A major role in cardiomyopathy biology essay

Science, Biology

the heart muscle characterized by cardiac dysfunction. Several miRNAs includingthose involved in heart development are found to be dysregulated in cardiomyopathy. These miRNAs act either directly or indirectly by controlling the genes involved innormal development and functioning of the heart. Indirectly it also targets modifiergenes and genes involved in signaling pathways. In this review, the miRNAs involvedin heart development, including dysregulation of miRNA which regulate various genes, modifiers and notch signaling pathway genes leading to cardiomyopathy arediscussed. A study of these miRNAs would give an insight into the mechanismsinvolved in the processes of heart development and disease. Apart from this, theinformation gathered from these studies would also generate suitable therapeutictargets in the form of antagomirs which are chemically engineered oligonucleotidesused for silencing miRNAs. MICRO RNA REGULATION DURING CARDIAC DEVELOPMENT ANDREMODELING IN CARDIOMYOPATHYAbstractmiRNAs have been found to play a major role in cardiomyopathy, which is a disease of the heartmuscle characterized by cardiac dysfunction. Several miRNAs including those involved in heartdevelopment are found to be dysregulated in cardiomyopathy. These miRNAs act either directlyor indirectly by controlling the genes involved in normal development and functioning of theheart. Indirectly it also targets modifier genes and genes involved in signaling pathways. In thisreview, the miRNAs involved in heart development, including dysregulation of miRNA whichregulate various genes, modifiers and notch signaling pathway genes leading to cardiomyopathyare discussed. A study of these miRNAs would give an insight into the mechanisms involved inthe processes of heart

development and disease. Apart from this, the information gathered fromthese studies would also generate suitable therapeutic targets in the form of antagomirs which arechemically engineered oligonucleotides used for silencing miRNAs. IntroductionCardiomyopathy is a disease of the heart muscle characterized by cardiac dysfunction, arrhythmia, heart failure and sudden death. It is a major cause of morbidity and mortalityworldwide. Cardiomyopathies can be classified into 2 major groups based on predominant organinvolvement: Primary cardiomyopathies (genetic, nongenetic, acquired) are those confined toheart muscle and Secondary cardiomyopathies which show pathological myocardial involvementas part of a large number and variety of generalized systemic (multiorgan) disorders (Elliott P etal., 2008 ; Barry J. M et al, 2006). ManuscriptmiRNAs have been found to play a major role in cardiomyopathy, which is a disease of the heartmuscle characterized by cardiac dysfunction. Several miRNAs including those involved in heartdevelopment are found to be dysregulated in cardiomyopathy. These miRNAs act either directlyor indirectly by controlling the genes involved in normal development and functioning of theheart. Indirectly it also targets modifier genes and genes involved in signaling pathways. In thisreview, the miRNAs involved in heart development, including dysregulation of miRNA whichregulate various genes, modifiers and notch signaling pathway genes leading to cardiomyopathyare discussed. A study of these miRNAs would give an insight into the mechanisms involved inthe processes of heart development and disease. Apart from this, the information gathered fromthese studies would also generate suitable therapeutic targets in the form of antagomirs which arechemically

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IntroductionCardiomyopathy is a disease of the heart muscle characterized by cardiac dysfunction, arrhythmia, heart failure and sudden death. It is a major cause of morbidity and mortalityworldwide. Cardiomyopathies can be classified into 2 major groups based on predominant organinvolvement: Primary cardiomyopathies (genetic, nongenetic, acquired) are those confined toheart muscle and Secondary cardiomyopathies which show pathological myocardial involvementas part of a large number and variety of generalized systemic (multiorgan) disorders (Elliott P etal., 2008 ; Barry J. M et al, 2006). It is also considered as a disease of sarcomere and cytoskeleton and recent studies have revealednew facets about the role of micro RNAs in cardiac development and remodeling. A growingbody of exciting evidence suggests that miRNAs are regulators of cardiovascular celldifferentiation, growth, proliferation, angiogenesis and apoptosis. It has provided glimpses ofundiscovered regulatory mechanisms and potential therapeutic targets for the treatment ofcardiomyopathies. miRNA, an endogenous ~22nt RNA, plays important regulatory roles in animals and plants. They cleave the target mRNA or translationally repress them. The first miRNA discovered, waslin-4 in C. elegans, which was found to produce a pair of short RNA transcripts that regulate thetiming of larval development by translational repression of lin-14, which encodes a nuclearprotein (Lee R. C et al. 1993). Since the discovery of let-7, thousands of miRNAs have beenidentified in organisms as diverse as viruses, worms, and primates through random cloning andsequencing or computational prediction. A hepta nucleotide sequence at the 5’ end of themiRNA is essential in the base pairing specificity with the

