Editorial

CELF1 regulates gap junction integrity contributing to dilated cardiomyopathy

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Heart disease is a major public health problem

Cardiovascular disease is a major contributor of adult mortality and accounts for approximately 801,000 deaths annually throughout the United States alone (1). Heart disease continues to be at the forefront of scientific research not only due to its prevalence but also its complexity (2,3). Additionally, cardiovascular disease has become a significant economic strain to the health care system with continuous hospitalization (4) as well as high morbidity and mortality (5). Cardiovascular disease can be caused by a variety of different factors including cell-to-cell communication defects that result in a breakdown between important cell connections (6). A malfunction of cell-to-cell communication in the myocardium can lead to pathologic cardiac remodeling which can ultimately result in heart disease (6).

Specifically, dilated cardiomyopathy (DCM) is a prominent cause of heart failure, heart transplantation, and death (1-4,7-12). DCM is described as dilation of the left ventricle as well as impaired systolic function with a reduced ejection fraction (2,11). As DCM progresses, the left ventricle wall starts to thin and becomes weak, causing the heart to be inefficient at pumping blood to the systemic circulation (2). DCM can be caused by a number of factors including hypertension (1), coronary artery disease (3,12), obesity (1), an autoimmune response (2), genetic defects (3,12), and myocarditis (2).

Gap junctions are essential for cell communication and Cx43 expression plays an important role in heart failure

Cell-to-cell communication is important for healthy heart function, and importantly, disruptions to this necessary coupling event can lead to ventricular arrhythmias (6,7,9,13). This connection processes occur through intercalated discs within the cardiac muscle, and consist of three complexes including gap junctions, fascia adherins, and desmosomes (7). Changes to these cell-to-cell connections at intercalated discs can lead to DCM (7). Gap junctions are at the center of these events and allow for proper electrical coupling (8,9,13,14). Gap junctions are cell passages that help exchange micro-molecular metabolites to coordinate electrical activity (10,13). They rely on connexin isoforms in order to carry out cardiac conduction (6-8,14,15). Each individual gap junction is composed of two hemichannels or connexons (13,14). These connexons are hexameric oligomers that make intercellular channels along with corresponding cells (14).

Connexin is a membrane protein group that is a vital component of gap junctions (8,15). Connexin 40 (Cx40), connexin 45 (Cx45), and connexin 43 (Cx43) are the three main gap junction proteins found in the heart (5). Cx43 is the most common connexin (5-7,13-16) and is expressed in over 46 different cell types, but most predominantly in the heart (14). Cx43 is typically located at intercalated

discs of cardiomyocytes (13) and is predominantly expressed between the ventricular and atrial myocytes (5). Impulse conduction changes can result from an anomalous expression of important gap junction proteins such as Cx43 (6,13-15) which can lead to arrhythmias, DCM, and ultimately heart failure (5,6,13). DCM patients for example, display significantly decreased Cx43 expression levels (6-9), while it is thought that an increase in Cx43 expression is a part of the adaptive cardiac pathologic remodeling phase (6). Alterations in cell-cell communications at intercalated discs can disrupt chemical exchanges and electrical coupling, and is known as gap junction remodeling (7). Recent work by Chang *et al.* demonstrated that CELF1 is involved in the degradation of Cx43 mRNA and suggested a role for CELF1 in DCM (6).

RNA binding proteins are important regulators to Cx43 expression where corresponding expression levels can result in DCM

The RNA binding protein CUGBP, Elav-like family member 1 (CELF1 or CUGBP1) is involved in many different transcriptional and posttranscriptional regulatory systems that are important for both normal development and disease progression (6,16,17). CELF1 has been shown to regulate mRNA stability, polyadenylation status, and cytoplasmic translation of target transcripts (16). Interestingly, CEFL1 has been found to be relevant in a number of disease processes, including some cancers, myotonic dystrophy type 1, and heart disease (6,16,17). CELF1 is highly expressed in the developing myocardium with a strong nuclear presence and is an important RNA binding protein for fetal development (6,16,17). CELF1 protein levels start to decrease 6–7 days after birth and are significantly decreased during adulthood (6,17). Protein kinase C (PKC) is responsible for the increased CELF1 levels during development, and mediates its downregulation in the adult heart through hyperphosphorylation (6). When CELF1 was up-regulated in adult cardiomyocytes it led to arrhythmia, DCM, and eventual heart failure (6,17). Additionally, mouse models have shown that CELF1 over-expression in the heart results in splicing defects which leads to cardiomyopathy and ultimately cardiac failure (16,17).

