Chapter

Animal Models of Cardiomyopathies

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Abstract

Cardiomyopathies are a heterogeneous group of disorders of heart muscle that ultimately result in congestive heart failure (CHF). Rapid progress in genetics as well as in molecular and cellular biology over the past three decades has greatly improved the understanding of pathogenic signaling pathways in inherited cardiomyopathies. This chapter will focus on animal models of different clinical forms of human cardiomyopathies with their summaries of triggered key molecules, and signaling pathways will be described.

Keywords: cardiomyopathy, heart failure, genetic mutation

1. From genetic abnormality to cardiomyopathy phenotype

It's widely accepted that inherited cardiomyopathies are a group of heterogeneous diseases of heart muscle resulting from genetic alterations in cardiac myocytes, the chief contractile cell type in the heart [1]. The genes encoding proteins that build muscle cytoskeleton and contractile apparatus are responsible for a cardiomyopathy phenotype with distinctive morpho-/histological cardiac remodeling [2]. Further, disruption of particular genetic and protein networks and pathways may intersect with other intracellular and intercellular pathways and disturbances in molecular signaling. Apoptosis, necrosis, autophagy, and metabolic and arrhythmogenic fluxes—which may present as the sole features or as overlapping signs of decompensated cardiac homeostasis—result in definitive forms of cardiac remodeling including fibrosis, cardiomyocyte hypertrophy, and atrophy. Typically, molecular signaling activates associated compensatory responses and cooperates with other modifiers such as genetic modifiers and environment, stress, or toxicity related that, in turn, may or may not influence the final cardiomyopathy phenotype. Alterations in cellular morphology and size, gene expression patterns, and metabolic shifts in cardiomyocytes initially compensate and maintain cardiac function in the subtle, preclinical stages of cardiomyopathy. Thus, inherited forms of cardiomyopathy, irrespective of the specific genetic or morpho-/clinical condition, may or may not present signs of a failing heart. Five types of inherited cardiomyopathies are distinguished based on clinical features: dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), arrhythmogenic ventricular cardiomyopathies (ACM), and left ventricular noncompaction cardiomyopathy (LVNC) [3] as demonstrated in **Table 1**. DCM is characterized by left ventricular (LV) dilation and systolic dysfunction; HCM is characterized by LV hypertrophy with diastolic dysfunction; and RCM is accompanied by increased stiffness of the myocardium and dilated atria due to

Types	Cause / Inheritance /Prevalence	Clinical symptoms	Pathology	Features
DCM	Mutations in cytoskeletal genes, autosomal dominant, X-chromosome linked, 1:2500	Progressive CHF, arrhythmia, heart block, thromboembolism, sudden death	LV and atrial dilation, systolic dysfunction, and normal LV thickness, large, distorted myocytes	Most common cause of heart transplant
HCM	Mutations in sarcomeric genes, autosomal dominant, 1/500	Mitral regurgitation, dyspnea, syncope, myocardial ischemia, arrhythmia, sudden cardiac death	LV hypertrophy, fibrosis, myocardial disarray, mitochondrial abnormalities, thrombosis and obliteration of small vessels	Most common cause of sudden cardiac death in young and CHF disability
RCM	Mutations in sarcomeric and cytoskeletal genes, autosomal dominant, very rare.	Fatigue, dyspnea, ascites, JDV, peripheral edema, hepatomegally no cardiomegaly or systolic dysfucntion	Increased stiffness of myocardium, no dilation, no hypertrophy, dilated atria	The worst prognosis and lowest survival compared to other cardiomyopathies
ACM	Mutations in desmosomal genes, Autosomal dominant, 1/1000-1500	Ventricular tachyarrhthmia, syncope, or cardiac arrest, RV or LV chamber dilation	Myocyte loss, regional fatty of fibrofatty tissue replacement in RV and LV, or both ventricles	most common cause of sudden death in competitive athletes in Italy
LVNC	Autosomal dominant, X-chromosome linked recessive, 1/2000	Non-compacted "spongy" appearance of LV myocardium	Deep intertrabecular recesses (sinusoids) in ventricular muscle walls	Associated with thromboemboli, arrhythmia, CHF and sudden death