3’end of the mRNA (Gregory P. A., etal. 2008). Role of miRNA in heart development and function: Role of miRNAs in heart development was identified in Zebrafish and mice by targeting theDicer protein which is the main component of miRNA machinery. Zebrafish lacking maternaland endogenous Dicer exhibited heart developmental defects (Giraldez A. J et al. 2005 ; Wienholds E. et al. 2003). Cardiac-specific deletion of Dicer in mice resulted in pericardialedema and poorly developed ventricular myocardium resulting in embryonic lethality (Zhao Y. et al 2007). Adult mice lacking Dicer in the myocardium revealed high incidence of suddendeath, cardiac hypertrophy, reactivation of the fetal cardiac gene program (da Costa Martins P. Aet al 2008). Further studies also showed that additional miRNAs, miR1, miR133, miR1/133(bicistronic), miR21 and miR138 are involved in the regulation of heart development. miR-1/miR-133: The most abundant miRNA in cardiac myocytes and also the first miRNAimplicated in heart development was miR-1(Zhao Y. et al 2007). miR-1 and -133 are expressedin cardiac and skeletal muscles and are transcriptionally regulated by the myogenicdifferentiation factors MyoD, Mef2, and serum response factor (SRF) (Chen J. F et al 2008, Kwon C et al. 2005 ; Lagos-Quintana M et al 2001 ; Rao P. K et al 2006 ; Sokol N. S et al2005 ; Zhao Y et al 2005). Targeted deletion of the muscle-specific miRNA, miR-1-2, was found to cause ventricular septaldefects (VSD) in mice embryos resulting in immediate death and in some embryos it causedpericardial edema which contributes to embryonic mortality (Yu X et al 2008). In mice thatsurvived postnatally, some died within months due to rapid dilatation of the heart and ventriculardysfunction, while many others suffered sudden cardiac death

because of abnormalities incardiac conduction and repolarization. miR-1-2 also directly targets irx5, which is known torepress the potassium channel, Kcnd2, ensuring coordinated cardiac repolarization (Costantini D. L et al 2005). In adult miR-1-2 mutants, cardiomyocyte division continues postnatally due toabnormalities in cell-cycle leading to hyperplasia of the heart. miR-1 levels are low during cardiac development but seem to increase as developmentprogresses (Zhao Y et al 2005). In mice, overexpression of miR-1 under the control of themyosin heavy chain (MHC) promoter negatively regulates cardiac growth, partly by inhibitingimplicated in heart development was miR-1(Zhao Y. et al 2007). miR-1 and -133 are expressedin cardiac and skeletal muscles and are transcriptionally regulated by the myogenicdifferentiation factors MyoD, Mef2, and serum response factor (SRF) (Chen J. F et al 2008, Kwon C et al. 2005 ; Lagos-Quintana M et al 2001 ; Rao P. K et al 2006 ; Sokol N. S et al2005 ; Zhao Y et al 2005). Targeted deletion of the muscle-specific miRNA, miR-1-2, was found to cause ventricular septaldefects (VSD) in mice embryos resulting in immediate death and in some embryos it causedpericardial edema which contributes to embryonic mortality (Yu X et al 2008). In mice thatsurvived postnatally, some died within months due to rapid dilatation of the heart and ventriculardysfunction, while many others suffered sudden cardiac death because of abnormalities incardiac conduction and repolarization. miR-1-2 also directly targets irx5, which is known torepress the potassium channel, Kcnd2, ensuring coordinated cardiac repolarization (Costantini D. L et al 2005). In adult miR-1-2 mutants, cardiomyocyte division continues postnatally due toabnormalities in cell-cycle leading to hyperplasia of the

