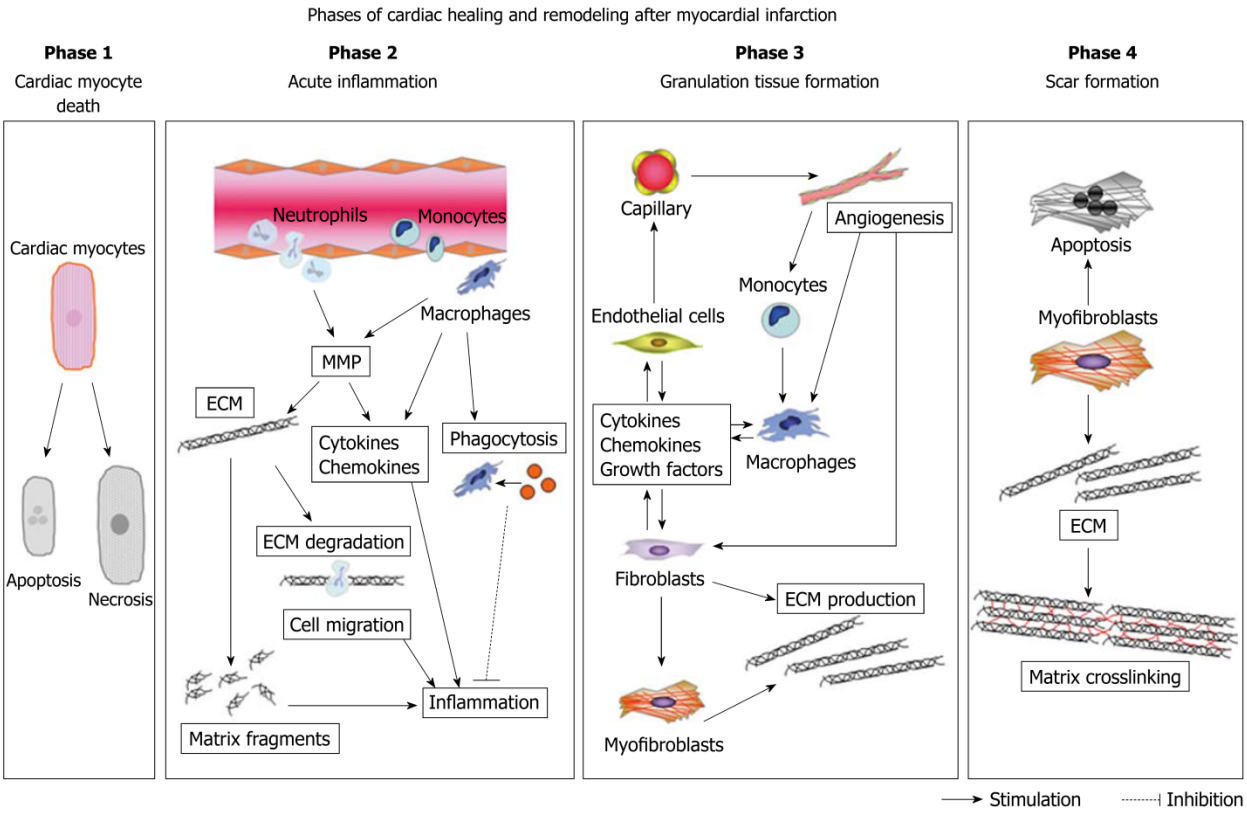

Figure 3: Phase of cardiac healing and remodeling after myocardial infarction.

interferons, which is produced by T lymphocytes or by direct contact of monocytes with T-lymphocytes.[49] Therefore, both monocytes and lymphocytes may play a pivotal role in ventricular remodeling after Acute Myocardial Infraction. Many epidemiological studies have shown an elevated peripheral white blood cell (WBC) count is associated with LV remodeling.[50] The PBMC count may be more closely associated with LV remodeling after AMI than the WBC count. After the onset of AMI, inflammation is initiated from the infiltration of monocytes and lymphocytes from the circulating blood to the infarct region, followed by infiltration of neutrophils.[51] Monocytes in the peripheral blood might be maximized at 2 or 3 days after the onset of AMI[52] and some of these infiltrate to the infarct region, then differentiate to macrophages and stay for several weeks. Macrophages phagocytize necrotic tissues and produce matrix metalloproteinase, which degrade the extracellular matrix. They also excrete inflammatory cytokines such as tumor necrosis factor-α and interleukin-6. Tumor necrosis factor-α induces apoptosis of myocytes in the acute phase and enhances matrix metalloproteinase production and activation, resulting in weakening and expanding of the infarct region in the acute phase and global LV dilatation in the late phase.[53] Lymphocytes also infiltrate the infarct regionand mediate myocardial injury in-vitro.[54]