Table 1.
Clinical types of inherited cardiomyopathy and specific hallmarks of different types of cardiomyopathy.

diastolic dysfunction without significant hypertrophy [4]. Frequent and often life-threatening arrhythmias and associated sudden cardiac death and progressive heart failure are the main hallmarks of ACMs [5], while myocardial hypertrabeculation, intertrabecular recesses, and thin compact LV wall are the characteristics of LVNC [6]. Sustained maladaptive remodeling due to pathologic genetic insult results in the development of decompensated cardiomyopathy when the failing heart is unable to keep up with the hemodynamic demands at all levels, from the molecule to the whole organism. When compensatory mechanisms fail, additional neuroendocrine signaling and other pathways are activated on an organ and whole organism level, leading to CHF. Cellular and molecular level alterations of end-stage cardiomyopathy and CHF respond to irreversible cardiac remodeling with significant changes in membrane ion currents and intracellular Ca^{2+} metabolism, fibrosis, hypertrophic or atrophic remodeling, and cell death. Cardiac function is significantly depressed with depleted contractile force development and slowed relaxation [7].

2. Animal models of human cardiomyopathies

Translational comparative animal research is of considerable value in inherited cardiomyopathies, because animal models enable to explore and investigate the cellular and molecular pathology originating from the initial genetic assault but also may closely recapitulate the effects of cardiac remodeling culminating into a specific cardiomyopathy type seen in humans. Animal models carrying human gene mutations may not present clinical phenotypic signs of cardiomyopathy resembling the human disease until adulthood, supporting a temporal mechanism by which chronically altered cellular responses and cardiac remodeling lead to the clinically relevant phenotype.

2.1 Naturally occurring animal models of cardiomyopathy

Naturally occurring cardiomyopathy among small and large animals is commonly observed in canine and feline species [8, 9]. HCM is a common disease in pet

cats, affecting 10–15% of the pet cat population [10], while DCM is more typical in dogs [11]. The similarity to human HCM or DCM, the rapid progression of disease, and the defined and readily determined endpoints of feline HCM or in canine DCM make them excellent natural models that are genotypically and phenotypically similar to human heart muscle disease [12]. The Maine Coon and Ragdoll cats are particularly valuable models of HCM associated with myosin binding protein C (*MyBP-C*) mutations and even higher disease incidence compared to the overall feline population [13, 14]. In canine, mutations in genes such as dystrophin (*DYST*) in German Shorthaired Pointers [15], desmin (*DES*) and α-actinin in the Doberman [16, 17], titin-cap (*TCAP*) in Irish Wolfhounds [18], and striatin in Boxers [19] were reported to be associated with DCM. In addition, many naturally occurring porcine HCM and DCM have been described offering the useful models for translational research [20–22].

2.2 Genetically engineered animal models of cardiomyopathy

Experimentally, numerous small and large animal models including fruit fly, fish, rodents, rabbit, canine, pig, and other species have been developed to discover pathogenetic mechanisms involved in cardiomyopathy in the research field [23–25]. Characterization of the mechanisms of cardiomyopathies using the study of animal models is challenging owing to the complexity of disease-causing mechanisms and modulators of pathology [25]. Moreover, animal models are successfully used for genome-wide screening, assessing of cardiac phenotypes and disease symptoms, genotype-phenotype association studies, and drug discovery and development assays. The accessibility of transgenic (TG), knockout (KO) and knock-in (KI) murine models has, however, been one of the most successful approaches for studying genetic cardiomyopathies [26]. With recent advances in CRISPR/Cas9 technology, researchers are able to achieve more effective and precise genome editing because of its simplicity, design, and efficiency over other traditional methods for genetic editing such as transgenesis and homologous recombination targeting techniques [27–29].