heart. miR-1 levels are low during cardiac development but seem to increase as developmentprogresses (Zhao Y et al 2005). In mice, overexpression of miR-1 under the control of themyosin heavy chain (MHC) promoter negatively regulates cardiac growth, partly by inhibitingtranslation of heart and neural crest derivative-2 protein, Hand2, which is involved in ventricularmyocyte expansion (Zhao Y et al 2005). In Drosophila, dmiR-1(miR-1 of drosophila) plays animportant role in differentiation of cardiac progenitor cells by targeting transcripts of delta, aligand involved in Notch signaling pathway, which regulates the expansion of cardiac andmuscle progenitor cells (Kwon C et al 2005). vaguely defined. This particular miRNA is stress induced and is a regulator of cardiac growth(Van Rooij E et al 2006). Hence its interaction with the HSP-70 gene family needs to beelucidated, as HSP is also a cardiac specific development gene. Sabatel et al(2011) showed thatover-expression of miR-21 reduced endothelial cell proliferation, migration, and tube formationby targeting RhoB, whereas knockdown of miR-21 led to an opposite effect (Sabatel C et al2011)miR-138: embryo, but within the zebrafish heart, it is specifically expressed in the ventricular chamber(Morton S. U et al 2008). Disruption of miR-138 function led to the expansion of theatrioventricular canal into the ventricle and failure of maturation of ventricular cardiomyocytes. It has thus been suggested that other region-specific miRNAs may reinforce known signaling andtranscriptional networks that establish patterns of gene expression throughout thedeveloping heart tube (Heitzler P. & Simpson P. 1991). Hence the relation between modifiergenes and miRs during embryogenesis needs to be substantiated. miRNA in cardiomyopathy and cardiac remodeling:

miRNA mediated gene repression is an important regulatory mechanism to modulatefundamental cellular processes such as the cell cycle, growth, proliferation, phenotype, death, which in turn have major influences on pathophysiological outcomes like cardiac fibrosis, hypertrophy, angiogenesis, and heart failure(Catalucci D et al 2009 ; Thum T et al 2007 ; ThumT et al 2008). Although miRNAs are highly expressed in heart, their role in heart diseasesespecially cardiomyopathies still remains unclear. Multiple aberrant miRNA expression is a remarkable characteristic of the hypertrophic heart (YCheng et al 2007). The dysregulation and the time course changes of these multiple aberrantlyexpressed miRNAs match the complex process of cardiac hypertrophy formation in whichseveral genes have been reported to be dysregulated (Dorn II G. W., Hahn H. S. 2004). Determining the effects of these dysregulated miRNAs in cardiac hypertrophy is the prerequisitefor a novel research on cardiomyopathy. It was reported that a cardiac-specific knockout of the Dicer gene leads to rapidly progressivedilated cardiomyopathy (DCM), heart failure, and postnatal lethality. Dicer expression decreasedin end-stage human DCM and heart failure. These findings suggest that Dicer function andmiRNAs play critical roles in normal cardiac function and heart diseases especially during heartfailure (Chen J. F et al 2008). miR-1/miR-133: miR-133 and miR-1 play critical roles in cardiac hypertrophy. In human andmouse models of cardiac hypertrophy, decreased expression of both miR-133 and miR-1 isreported. In vitro, overexpression of miR-133 or miR-1 inhibited cardiac hypertrophy. Incontrast, suppression of miR-133 induced hypertrophy. In vivo inhibition of miR-133 by a singleinfusion of an antagomir caused marked and sustained cardiac