3. Muscle LIM(Lin11, **I**sl-1, **M**ec-3)**protein-calcineurin signaling at the sarcomeric Z-disc**

LIM domains are protein structural domains, composed of two contiguous zinc finger domains, separated by a two-amino acid residue hydrophobic linker.[55] They are named after their initial discovery in the proteins Lin11, Isl-1 & Mec-3. LIM-domain containing proteins have been shown to play roles in cytoskeletal organization, organ development and oncogenesis.[56] LIM-domains mediate protein: protein interactions that are critical to cellular processes. MI induces profound alterations of left ventricular (LV) architecture with scar formation, ventricular dilatation and hypertrophy of the noninfarcted (remote) myocardium. Biomechanical stress and humoral growth factors are important mediators of this remodeling process. At the level of the single cardiomyocyte, post-MI LV remodeling is characterized by increases in cell diameter and cell length andalterations in gene expression levels.[57] The Z-disk is a multiprotein complex located at the interface of the cytoskeleton, the contractile apparatus, and the sarcolemma in cardiomyocytes.[58] Muscle LIM protein (MLP), which is tethered to the Z-disk via its interacting partners, α-actinin and telethonin, has been proposed to be an essential part of the mechanical stretch sensor machinery[59] and to be involved in the transmission of humoral growth signals in cardiomyocytes.[60] Intriguingly, myocardial MLP levels are reduced by nearly 50% in patients with heart failure after MI.[61] However, the functional significance of this observation is not clear.[62] Moreover, the downstream effector pathways activated by MLP have remained elusive. Interestingly, the Ca^{+2}/calmodulin dependent phosphatase calcineurin, which has a major impact on cardiomyocyte growth and gene expression by promoting dephosphorylation and nuclear translocation of nuclear factor of activated T cells (NFAT) transcription factors[63], forms a trimeric complex with α-actinin and calsarcin-1 at the Z-disk, suggesting a close proximity between MLP and calcineurin.[64]

4. Late exercise effects on cardiac remodeling following myocardial infarction:

Exercise is one post-MI therapeutic option that has been evaluated in both humans and animal models, and has been shown to improve outcomes.[65] Previous studies have shown that exercise training post-MI has favorable effects on LV remodeling and improved LV functional capacity, ejection fraction, and early LV diastolic filling.[66] Furthermore, exercise increases antioxidant activity in the heart. Increased manganese superoxide dismutase in skeletal muscle has been strongly linked to exercise, but there are also reports that glutathione peroxidase and catalase are induced with exercise training.[67] While the effect of exercise on post-MI remodeling is complicated, not all patients seem to benefit equally from exercise post-MI and the effects appear to be context dependent. The timing of when to start the exercise regimen is

controversial, in part due to the different experimental designs used, which include different infarct size groups and different exercise programs that vary in mode (swimming v/s running), intensity, duration and the course of training.[68] Previously reported the cardio protective effects of exercise training post-MI specifically at the molecular and cellular level in rats, showing that early exercise training post-MI reduces the expression of endogenous tissue inhibitors of metalloproteinase (TIMPs) at the gene and protein levels, improves the balance between matrix metalloproteinase (MMPs) and TIMPs, lowers the expression of angiotensin converting enzyme (ACE) and angiotensin II receptor type I (AT1), significantly reduces total collagen content, and, importantly, improves post-MI LV function.[69] However, a proteomic evaluation of post-MI infarct tissue from exercised rats has not been made, to determine global changes in protein expression that result from exercise. Arvin Bansal et al[70] reported proteomic approach to identify proteins altered in the infarct region of post-MI rats following an endurance exercise regimen. The most significant findings of this study were: 1) LV function improved in the exercise group post-MI, even when exercise was initiated four weeks post-MI; 2) VDAC 2 decreased; and 3) and GPX 1 and MnSOD(Manganese Superoxide Dismutase) increased in the of the exercise group compared with the sedentary MI group.

