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Journal of Molecular and Cellular Cardiology 39 (2005) 581–593
Journal of Molecular and Cellular Cardiology
www.elsevier.com/locate/yjmcc

Review article

Genetic modification of the heart: Transgenic modification of cardiac lipid and carbohydrate utilization

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Received 1 February 2005; received in revised form 25 May 2005; accepted 8 July 2005

Available online 02 September 2005

Abstract

Many recent advances in cardiovascular research have been made possible by the use of transgenic technology. This review will discuss a number of mouse models where transgenic technology has been utilized to alter expression of genes involved in cardiac uptake and metabolism of either lipid or carbohydrate. Particular attention will be paid to the proteins which regulate (1) carbohydrate and lipid transport into cardiomyocytes and (2) the subsequent metabolic process which occur within the cytosol. These steps are important in determining substrate availability for mitochondrial oxidative metabolism. The heart relies predominantly on fatty acids as its major fuel supply, while glucose and lactate provide a small percentage. Under certain conditions, this balance becomes altered such that the heart relies more on glucose, as seen in pathological hypertrophy or may rely almost solely on fatty acids, as observed in cardiac tissue of animal models of diabetes. Initially this switch in metabolic substrate provides adequate energy to maintain normal cardiac function however with time diastolic dysfunction and cardiac failure often occur associated with depletion in high-energy phosphates. The creation of transgenic mice with altered expression of genes involved in carbohydrate and lipid metabolism have provided a unique insight into the fine balance which exits in the mouse heart to maintain energy status and cardiac function. The models discussed in this review define both transport and cytosolic metabolism of lipid and carbohydrate as key cellular processes in the regulation of cardiac function and the pathogenesis of cardiac disease.

Keywords: Metabolism; Diabetes; Failure; Function; Disease; Transgenic; Glucose; Fatty acids; Hypertrophy

1. Introduction

A number of myocardial pathologies such as hypertrophy, heart failure, diabetes, dilated cardiomyopathy and myocardial infarction (MI) are associated with disturbances in energy metabolism [1]. The metabolic changes, which accompany these pathologies have been reviewed extensively [2–5] and will be reviewed briefly here. The key role that mitochondrial metabolism and the expression of genes controlling mitochondrial metabolism have in maintaining cardiac function has recently been reviewed by Russell et al. [6] and will not be reviewed here. The aim of this review will be to focus on how the genetic modification of key steps in the uptake and cytosolic metabolism of glucose and fatty acids, by the use of transgenic (Tg) technology, has enhanced our understanding of how these pathways influence the pathogenesis of cardiac disorders. Tg technology has identified proteins whose expression when altered produces cardiomyopathies similar to those observed in individuals with heart failure or diabetes, a summary of these and other Tg models, not discussed in this review, can be found in Table 1. Identifying proteins whose expression, when altered, produces myopathies, or provides cardioprotection could provide potential therapeutic strategies for the treatment of heart failure and cardiomyopathy.

The technology behind the creation of transgenic mice has been reviewed [7,8] and the potential this technology offers for cardiovascular research has been discussed recently in this journal by Robbins [9]. Global ablation, or 'knocking out' of a gene of interest, is achieved using homologous recombination. However, it is difficult to determine whether effects on individual tissues are a specific result of ablating gene expression in that tissue per se, or whether it is a systemic effect resulting secondary to alterations in gene expression in other tissues. Tissue specific gene disruption can be used to prevent embryonic or fetal lethality that is often associated with

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doi:10.1016/j.yjmcc.2005.07.005