The lowest species that has typically been used for cardiomyopathy research is *Drosophila melanogaster* as a tool to study various developmental biological processes and mechanisms underlying congenital defects and inherited heart diseases [30, 31]. The *Drosophila* heart looks as a primitive linear tube similar to embryonic heart tube in vertebrates, and many heart development, function, and aging regulatory genes and networks such as NK-2, MEF2, GATA, Tbx, and Hand have been evolutionarily conserved. The conserved development of the heart in simple model organisms and vertebrates provides a unique ability to use many different animal models in cardiomyopathy research [32]. Important advantages of the use of animal models are the ability to manipulate gene expression and identify genes and mechanisms regulating heart development, cardiac pathology, and pathophysiology [33, 34]. Advanced systems to identify genes causing human cardiomyopathies such as UAS/GAL4 [35], techniques for accurate phenotyping of cardiac diseases such as optical coherence tomography [36], powerful electrophysiological, mechanical, and histological approaches to characterize heart development, cardiac tissue properties, and structure in the *Drosophila* heart have emerged as a pioneering model system in basic, genetic, and molecular studies of cardiac development, function, aging, and disease [37]. Numerous *Drosophila* models have been used to elucidate the pathophysiology of human HCM and DCM and other heart diseases, such as heart failure, cardiac tachycardia, atrial fibrillation, and congenital heart diseases [38–40].

The zebra fish (*Danio rerio*) model remains one of the most effective technologies for discovering and functional studying novel cardiomyopathy candidate

genes, especially the ability to use morpholino knockdown techniques in fish models [26, 41, 42]. Compared with other vertebrate models, the zebra fish embryos are transparent allowing genetic engineering approaches to apply fluorescent reporter transgenes with genetic fate mapping strategies combined with high-resolution, high-throughput microscopy imaging in vivo of the heart [43, 44]. The transparency of the embryos allows to observe fluorescent proteins that are expressed in various cell types of the cardiovascular system, and these research advances have opened avenues to improve our knowledge of regulatory mechanisms of cardiomyocyte and other cardiac cells' differentiation [45, 46], regeneration [44], morphogenesis [47], drug effects and toxicity [48], and gene regulation [49]. The advancement in high-speed video imaging and automated image analysis techniques including light sheet planar illumination microscopy not only allows to precisely monitor morphologic and functional characteristics such as heart rate, arrhythmias, and ejection fraction in zebrafish but also progresses our current understanding of the different types of cardiomyopathy.

Rodent models are the most used model species for cardiomyopathy research, including genetics, pharmacology, and long-term survival considering that rodents have a short gestation time, have the ability to be genetically manipulated to generate transgenic or mutant strains, and are easy to handle and house with low maintenance costs [24, 50]. In addition, a fact that mice have short life span allows investigators to generate genetic models in a shorter time period and follow the natural history of genetic diseases at an accelerated pace, enabling to rapidly launch proof-of-principle experiments and potentially translating and exploiting the results into human studies. Significant advantages to rodents as the species of choice can limit the murine data's applicability to human cardiovascular function; there are significant differences between the mouse models and human disease presentation [25]. Rodents are phylogenetically farthest distant from humans compared to other mammals, and some pathophysiological features of cardiomyopathy phenotypes and their response to environmental stress and treatments may not be reliable for human diseases [23].

The rabbit and pig experimental models of cardiomyopathy offer significant advantages for cardiovascular research [50]. Compared with the mouse, the larger size and slower heart rate of the rabbit and pigs are advantageous for physiological analyses such as echocardiography and cardiac catheterization.

2.2.1 Hypertrophic cardiomyopathy animal models

Animal models of HCM mostly carry human mutations in sarcomeric protein-encoding genes such as a-MHC, a-tropomyosin, troponins, myosin binding protein C (MyBP-C), and other genes shown in **Table 1** [51–55]. Many models carry cardiac-specific (CS) expression or ablation of the proteins of interest. These models have demonstrated that HCM mutations enhance contractile properties with increased force generation, ATP hydrolysis, and actin-myosin sliding velocity, showing that the hypertrophy is not a compensatory response to diminished contractile function [56–58]. Models of HCM also show abnormal Ca^{2+} cycling in cardiomyocytes before overt histopathologic changes occurred in the myocardium and delayed myocardial relaxation that occurs before the onset of hypertrophy, suggesting that diastolic dysfunction is a direct consequence of HCM mutations [59, 60]. Hearts from models of HCM progressively accumulate myocardial fibrosis in the same manner as human patients, and fibrosis is considered to be a cellular substrate for cardiac arrhythmias and sudden cardiac death in humans [61–63].