5. Influence of AIN-93(American Institute of Nutrition) **diet on mortality and cardiac remodeling after myocardial infarction in rats**

The AIN-93 diet was proposed by the American Institute of Nutrition with the objective of standardizing studies in experimental nutrition. The intent of standardizing diets for laboratories was to reduce the variations inherent in cereal-based diets and facilitate interpretations of results from different laboratories.[71] However, the effects of AIN-93 diet on mortality, morphological and functional cardiac variables after myocardial infarction are unknown. The composition of diet is given below in table-2.

Myocardial remodeling after Heart Failure

Cardiac remodeling is generally accepted as a determinant of the clinical course of heart failure (HF) defined as genome expression resulting in molecular, cellular and interstitial changes and manifested clinically as changes in size, shape and function of the heart resulting from cardiac load or injury, cardiac remodeling is influenced by hemodynamic load, neurohormonal activation and other factors still under investigation.[72] Heart failure (HF) can no longer be considered a simple contractile disorder or a disease of the heart alone. Clinical manifestations are, in fact, the result of changes to the heart's cellular and molecular components and to mediators that drive homeostatic control. There is general acceptance that as heart disease progresses into HF, heart

Table 2: Composition of AIN-93 diet.

Diet constitutions.	Control	AIN-93
Boron (mg/kg)	14	6.0
Calcium (mg/kg)	16000	6000
Copper (mg/kg)	35	7
Chromium (mg/kg)	2.9	2.0
Cobalt (mg/kg)	1.4	0.01
Cadmium (mg/kg)	0.01	0.007
Lead (mg/kg)	0.1	0.1
Phosphorus (mg/kg)	9300	3500
Iron (mg/kg)	271	83
Manganese (mg/kg)	115	9.0
Magnesium (mg/kg)	290	500
Molybdenum (mg/kg)	2.0	0.02
Mercury	0.04	0.06
Níckel (mg/kg)	1.8	1.0
Sodium (mg/kg)	40000	36000
Potassium (mg/kg)	12000	4000
Selenium (mg/kg)	0.096	0.15
Silicon (mg/kg)	2.0	1.6
Zinc (mg/kg)	370	58
Carbohydrates (%)	68	64
Fat (%)	7.2	16.7
Protein (%)	24.8	19.3
Total energy, kcal/100g	383	427

size increases, and cardiac function deteriorates and symptoms of HF become evident. Although different terms have been used to describe it, cardiac remodeling encompasses many changes associated with progressive HF.[73] Therapeutic interventions aimed solely at correcting a low cardiac output or reduced blood flow, those offering symptomatic relief or improved cardiac emptying, do not necessarily slow HF progression or reduce mortality.[74] Cardiac remodeling is generally an adverse sign and is linked to HF progression. Patients with major remodeling demonstrate progressive worsening of cardiac function, and it may underlie a sizeable proportion of cardiovascular morbidity and mortality. Mechanisms other than remodeling can, however, also influence the course of heart disease, and disease progression may occur in other ways in the absence of cardiac remodeling.[75]

Adaptive versus maladaptive disease processes

Cardiac remodeling has been described as both an adaptive and a maladaptive process, with the adaptive component enabling the heart to maintain function in response to pressure or volume overloading in the acute phase of cardiac injury[76] reviewed by Sabbah and Goldstein.[77] Increments in load, such as those seen in mitral insufficiency, modulate remodeling of the ventricle to maintain forward flow, but often after cardiac injury (such as MI), continued

remodeling may not be necessary to maintain the integrity of the circulation. Under such circumstances, remodeling may be viewed as an adverse phenomenon that leads to progressive decompensation. Progressive remodeling, irrespective of the criteria used to measure it, can always be considered deleterious and is associated with a poor prognosis.[78, 79] There are no data to indicate when the transition from possible adaptive to maladaptive remodeling occurs or how this might be identified in patients. The occurrence of such a transition and its time course may be expected to vary greatly. However, once established beyond a certain phase, it is likely that remodeling actually contributes to HF progression. As a result of progressive ventricular dilation and insufficient development of reactive ventricular hypertrophy, global LV wall tension and stresses increase considerably during this period reviewed by Rumberger.[80]

