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SCN5A Splicing Variants and the Possibility of Predicting Heart Failure-Associated Arrhythmia

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Inadequacy of predictors of heart failure (HF)-associated sudden death

It has been estimated that approximately five million patients in the US have HF, and nearly 550,000 people are diagnosed with this disease annually.[1] The risk for sudden cardiac death is 6 to 9 times greater in the heart failure population, and cardiac arrhythmias are a leading cause of death in HF patients.[2,3] Currently, both the American College of Cardiology and the American Heart Association endorse the placement of implanted cardiac defibrillators (ICDs) for primary prevention of sudden cardiac death to reduce total mortality in high risk HF patients. Nevertheless, risk models derived from major clinical trials have not shown statistically significant survival benefits for patients in the highest 10% to 20% of predicted risk after ICD implantation. In SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), patients in the highest quintile of risk had a 2-year mortality rate of 30% and did not have any statistically significant benefit as a result of ICD implantation.[4,5] In the MADIT II (Multicenter Automatic Defibrillator Implantation Trial II) model, neither the 14% of ICD patients with 3 or more risk factors nor the 5% of ICD patients in the prespecified very high risk group had a statistically significant survival benefit from ICD implantation.[4,6] In part, this situation occurs, because current sudden death risk stratification techniques do not separate low and high arrhythmic risk patients well, possibly because they do not reflect directly an arrhythmogenic pathophysiological process. Therefore, there is an unmet need for sudden cardiac death risk assessment in the HF population.

SCN5A and HF-associated arrhythmia

Voltage-gated Na^+ channels are responsible for generating the main current for excitation propagation in the membrane of most excitable cells, such as cardiomyocytes (CMs) and neurons.[7,8] The cardiac Na^+ channel consists of a main pore-forming α-subunit and the auxiliary β-subunits. The α-subunit alone is sufficient to produce a functional channel. Co-expression of the β-subunits can increase the level of Na^+ channel expression and alter the voltage-dependent gating.[9] SCN5A, encoding the α-subunit of the Na^+ channel, was cloned by Gellens et al. in 1992[10] and mapped to the chromosomal region 3p21 by George et al. in 1995.[11] Since SCN5A was cloned, more than one hundred mutations have been found in the gene. These mutations cause inherited sudden death syndromes such as

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Brugada syndrome, the third variant of Long QT syndrome (LTQ3), and sudden infant death.[12,13,14] Alterations in the Na^+ current, either up or downregulation, lead to arrhythmias. Human HF is associated with decreased cardiac voltage-gated sodium channel current,[15] and the Na^+ channel changes have been implicated in the increased risk of sudden death in HF. These changes appear to happen in the absence of significant alterations in β subunits, suggesting an issue involving SCN5A regulation.

The splicing regulation of SCN5A during HF

Alternative splicing is a post-transcriptional mechanism that can substantially change the pattern of gene expression. Up to 95% of human genes have multi-exon alternative spliced forms, suggesting that alternative splicing is one of the most significant components of the functional complexity of the human genome.[16] Although our understanding of the role of alternative mRNA splicing is elemental, a growing list of human diseases, such as cancer, neurodegenerative disorders and autoimmune disease are associated with alternative splicing.[17,18,19] We reported previously that 47 of 181 known splicing factors were upregulated in HF tissue when compared to normal heart tissue. Among those factors, AngII and hypoxia, signals common to HF, increase two splicing factors, RBM25 and hLuc7A. Activated RMB25/hLuc7A-mediated splicing regulation increases SCN5A splice variant abundances, decreases full-length SCN5A mRNA and protein, and decreases Na^+ current. SCN5A mRNA variants result from splicing at cryptic splice sequences in the terminal exon of SCN5A (exon 28). SCN5A variants are shorter and encode prematurely truncated, nonfunctional Na^+ channel proteins missing the segments from domain IV, S3, or S4 to the C terminus. When the SCN5A gene is substituted by a model variant, a 80% reduction in cardiac Na^+ current and a significant reduction in electric conduction velocity has been recorded.[15]

The possibility of a blood test to predict HF-associated arrhythmic risk

In addition to heart, SCN5A Na^+ channels have been described in lymphocytes, macrophages, and skeletal muscle. Our published data have shown that SCN5A splice variants can be detected in the human lymphoblasts.[20] Further in vitro studies have shown that identical SCN5A splice variant regulation is found in Jurkat cells (human leukemia cell line) as in human induced pluripotent stem cells-derived cardiomyocytes, suggesting that white blood cells (WBCs) might serve as readily accessible surrogates for the status of Na^+ channel splicing in the myocardium.[15] In that regard, microarray analysis was used to identify and compare splicing factor genes in both normal and human HF blood white cells (WBCs). The results showed that ~90 splicing factors were upregulated in WBCs from HF patients (unpublished data). This indicates that splicing regulations is activated in WBCs during HF. Further, RBM25 and hLuc7A showed concomitant upregulation in HF WBCs and HF myocardium. Additionally, the AngII receptor, which is upstream of the RBM25/hLuc7A-mediated splicing pathway, is increased on WBCs during HF.[15] These data indicated that SCN5A splicing in cardiomyocytes and WBCs could be similar during HF. Because of the critical nature and tissue localization of SCN5A, any test based on SCN5A variants is likely to be sensitive and cardiac specific.

The advantage of a successful blood test to predict HF-associated arrhythmic risk

It has been known for some time that, even though ICDs represent a highly effective therapy to prevent sudden death, the majority of sudden death occurs in patients that do not meet current indications for device implantation. Contemporary screening methodologies are too expensive and have insufficient positive predictive power to be used effectively in larger population screening programs. A rapid, inexpensive blood test to predict risk could increase the efficacy of ICDs by directing them towards the patients at highest risk and could allow for screening and treatments, ICD or otherwise, of intermediate risk populations currently not evaluated.

A viable blood test for sudden death risk would direct treatments to patients with the highest risk, including those not currently receiving intensive therapy, and would allow for repeat risk stratification as the disease progresses or the environment changes. In addition, this technology potentially allows for safer use of Na^+ channel blocking antiarrhythmic drugs and could be useful for directing therapies to increase Na^+ current. Finally, the test could be used to guide therapy with small molecules or inhibitory RNA directed toward RBM25 and hLuc7A to prevent directly the abnormal SCN5A splicing regulation.

Future directions

HF is associated with reduced Na^+ current, at least in part, as a result of abnormal SCN5a mRNA processing. Whether this reduction is directly proportional to the amount of variants present and whether SCN5A variants change in a useful, correlated manner between heart and WBCs will need to be determined. If so, a prospective study to determine whether altered WBCs SCN5A variant abundances are associated with an elevated likelihood of sudden death risk would be appropriate. With affirmative answers to these questions, it might be possible to develop a blood test to predict HF-associated arrhythmic risk.

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