2.2.2 Dilated cardiomyopathy animal models

Animal models of DCM mostly resemble human mutations in genes encoding cytoskeletal, sarcomeric, and Z-disk proteins and present with ventricular dilation and thinning of the ventricular walls correlated with loss of heart muscle mass. In addition, functional changes in non-myocytes induce fibrotic scars that

Gene	Human phenotype	Animal model	Animal phenotype	Pathogenesis
a-MHC	HCM	murine TG R403Q [51]	HCM	myocyte disarray, fibrosis, atrial dilation
Caveolin3	HCM	murine KO [52]	HCM, DCM, cardiac dysfunction	ERK1/2 activation, Src signaling
Caveolin3	HCM	murine TG P104L [53]	HCM, enhanced contractility, apoptosis	nNOS production, altered endoplasmic reticulum (ER) stress response
Caveolin3	HCM	zebrafish KO [54]	cardiac edema	myoblast fusion defects
Titin	DCM, HCM	zebrafish [55]	cardiac edema, poor contraction	blockage of sarcomere assembly
Tropomyosin	HCM	murine TG E180G [56]	HCM, fibrosis and atrial enlargement	increased myofilament sensitivity to Ca^{2+}.
Tropomyosin	HCM	murine TG D175N [57]	HCM, contractility and relaxation reduction	thin filament enhanced Ca^{2+} sensitivity
Troponin T	CM	murine TG MyHC [58]	HCM, reduced number of myocytes	multiple cellular mechanisms
Troponin T	CM	murine TG R92Q [60]	mitochondrial pathology, diastolic dysfunction	induction of ANP and bMHC
Troponin T		zebrafish KO [64]	sarcomere loss and myocyte disarray	dysregulation of thin filament protein expression
Troponin I	HCM	murine TG R145G [65]	HCM, diastolic dysfunction, death.	increased Ca^{2+} sensitivity and hypercontractility
Troponin I	HCM	rabbit TG R145G [66]	HCM and Cx43 disorganization	altered fractal pattern of the repolarization phase
Troponin I	HCM	murine KO [67]	acute HF, shortened sarcomeres	reduced Ca^{2+} sensitivity, elevated resting tension
MyBPC	HCM	murine TG [68]	sarcomere disorganization	stable truncated protein
MyBPC		murine KO [69]	HCM, reduced myofilament stiffness	abnormal sarcomere shortening velocity
MyBPC	HCM	cat TG [70]	sarcomeric disorganization	
Myopalladin	DCM HCM	murine TG Y20C [63]	HCM and heart failure	desmin, DPS, Cx43 and vinculin disruption
CARP	HCM DCM	murine TG αMHC [62]	HCM in response to pressure overload stress	reduced TGF-β, ERK1/2, MEK and Smad3
CARP	HCM DCM	murine KO [71]	No cardiac phenotype	
Talin	HCM	murine CS-KO [61]	HCM, hypercontraction to pressure overload	blunted ERK1/2, p38, Akt, and Gsk3 after stress
SGLT1		Tg CS-siRNA KD [72]	HCM, HF	
Meox1		Tg CS [73]	HCM	
ROCK		murine KO [74]	HCM	re-activation of fetal gene expression
cMyBPC	CM	murine KO [75]	HCM	dysregulation of Xirp2 and Zbtb16
β-MHC		rabbit TG R403Q [76]	HCM	reduced rates of force development and relaxation
CSRP3	HCM	murine KI C58G [77]	HCM	protein depletion via Bag3 and proteasomal overload
MYH7	HCM	pig KI R723G [78]	HCM, HF	myocyte disarray and malformed nuclei
TNNT2		murine R92Q; E163R [79]	HCM	altered myofilament Ca^{2+} sensitivity
αMHC	HCM	murine Arg403Gln [80]	HCM	altered repolarizing voltage-gated K^+(Kv) current
ERBB2		murine Tg [81]	HCM, diastolic dysfunction	ErbB2 signaling

Table 2.
Animal models of hypertrophic cardiomyopathy [51–58, 60–81].

stiffen the heart tissue and impede normal cardiomyocyte contractility. Novel DCM mechanisms such as impaired Z-disk assembly, sensitivity to apoptosis and abnormalities in myofibrillogenesis under metabolic stress, protein folding, inhibition of protein aggregation, and degradation of misfolded proteins have been explored (**Table 2**).