Neurohormonal activation in HF

Neurohormonal activation in HF is known to mediate compensatory changes in response to falling cardiac output, but it is also a major component of disease progression and of the remodeling process. Plasma norepinephrine levels, reflecting increased adrenergic activation, are elevated in HF patients and relate to prognosis. Higher levels of circulating plasma norepinephrine correlate with a poorer long-term prognosis. Increased plasma or tissue levels of other neurohormones also occur in patients with LV dysfunction and in asymptomatic patient's post-MI without HF, with activation increasing further as overt HF ensues.[81, 82]

Additional factors that influence remodeling.

The effects on remodeling of factors other than those related specifically to the renin angiotensin system (RAS) and the sympathetic nervous system (SNS) are currently under investigation and include endothelin, cytokines (tumor necrosis factors TNF and interleukins) and nitric oxide (NO) production and oxidative stress. Endothelins are potent vasoconstrictor peptides, the levels of which are known to be elevated in HF. Endothelin blockade has been shown to be beneficial in animal models and patients with HF. Cytokines are proteins secreted by cells in response to a variety of stimuli including environmental stress. Circulating levels of the cytokine TNF-alpha are known to be raised in cachectic patients with chronic HF[83] Oxidative stress is the term used to describe an imbalance between production of oxygen free radicals and antioxidant defenses, the importance of which is increasingly emerging with respect to LV dysfunction and HF progression; reviewed by Ferrari, et al[84] Cell viability depends on a complex interaction of inducers and suppressors of apoptosis, which are susceptible to modulation by cytokines such as TNF-alpha. Cytokines indirectly increase apoptosis through their effect on the death domain within the cytoplasmic portion of the TNF receptor-1.[85, 86]

Cardiac myocytes

Myocytes and other cardiac cell types are believed to be fundamentally involved in the remodeling process. Of all cardiovascular wall components, myocytes have received much attention in view of their contractile activity and numeric contribution to heart mass. As the result of an insult, myocyte numbers decrease and surviving myocytes become elongated or hypertrophied as part of an initial compensatory process to maintain stroke volume after the loss of contractile tissue. The thickness of the ventricular wall also increases.[87]

The role of fibroblast proliferation

Both fibroblasts and endothelial cells are activated in response to an ischemic insult. In human and animal models, fibroblast stimulation increases collagen synthesis and causes fibrosis of both the infarcted and no infarcted regions of the ventricle, thus contributing to remodeling.[88]

The role of collagen degradation

The myocardium consists of myocytes tethered and supported by a connective tissue network composed largely of fibrillar collagen, which is synthesized and degraded by interstitial fibroblasts. Myocardial collagenase is thought to be an important proenzyme present in the inactive form in the ventricle. Its activation after myocardial injury contributes to an increase in chamber dimension in response to the distending pressure that is thought to be a possible cause of myocyteslippage, which some consider one contributor to chamber remodeling.[89]

The role of apoptosis

A working hypothesis for the role of apoptosis in HF is that progressive LV dysfunction occurs, in part, as a result of ongoing myocyte cell death.[90] The importance of this type of cell death in human cardiac remodeling is not yet firmly established, but it has been demonstrated to occur at an increased rate after injury due to ischemia, reperfusion and MI.[91] Apoptosis may be an important regulatory mechanism involved in the adaptive response to pressure overload in which initial apoptosis is linked to cardiac hypertrophy.[92]

CONCLUSION AND FUTURE ASPECTS

Molecular mechanisms of myocardial remodeling are useful in various horizons as like exact pathogenesis and targeted treatment of various cardiac diseases and myocardial remodeling. Atrial natriuretic peptides/factors (ANP/ANF), Renin inhibitors, ACE inhibitors, TNF-α inhibitors will be targets for treatment of myocardial remodeling. Extracellular matrix (ECM) proteins, matrix metalloproteinases, muscle LIM (Lin11, Isl-1, Mec-3) protein, exercise, diet,

fibroblast, diabetes treatment, salt, mineralocorticoids, glucocorticoid, B6 vitamins and thyroxin would become great therapeutic research era for myocardial remodeling in future.

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