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β-adrenergic receptors signaling and heart failure in mice, rabbits and humans

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Heart failure, the common “end” phenotype of many cardiovascular diseases, has an annual incidence of 550,000 and a prevalence of approximately 5 million cases in US [1]. Over the past 2 decades, there have been considerable advances in our understanding of the pathogenesis and treatment of heart failure. Treatment with β-blockers and inhibitors of the rennin–angiotensin–aldosterone system has reduced total mortality from heart failure by approximately 30%. However, despite the advances, heart failure accounted for approximately 1,093,000 hospitalizations and 57,000 deaths in 2003 [1]. The estimated total cost of treatment of patients with heart failure in the United States for 2006 is $29.6 billion [1]. Accordingly, heart failure has remained an important topic of research in need of further studies to delineate its molecular pathogenesis and to develop new diagnostic markers and therapeutic targets.

Heart failure, as a clinical entity, is a complex phenotype. Susceptibility to heart failure and its clinical outcomes are determined by complex interactions between the causal factors, genetic background of the individual (modifier genes) and the environmental factors. Accordingly, the molecular mechanisms involved in the pathogenesis of heart failure, whether caused by genetic defects, myocyte loss or acquired forms of load mismatch, are diverse and entail multiple interacting pathways. Among them, the β-adrenergic receptors (ARs) signaling is one of the most prominent and well-characterized pathways involved in regulating cardiac function and determining the clinical outcome in patients with heart failure (reviewed in [2]). All three β-ARs, namely β-1, β-2 and β-3 as well as the three isoforms of α1-ARs (α1A, α1B and α1D) are expressed in the heart [3]. The β-1 isoform is the predominant isoform comprising about 70 to 80% of the β-ARs in the normal heart [4,5]. Classically binding of agonists to β-1 ARs instigates signaling by activating the stimulatory subunit of the G proteins (Gsα) and subsequently, adenylyl cyclase. The latter leads to production of cyclic adenosine 3′,5′ monophosphate (cAMP) levels and activation of protein kinase A (PKA), which then phosphorylates several downstream target proteins including phospholamban, ryanodine receptors, L-type calcium channels and cardiac troponin I (cTnI), among the others. The net effect is enhanced myocyte and myocardial contractility. In contrast to β-1 ARs, the β-2 ARs activate both Gsα and Giα (inhibitory) subunits of the G proteins. Hence, signaling and functional effects of activation of β-2 ARs on cardiac myocytes are more complicated [6]. The effects of signaling through other members of the ARs on cardiac structure and function and their interactions with the β-1 and β-2 ARs signaling pathway are less clear, but appears to vary developmentally and across species [3].

In patients with heart failure, β-1 ARs signaling is attenuated, despite a significant increase in circulating catecholamine levels [4,7]. The attenuation is partly because of decreased number of the β-1 ARs and partly because of internalization and desensitization of the receptors [4, 7]. Agonist-induced expression the mRNA binding proteins, such as AUF-1, has been implicated in degradation of the mRNA and down-regulation of the number of β-ARs in heart failure [8]. Receptor desensitization occurs because of phosphorylation of the ARs by kinases including the β-AR kinase, also known as G-protein coupled receptor kinase 2, which is activated in the myocardium in heart failure [9]. Phosphorylation of the ARs increases the receptor affinity for binding to β-arrestin regulatory proteins and uncoupling of the receptors from the Gsα subunit. The uncoupling has adaptive effects as it prevents cardiac myocytes from the harmful effects of excess catecholamines, such as myocyte apoptosis in patients with heart failure [10]. However, chronic attenuation of β-ARs signaling deprives the cardiac myocytes from the positive inotropic effects of β-AR signaling.

The seminal discovery of decreased β-adrenergic responsiveness in the heart in humans with heart failure more than 2 decades ago evoked considerable interest in the potential utility of restoration of β-adrenergic responsiveness in treatment of heart failure [11]. Since the initial report of enhanced myocardial contractile performance in transgenic mice over-expressing the β-2 adrenergic receptors in the heart [12], several dozens of genetically modified mouse models, targeting various components of the β-ARs pathway, have been generated and characterized. The collective results have substantiated the merit of restoration of the β-adrenergic responsiveness in improving myocardial function. Yet at the same time, the results have demonstrated the deleterious effects of prolonged stimulation of the β-ARs system as well as the complexity of the β (as well as α) -adrenergic signaling in the heart. Significant interactions between the β-ARs subunits as well as between β-ARs and α-ARs and between ARs and muscarinic acetylcholine receptors have been illustrated (reviewed in [13]).