Gene	Human phenotype	Animal model	Animal phenotype	Pathogenesis
Sarcoglycan (delta)	DCM	murine KO [82]	focal necrosis, fibrosis after stress	destabilization of dystrophin glycoprotein complex (DGC), membrane permeability defect, Ca^{2+} imbalance
Sarcoglycan (delta)	DCM	murine KI S151A [83]	mild DCM	
Sarcospan	DMD	murine KO [84]	progressive DMD, extensive degeneration and regeneration.	
Laminin-a2		murine KO [85]	DCM	disruption of extracellular matrix (ECM) - cytoskeleton connection
Dystrophin	XL-DCM	murine [86]	dilated ventricles	destabilization of DGC, sarcolemma-actin connection, Ca^{2+} alteration
Dystrophin	XL-DCM	zebrafish [87]	mutants are less active	
Dystrophin	XL-DCM	canine [88]	DMD and DCM phenotype	
Tropomyosin	DCM	murine KO [89]	homozygous null mice are embryonic lethal (E8-E11.5)	
Tropomyosin	DCM	murine TG E54K [90]	DCM, impaired cardiac function	decrease in Ca^{2+} sensitivity and tension generation
Desmin	DCM	murine TG R173del179 [91]	DCM, intra-sarcoplasmic granular aggregates	blunted response to beta-agonist stimulation
Desmin	DCM	zebrafish [92]	disorganized muscles, small larvae	vulnerability during eccentric work
Desmin	DCM	murine KO [93]	DCM, mitochondrial abnormalities, necrosis	multisystem disruption of muscle architecture
MLP	DCM	murine KO [94]	DCM with hypertrophy and heart failure	altered mechano-sensation
Nebulette	DCM	murine TG [95]	DCM, mitochondrial abnormalities	stretch induced alteration of Z-disk assembly
Nexilin	DCM	zebrafish [96]	Z-disk damage, heart failure	stretch induced Z-disk destabilization
Telethonin	DCM	murine KO [97]	heart failure following biomechanical stress	modulation of nuclear p53 turnover after stress
Telethonin	DCM	zebrafish [98]	deformed muscle structure and impaired swimming ability	disruption of sarcomere-T-tubules ILK
Cypher/ ZASP	DCM	murine KO [99]	DCM, Z disk disruption, muscle weakness	a-actinin or other Z-line components disruption
Filamin C	DCM	medaka zacrofish K1680X [100]	DCM, myocardial wall rupture	Disrupted structure of cardiac and skeletal muscles
Lamin A	DCM	murine KO N195K [101]	nucleo-cytoplasmic shuttling of Mlk1	modulation of actin polymerization via Mlk1
Lamin A	DCM	murine KO [102]	Cardiomyocyte degeneration and mineralization	emerin dislocation
αMHC-cre		CS-Cre [103]	DCM	activated p38, JNK, p53, Bax
Dhcr24 x cTnT R141W		Double Tg Dhcr24 x cTnT [104]	DCM	activation of PI3K/Akt/HKII pathway
MST1 x Gal3		murine TG x KO [105]	DCM, HF	dysregulated transcriptional signaling
MGAT1		CS KO [106]	DCM	altered Ca^{2+} handling
RBM20	DCM	murine KI S637A [107]	DCM	disturbed nuclear localization of RBM20
MLP x MYBPC3	Varied CMs	Double KO [108]	DCM	increased Ca^{2+} sensitivity
FXR1		CS-KO [109]	DCM	altered levels of FCR1
GSK-3β x cTnT		KO, DKO [110]	DCM, HF	myocardial fibrosis, and cardiomyocyte apoptosis
NEXN	DCM	KO [111]	DCM, EFE	collagen and elastin deposits
BIN1		CS-KO [112]	DCM	mislocalization of the Cav1.2

Table 3.
Animal models of dilated cardiomyopathy [82–112].