hypertrophy. RhoA, a GDP-GTPexchange protein (regulator of cardiac hypertrophy); Cdc42, a signal transduction kinase(implicated in hypertrophy); and Nelf-A/WHSC2, a nuclear factor (involved in cardiogenesis)are all targets of miR-133 (Carè A et al 2007). When overexpressed in normal or infarcted rat hearts, miR-1 aggravates arrhythmogenesis andelimination of miR-1 by an antisense inhibitor relieved arrhythmogenesis. The target of miR-1was found to be gap junction protein a1 (GJA1) which encodes Cx43, the main cardiac gapjunction channel important for conductance in the ventricles (Luo X et al 2007) and potassiuminwardly-rectifying channel, subfamily J, member 2 (KCNJ2) (Yang B et al 2007). miR-21: Inhibition of miR-21 in neonatal rat cardiomyocytes by transfecting locked nucleic acid(LNA)-modified antisense oligonucleotides(miR-LNA) to miR-21 or miR-18b induced myocytehypertrophy while transfection of miR-21 and miR-18b duplexes slightly decreasedcardiomyocyte size and decreased hypertrophy thus suggesting their role in regulatingmouse models of cardiac hypertrophy, decreased expression of both miR-133 and miR-1 isreported. In vitro, overexpression of miR-133 or miR-1 inhibited cardiac hypertrophy. Incontrast, suppression of miR-133 induced hypertrophy. In vivo inhibition of miR-133 by a singleinfusion of an antagomir caused marked and sustained cardiac hypertrophy. RhoA, a GDP-GTPexchange protein (regulator of cardiac hypertrophy); Cdc42, a signal transduction kinase(implicated in hypertrophy); and Nelf-A/WHSC2, a nuclear factor (involved in cardiogenesis)are all targets of miR-133 (Carè A et al 2007). When overexpressed in normal or infarcted rat hearts, miR-1 aggravates

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cardiomyocytes occurred at 2 weeks of age, which later progressed to a dilated cardiac hypertrophic phenotype by 6 weeks of age thussuggesting the critical role played by miR-195 in cardiac remodeling (Van Rooij E et al 2006). miR-29: The miR-29 family, which is downregulated after myocardial infarction, inhibits theexpression of several collagens and extracellular matrix proteins, thereby contributing to scarformation and fibrosis, as seen in DCM, during heart failure. miR-208: miR-208 is required for the development of cardiac hypertrophy and myocardialfibrosis and it is also a positive regulator of MHC gene expression (van Rooij E et al 2007). expression of several collagens and extracellular matrix proteins, thereby contributing to scarformation and fibrosis, as seen in DCM, during heart failure. miR-208: miR-208 is required for the development of cardiac hypertrophy and myocardialfibrosis and it is also a positive regulator of MHC gene expression (van Rooij E et al 2007). Regulation of Modifiers by miRNAs: Stress is a major etiologic factor that may contribute to heart diseases. Stress overload can causetissue injury; cardiomyocyte death is considered an important cellular basis for stress-inducedinjury in cardiomyopathies (Feuerstein G. Z., Young P. R. 2000). miR-199 family is rapidlydownregulated in cardiac myocytes under hypoxic conditions, relieving the repression of sirtuin1 and hypoxia inducible factor 1-a in a model of hypoxia preconditioning. The miRNA thatrepeatedly showed dynamic regulation after cellular stress is miR-21, which promotes cardiachypertrophy and fibrosis in response to pressure overload (Rane S et al 2009). Under stress a change in expression of HSP70 in rat myocardium is observed. HSP70 protectscardiomyocyte from stress induced injury by inhibiting Fas-mediated