In the current issue of the *Journal*, Nishizawa and colleagues provide data suggesting the presence of cross-species (rabbits vs. mice) differences in the response of the heart to adrenergic over-stimulation [14]. They show that over-expression of Gα-s by 3-fold increased heart rate, enhanced cardiac contractility in juvenile as well as adult rabbits. The observed enhanced myocardial function in transgenic rabbits is in apparent contrast to the previously reported phenotype in transgenic mice in which the phenotype evolved from that of enhanced left ventricular function in young age to dilated cardiomyopathy at old age [15]. The findings are provocative and if substantiated, could raise considerable concerns on the utility of the mouse models of adrenergic over-stimulation in deciphering the pathogenesis of human heart failure. How do we reconcile the differences in the phenotype between transgenic Gsα mice and rabbits? The hypothesis, i.e., presence of cross-species differences in the phenotypic response of the heart to β-adrenergic stimulus, is biologically plausible. Accordingly, inter-species and inter-individual variability in the expression of the phenotype, which is partly determined by the genetic background and partly by the environmental factors, is anticipated. In the case of β-ARs, the variability is best illustrated by the differential effects of polymorphisms in the β-ARs on clinical outcome and response to therapy in patients with heart failure [16–18]. It is also illustrated for genetic cardiomyopathies, wherein mutations in a given gene could cause the contrasting phenotype of hypertrophic or dilated or restrictive cardiomyopathy [19,20]. Whether there are differences in the sequence, density of the β-ARs or the downstream signaling molecules and their targets between mice and rabbits are unknown. Until then, the molecular basis for the observed phenotypic differences in Gsα transgenic mice and rabbits will remain unexplained. Nishizawa and colleagues implicate increased expression levels of Giα in the hearts of 11–16 months rabbits, as a potential mechanism that could abrogate the deleterious effects of sustained stimulation of Gsα on cardiac function. While plausible, the data, which document increased expression levels of Giα in 11–16-month-old transgenic rabbits, require complementary studies to substantiate the potential salutary effects of increased

levels of Giα. It is noteworthy that increased myocardial levels of Giα isoforms were detected in rabbits with heart failure following myocardial infarction, a finding that suggest lack of sufficient protective effect against heart failure [21]. The molecular basis of increased expression levels of Giα in the hearts of transgenic rabbits, which is primarily regulated by the β2 ARs, also remains to be determined. One may postulate that increased Giα levels reflect the presence of complex interactions between β-ARs subtypes in rabbits but not in mice, which leads to activation of β2 ARs subtype, responsible for increased expression levels of Giα, in the rabbit [6,13]. Other aspects of the observed phenotype are also intriguing and require further molecular characterization. Increased heart rate (assuming due to sinus node cycle length shortening) following cardiac myocyte-restricted expression of Gsα as well as increased muscarinic acetylcholine receptors responsiveness are not fully explained and probably are reflective of complex and yet-to-be-defined interactions not only between the β-ARs subtypes but also between the ARs and muscarinic receptors.

The rabbit as the model to study human heart failure has several advantages and disadvantages over mice. One major advantage is the similarity in the composition of sarcomeric proteins between humans and rabbits as opposed to mice. The β-MyHC protein is the predominant isoform in the human and rabbit ventricular myocardium, comprising more than 90% and 80% of the total myofibrillar myosin, respectively [22]. This is in contrast to mouse, in which the α-MyHC isoform comprises more than 95% of the total myofibrillar myosin protein [22]. Differences in ATPase activity and the kinetics of force generation by myofibers predominantly containing β-MyHC or α-MyHC could affect the phenotypic response of the heart to injury or genetic mutations. Furthermore, alterations in expression levels of β-MyHC and α-MyHC proteins have been implicated in human heart failure (discussed in [23]). Thus, the desirable sarcomeric protein composition makes the rabbit a preferable model as opposed to mouse in heart failure studies. In addition, molecular changes in the β-ARs signaling pathways similar to those observed in humans with heart failure have been reported in rabbits with heart failure [21]. However, the two major disadvantages of the transgenic rabbit models, as opposed to mouse models of heart failure, are the cost associated with generation and maintenance of a colony and more importantly, the relatively long period of time that it takes for the evolution of the full-blown phenotype. In addition to the extra-cost of generation of transgenic rabbits, the cost of housing of a single rabbit is about $2.00 to $2.50 per day, which is about 20 times higher than the cost housing of a single mice (assuming 4–5 mice per cage). More importantly, expression of the phenotype, which is age-dependent, takes longer time in rabbits. One has to wait years for the phenotype to develop fully in the transgenic rabbits as opposed to months in the transgenic mice. For example, in our β-MyHC-Q403 transgenic rabbit model of human hypertrophic cardiomyopathy, the phenotype evolved over a span of 4 years [24]. There was no discernible cardiac hypertrophy within the first 6 months of life in the β-MyHC-Q403 transgenic rabbits. At 18 months of age, approximately 2/3 exhibited cardiac hypertrophy, while transgenic rabbits older than 30 months of age exhibited a fully manifested phenotype [24]. Accordingly, the study by Nishizawa and colleagues will require follow-up studies to determine whether Gsα transgenic rabbits will develop heart failure later in life, which was also the case in the Gsα transgenic mice [15]. The Gsα transgenic mice developed cardiomyopathy at a mean age of 15 months [15]. The corresponding age in rabbits is approximately 4 years. The oldest Gsα transgenic rabbits that underwent thermodynamic studies were 11–16 months of age. Thus, the apparent contrasting phenotype between the transgenic Gsα mice and rabbit could simply reflect the age-dependent penetrance of the transgene and expression of the phenotype. We will eagerly wait the results of characterization of cardiac function in 3–4-year-old Gsα transgenic rabbits. Meanwhile, the mouse models will continue to provide meaningful data in elucidation of the molecular pathways involved in the pathogenesis of heart failure.

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