2.2.3 Restrictive cardiomyopathy animal models

RCM is the least common but most lethal form of cardiomyopathy where impaired ventricular relaxation due to increased stiffness of the myocardium and pressure in the ventricles overcomes the changes in myofibrillar arrangement and cardiomyocyte gross abnormalities [113]. Animal models carrying human RCM-associated mutations have also been generated to mimic human RCM phenotype. These mutations are identified mainly in sarcomeric protein-encoding genes such as troponins, myosin and MYPN (summarized in **Table 3**).

Gene	Human phenotype	Animal model	Animal phenotype	Pathogenesis
cTnI	CMs	murine KO [67]	shortened sarcomeres and elevated resting tension	reduced myofilament Ca^{2+} sensitivity
cTnI	RCM	murine Tg R193H [114]	RCM	increased Ca^{2+} sensitivity
cTnI	RCM	murine Tg R145W [115]	diastolic dysfunction	prolonged force and intracellular Ca^{2+} transients
MYPN	RCM	murine KI Q529X [116]	disrupted intercalated discs, heart failure	desmin, DSP, connexin43 and vinculin disruption
myosin		E143K [117]	RCM	

Table 4.
Animal models of restrictive cardiomyopathy [67, 114–117].

Gene	Human phenotype	Animal model	Animal phenotype	Pathogenesis
Cx43	ARVC	murine KO, CS-KO [120, 121]	conduction abnormalities	intercellular channels abnormalities in SA node and ventricular conduction cells
Cx43	ARVC	murine TG aMHC [122]	cono-truncal abnormalities	
DSP	ACM	murine KO [123]	RV dilation, apoptosis, necrosis, fibro-fatty infiltration	Cell-cell contact disruption
DSP	ACM	murine TG [124]		
PKP2	ACM	murine KO [125, 126]	embryonic lethality	
PKP2		zebrafish [127]	disruption of heart development	
DSC2	ACM	zebrafish [128]	contractile dysfunction	loss of desmosomal plaque and midlines
DSG2	ACM	murine TG N271S [119]	biventricular dilatation, arrhythmias, death	Necrosis, cell-cell contact disruption
DSG2	ACM	murine TG Q558* [129]	ACM, fibrosis	miR-708-5p, miR-217-5p, miR-499-5p
DSG2	ACM	murine KO, CS-KO [119, 130]	embryonic lethality	
DSG2	ACM	murine TG [131]	LV dilation and arrhythmias	Wnt/b-Cat signaling
JUP	ACM	zebrafish KO [132]	bradicardia, cardiac edema	
JUP	ACM	murine KO [133]	VT and RV dilation and dysfunction	
SCN5a	ACM	murine KI delQKP 1510-1512 [134]	ACM	increased Na+ current and SR Ca^{2+} load
miR-130a		murine TG [135]	ACM	reduction in DSC2 3UTR
LKB1		murine KO [136]	AF, LV dysfunction	inflammation, fibrosis, apoptosis and necrosis
JUP	ACM	zebrafish TG 2057del2 [137]	ACM	redistribution of JUP, Cx43, and Nav1.5
TMEM43	ACM	murine KO, KI S358L [138]	No phenotype	
TMEM43	ACM	murine KI S358L [139]	ACM	NF-κB-TGFβ pathways

Table 5.
Animal models of arrhythmogenic ventricular cardiomyopathy [119–139].