apoptosis (Basu N et al2001). The levels of miR-1 was found to increase significantly in response to oxidative stresswhich later reduced the levels of HSP70 favoring cardiomyocyte apoptosis, while decreasedlevels of miR-1 favored cardiomyocyte survival (Xu C et al 2007). The members of TGF-ß family have been found to have a cardioprotective role and are highlyinduced in affected hearts. Their putative roles during atherogenesis, infarct healing, cardiacrepair and left ventricular remodeling have been proposed (Os I et al 2002). miR24a andmiR34a seem to have a strong and specific regulatory effect on TGF ß while miR-373 and miR34bhave a constitutive role (Schultz N et al 2011). Stress is a major etiologic factor that may contribute to heart diseases. Stress overload can causetissue injury; cardiomyocyte death is considered an important cellular basis for stress-inducedinjury in cardiomyopathies (Feuerstein G. Z., Young P. R. 2000). miR-199 family is rapidlydownregulated in cardiac myocytes under hypoxic conditions, relieving the repression of sirtuin1 and hypoxia inducible factor 1-a in a model of hypoxia preconditioning. The miRNA thatrepeatedly showed dynamic regulation after cellular stress is miR-21, which promotes cardiachypertrophy and fibrosis in response to pressure overload (Rane S et al 2009). Under stress a change in expression of HSP70 in rat myocardium is observed. HSP70 protectscardiomyocyte from stress induced injury by inhibiting Fas-mediated apoptosis (Basu N et al2001). The levels of miR-1 was found to increase significantly in response to oxidative stresswhich later reduced the levels of HSP70 favoring cardiomyocyte apoptosis, while decreasedlevels of miR-1 favored cardiomyocyte survival (Xu C et al 2007). The members of TGF-ß family have been found to have a cardioprotective

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and vasculogenesis. Notch signaling is a highlyconserved and a complex mechanism initiated by the interaction of Notch receptors with theirUnderstanding complex diseases like cardiomyopathies not only requires identification of genesand upregulation/downregulation of miRNAs, but also of the proteins that are regulated andsignaling pathways that are affected by these miRNAs. Various intercellular signaling pathwayshave been implicated in the control of cardiogenesis viz. Notch signaling, FGF signaling, BMPsignaling, Wnt/b-catenin signaling, Wnt/JNK pathways etc. Notch signaling and cardiogenesis: Notch signaling mediates numerous developmental cell fate decisions in organisms ranging fromflies to humans, resulting in the generation of multiple cell types from equipotential precursors. Notch signaling is also involved in angiogenesis and vasculogenesis. Notch signaling is a highlyconserved and a complex mechanism initiated by the interaction of Notch receptors with theirligands both of which are transmembrane proteins whose extracellular domains are composed ofepidermal growth factor (EGF) like repeats (Eiraku M et al 2005). The Notch receptors includethe Notch1-4 in mammals and Notch in Drosophila. The Notch ligands include classical ligandssuch as Jagged –Jag1 and Jag2 -and Delta-like -DLL1, DLL3 and DLL4 -as well as severalatypical ligands DNER, F3/Contactin1, NB-3/Contactin6 and Delta-like 1 homologue. The Notch pathway is intricately involved in the development of the cardiovascular system. Oneof the major functions of Notch signaling is its ability to influence cell fate decisions duringdevelopment (Kwon C et al 2005). Several of the Notch pathway components have been linkedto the vascular system development, including Jagged1, Notch1, Notch2, Notch4

andpresenilin(Eiraku M et al 2005 ; Bray S. J et al 2008). It was reported that the Notch ligand andreceptor expression is restricted to either the endothelial or vascular SMC during different stagesof development. This is demonstrated by Notch1, Notch4 and Dll4 which are initially present inthe embryo in all blood cells and is later restricted to arteries. Similarly Notch2 expression isrestricted to the pulmonary artery (Bruckner K et al 2000). The epithelial-mesenchymaltransitions, a potential source of mesenchymal stem cells in the adult vasculature and cardiacvalves, may occur as a result of Notch activation by Jag1, which represses the activation of Wntpathway. Preferential expression of Jagged1 in the endothelial cells of injured blood vessels mayinduce high levels of Notch receptors in neighboring smooth muscle cells and reduce contactinhibition and cell adhesion through a reduction in cadherin levels indicating that Jagged1 maybe involved in the de-differentiation of vascular cells and the cellular proliferation phasecharacteristic for atherosclerosis (Ivey K. N et al 2008). It has been reported that constitutive activation of the Notch pathway significantly reducescardiac differentiation. The Notch1 receptor is responsible for the blockade of cardiogenesis. Notch1 also is involved in the suppression of catrdiomyocyte differentiation. It has also beenproposed that inhibition of cardiogenesis by Notch signalling is carried out by blockingmesodermal differentiation (Sethupathy P. Et al 2006). Hence Notch signaling pathway which isknown to influence cardiogenesis and heart development, in conjunction with miRNAs, needs tobe elucidated. Notch signalling and miRNA in cardiomyopathymiRNA regulation is essential for normal Notch signalling. Default repression by miRNAs doesnot necessarily have to target core