Chang *et al.* showed that CELF1 mediates Cx43 expression, which can contribute to the progression of DCM (6). Interestingly, CELF1 was found to be increased in end stage heart failure but not in hearts that were undergoing compensatory hypertrophy (6). However, the mechanisms that cause the transition from compensatory hypertrophy to decompensation and ultimately to heart failure are still unknown (6,17). Knockdown of CELF1 in HeLa cells resulted in stabilized transcripts that contained binding elements for CELF1 in their 3' UTRs, indicating that CELF1 plays a likely role in mRNA decay (16). Specifically, CELF1 has been suggested to be involved in regulating Cx43 (6), such that an increased expression of CELF1 degrades Cx43 mRNA (6). Cx43 contains several CELF1-recognized UG-rich motifs in its 3' UTR4 and CELF1 is able to downregulate Cx43 by binding to these motifs and recruiting a 3' to 5' exoribonuclease, referred to as ribosomal RNA processing protein 6 (RRP6) (6). RRP6 is involved in RNA degradation and processing in both the cytoplasm and nucleus (6). Additionally, the authors showed that RRP6 is a cofactor in Cx43 mRNA degradation, and nuclear localization of CELF1 and RRP6 were needed for Cx43 mRNA degradation (6). Chang *et al.* investigated CELF1-regulation of Cx43 in a myocardial infarction (MI) mouse model of cardiac dysfunction. The authors observed increased CELF1 expression in these animals (6). Down-regulation of CELF1 resulted in preserved, Cx43 levels and improved contractile function (6). Other RNA-binding proteins are important regulators of Cx43 and gap junction remodeling. Among those is FXR1 which has also been linked to DCM via gap junction cardiac conduction maintenance (7).

Fragile X mental retardation autosomal homolog 1 (FXR1), is a part of the Fragile X family that include FMRP and FXR2 (7,18). FXR1 is the only member of the Fragile X family to be expressed in striated muscle, thus is the only one found in cardiac tissue (18). In both human DCM and in mouse models of DCM, FXR1 expression is significantly increased (7). FXR1 knockout mice were used to determine FXR1's role in gap junction remodeling (7,18), and it was determined that a loss of cardiac specific FXR1 resulted in cardiac dysfunction/ventricular tachycardia possibly related to redistribution of Cx43 (7). Other studies however showed a postnatal lethality in a FXR1 knockout (*Fxr1* KO) mouse model likely due to cardiac or respiratory failure (18). Fxr1 KO resulted in alterations of gap junctions, desmosomes, and sarcomere spacing in the hearts of embryonic mice (18). Thus, *FXR1* protein levels are required for a normal functioning heart and maintained structural integrity (7,18). While more studies are required, FXR1 (7) in addition to CELF1 (6) could be a promising therapeutic target to improve gap junction function in patients with DCM for future therapeutic studies.

Future research directions for cardiovascular disease

Overall, cardiovascular disease remains an important issue that has a profound effect on human health (1,4). Gap junction integrity is important to maintain normal heart function, and changes in its levels can lead to pathologic cardiac remodeling (6,8-10,13). Pathologic remodeling may result in a decrease in Cx43 expression, which can interrupt fundamental cell-to-cell communication processes (5,6,13). Cx43 levels have been shown to be influenced by CELF1, such that when CELF1 levels were increased, Cx43 expression was decreased (6), other proteins such as RRP6 (6) have also been linked to Cx43. Additionally, the RNA binding protein FXR1 has been shown to disrupt cell-to-cell communication, where a decrease in FXR1 has been shown to be detrimental to cardiac function (7).

Further research on heart failure remains important given the prevalence and burden in the adult population (1). While some progress has been made with regard to DCM and what may contribute to disease progression, mechanisms involved in this transition still remain elusive. Potential novel therapeutic targets such as RNA binding proteins CELF1 and FXR1 along with the molecules that interact with these proteins may be an important step in better understanding the underlying causes of DCM and other cardiovascular diseases that contribute to heart failure.

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