Table 1
Transgenic models of metabolic modification in heart

Gene	Manipulation	Models	Cardiac phenotype	Refs
			Glucose metabolism	
GLUT4	Global knockout	G4N	Hypertrophy, increased expression of MCAD and LCAD, increased insulin stimulated glycogen synthesis, interstitial fibrosis, increased PCr:ATP	[85,86]
	Heterozygous knockout	G4+/–	Diabetic cardiomyopathy	[91]
	Cardiac specific knockout	G4H	Hypertrophy, increased ANF and BNP, increased basal glucose uptake, increased creatine	[92,93]
GLUT1	Cardiac overexpression	αMHC-GLUT1	Protection from contractile dysfunction following ascending aortic constriction	[94]
Yeast HKB	Overexpression	MyHex	Increased glucose metabolism, no cardiac abnormalities	[160]
IR	Cardiac knockout	CIRKO	Decreased myocyte size, decreased glucose uptake, mildly impaired cardiac function	[96]
IGF-R	Cardiac overexpression	αMHC-IGF-1R	Cardiac hypertrophy	[106]
IGF1	Overexpression	αMHC IGF-1B α-skeletal actin IGF1	cardiac hypertrophy, attenuation of cardiac Dysfunction following MI	[104,105,107,108,161]
PI-3Kinase γ	Cardiac specific knockout	PI3Kγ–/–	Enhanced contractility	[112,116]
PI-3Kinase α	Constitutively active	PI3K(p110α)	Cardiac hypertrophy with no alterations in cardiac function or fibrosis	[115]
	Dominant negative		Smaller hearts with normal cardiac function	[115]
PTEN	MCK knockout	PTEN–/–	cardiac hypertrophy, impaired contractility	[112]
Akt	Constitutively active	myr-Akt E40K	Cardiac hypertrophy, concentric LV hypertrophy, decreased infarct size following I/R, altered contractility	[125–128]
	Akt1 overexpression	Akt(T308D/S473D)αMHC-Akt1	Decreased phosphorylation of cardiac alpha-AMPK	[129]
	Akt knockdown	kdAkt(K179M)	No cardiac pathology detected	[128]
PDK1	Cre/LoxP MCK knockout	mPDK1–/–	Sudden death at 5–11 weeks due to heart failure	[162]
AMPKα2	Dominant negative	αMHC AMPK2α(D157A)	Decreased glucose uptake, LVEDP and ATP depletion following ischemia	[136]
	Kinase dead	MCK-AMPK(K45R)	Decreased heart weight and in vivo LV dP/dt, impaired glucose uptake, glycolysis and FA oxidation, increased apoptosis and impaired LV recovery in response to low-flow ischemia.	[140]
PFK2	Cardiac specific Kinase deficient	kd-PFK2	Multiple cardiac pathologies, fibrosis, decreased contractility, impaired glycolysis	[163]
G6PDH	Global knockout	G6PDH–/–	Myocardial dysfunction	[26]
GPX	Global knockout	GPX–/–	Susceptible to oxidative damage	[151,152]
	Overexpression	Tg[MGP]-41	Resistance to myocardial I/R damage	[153]
Fatty acid metabolism				
PPARα	Global knockout	PPARα–/–	Increased death rate, increased I/R damage, lipid accumulation, fibrosis	[48–50,52,53,156]
	Cardiac overexpression	αMHC-PPARα	Diabetic cardiomyopathy	[54,56]
CD36	Global knockout	CD36–/–	Dilated cardiomyopathy	[16,66–69]
	Muscle overexpression	MCK-CD36	No evidence of cardiac pathology	[65]
H-FABP	Global knockout	H-FABP–/–	Hypertrophy, increased ANF expression, decreased LCFA utilization,	[76,78,157]
ACS1	Cardiac overexpression	αMHC-ACS1	Cardiomyopathy, hypertrophy, LV dysfunction, heart failure, intramyocellular TG accumulation	[155]
LpL	GPI anchored LpL × LpL+/–	$hLpL^{GPI}$/LpL1	Dilated cardiomyopathy	[81,82]
	Muscle overexpression	MCK-LpL	Premature death, weight loss, increased mitochondrial number	[158]
	Cardiac specific knockout	LpL–/–	Hypertriglyceridemia	[83]
LCAD	Global ablation	LCAD–/–	Cardiomyopathy, lipid accumulation, myocardial fibrosis	[159]