pathway components; it may be equally effective when itintercepts their transcriptional targets as shown by the default repression of the E (spl) andBearded (Brd) gene clusters whose activation is dependent on signalling by Notch in Drosophila. This is a highly redundant system, in which families of related miRNAs (miR-2, miR-4, miR-7, miR-11 and miR-79) promiscuously target a family of related mRNAs, preventing aberrantdeployment of Notch-mediated developmental programmes (Sabatel C et al 2011). Regulation ofthe expansion of cardiac and muscle progenitor cells is carried out by the notch ligand Delta, andthis is targeted for repression by dmiR-1 (Rao P. K et al 2006 ; Sethupathy P et al 2006 ; Zhao Yet al 2005). Several conserved putative miR-1-binding sites were found in the 3’-UTR of thegene encoding Delta (Artavanis-Tsakonas S et al 1999 ; Corbin V et al 1991 ; Heitzler P. &Simpson P. 1991). It was also found that miR-1 fine-tunes Notch ligand Delta that is criticallyinvolved in differentiation of cardiac and somatic muscle progenitors and targets a pathwaymiRNA regulation is essential for normal Notch signalling. Default repression by miRNAs doesnot necessarily have to target core pathway components; it may be equally effective when itintercepts their transcriptional targets as shown by the default repression of the E (spl) andBearded (Brd) gene clusters whose activation is dependent on signalling by Notch in Drosophila. This is a highly redundant system, in which families of related miRNAs (miR-2, miR-4, miR-7, miR-11 and miR-79) promiscuously target a family of related mRNAs, preventing aberrantdeployment of Notch-mediated developmental programmes (Sabatel C et al 2011). Regulation ofthe expansion of cardiac and muscle progenitor cells is carried out by the notch ligand Delta, andthis is targeted for

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Bodmer R. 2003). Hence miRs regulating the Notchsignaling pathway which is involved in cardiac development, differentiation and ultimatelycardiomyopathy, needs to be evaluated. ConclusionIn the preceding discussion, the involvement of miRNAs in regulating developmental processesin the heart and their involvement in cardiomyopathies via sarcomeric genes, modifiers andIn the preceding discussion, the involvement of miRNAs in regulating developmental processesin the heart and their involvement in cardiomyopathies via sarcomeric genes, modifiers andsignaling pathways such as the Notch pathway is reviewed. Mutations in sarcomeric genes arethe primary causatives of the disease, whereas the modifiers determine the severity. The miRNAs regulating these genes thus play an important role in development and disease. Theroles played by several miRNAs have been elucidated, but an in depth analysis of the miRNAs, and the genes that encode them and also the genes targeted by them is essential to bring forwardthe complex interplay that occurs during development and disease causation. Notch pathway isinvolved in the development of cardiovascular system, as it promotes cell proliferation andapoptosis. Many miRNA are known to regulate the Notch pathway and the dysregulation ofthese miRNA affects cell proliferation, differentiation, cardiac conduction, leading to cardiachypertrophy and arrhythmias. But the information available in this context is still obscure. Further studies are necessary to identify other miRNAs involved in regulation of notch pathway. A study of miRNAs would also give us potential therapeutic targets in the form of antagomirswhich are used for silencing miRNAs that are implicated in the manifestation

ofcardiomyopathies. Complete revelation of the roles played by miRNA may give crucial insightsinto many of the mysteries of the human heart.