Gene	Human phenotype	Animal model	Animal phenotype	Pathogenesis
alpha-dystrobrevin	DMD, LVNC	murine KO	Muscle dystrophy, cardiomyopathy	Alteration in cyclic GMP levels
NKX2-5	CHD	murine KI R52G [141]	LVNC, atrial septal anomalies	cardiomyocyte differentiation and heart development
NKX2-5	CHD	inducible Cx40-cre ERT2 [142]	hypertrabeculation, heart failure	cardiomyocyte differentiation and heart development
Fkbp1a		murine KO [143]	DCM, VSD and LVNC	immunoregulation and protein folding and trafficking
Jarid2		murine KO [144]	VSD, LVNC, Double outlet RV	dysregulated embryogenesis
Mest		murine KO [145]	thickness and less dense compact myocardium	dysregulated embryogenesis
Mib1		murine KO [146]	LVNC	dysregulated Notch signaling
BRAF		murine KI Q241R [147]	embryonic/neonatal lethality, LVNC	
CASZ1		murine KO [148]	hypoplasia of myocardium, VSD	abnormal genes expression
ANT2		murine KO [149]	embryonic lethality, LVNC	failure in cardiac developmental
Daam1		murine KO [150]	VSD, LVNC, Double outlet RV	Wnt/PCP signaling
S1PR1		murine KO [151]	LVNC, VSD	S1P signaling
NUMB / NUMBL		murine KO [152]	LVNC	ERBB2, YAP1 STAT5 signaling
RLF		murine KO [153]	LVNC	NOTCH pathway
LRP2		murine KO [154]	LVNC, aortic arch and coronary artery anomalies, VSD	
SLC39A8		murine KO [155]	LVNC, ECM accumulation	decrease MTF1 activity
DTNA		murine Tg N49S [156]	DCM, LVNC, cardiac dysfunction	
SRC-1/3		murine KO [157]	LVNC	up-regulate cyclin E2, cyclin B1 and myocardin
INO80		murine KO [158]	LVNC, defect in coronary vessels	upregulation of E2F-activated genes a
Tafazzin (TAZ)	LVNC	murine KD [159]	Neonatal death, LVNC, VSD	Fatty acid metabolism

Table 6.
Animal models of left ventricular noncompaction cardiomyopathy [141–159].

2.2.4 Arrhythmogenic ventricular cardiomyopathy models

Many models of ARVC with mutations in genes encoding desmosomal (DSP, PKP, DSC, DSG, and JUP) and non-desmosomal (RYR2, TMEM43, and ZASP) proteins have been developed [118]. Structural and functional alterations include progressive, diffuse, or segmental loss of cardiomyocytes, probably due to cardiomyocyte apoptosis or necrosis, and replacement with fibrotic and adipose tissue (**Table 4**). Fibro-fatty tissue primarily is seen in the right ventricle (RV), with common LV involvement in later stages of the disease [119] (**Table 5**).

2.2.5 Left ventricular noncompaction cardiomyopathy models

Animal models of LVNC typically demonstrate a spongiform ventricular myocardium and deep trabeculations, and many reports suggested that LV trabeculation and compaction processes are two distinct but tightly interconnected morphogenetic events resulting in the development of a functionally proficient ventricular chamber wall [140]. Animal models exhibiting LVNC phenotypes and potential pathogenetic mechanisms are summarized in **Table 6**.

3. Conclusion

Advances in molecular and genetic techniques have vastly improved the understanding of molecular mechanisms responsible for cardiomyopathies and cardiac

dysfunction. The wide range of innovative technologies and techniques used in animal models in vivo has led to advances in our knowledge on the etiology, pathophysiology, and therapeutics of inherited cardiomyopathies. It is clear that mutant proteins in cardiomyocytes can perturb cardiac function whether the prime distress occurs in the contractile apparatus or neighboring cellular complexes, yet persistent cellular stress leads to tissue-, organ-, and organism-level pathology and pathophysiology. However, development and investigation of animal models are complex processes and the outcomes of which could be difficult to translate to humans due to differences in human and animal cardiovascular anatomy and physiology as well as differing pathophysiology of human cardiomyopathies and experimentally induced diseases in animals [160]. Therefore, the choice of appropriate animal model(s) for cardiomyopathy research should utterly rely on clinical knowledge of human cardiovascular diseases, proper research questions, sufficient number of study animals, and correct and relevant interpretation of results and outcomes in animals to human population. Although animal models of human cardiomyopathies often represent incomplete or inaccurate pathological and pathophysiological features seen in humans, the use of animal models not only has improved our knowledge on the etiology and mechanisms of cardiac muscle diseases and therapeutic interventions but also has greatly promoted an advancement in cardiac tissue engineering, induced pluripotent stem cells (iPSCs) technology, in silico and in vitro techniques, and preclinical assessment of drug discovery and development [161].

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