Models for QT prolongation

By Tim Fulmer, Senior Writer

A group at the **Technion Israel Institute of Technology** and a team at the **Stanford University School of Medicine** have independently developed human stem cell-based models of long QT syndrome,^{1,2} a potentially fatal cardiac disorder that can be triggered by environmental and pharmacological stimuli in susceptible patients. The models could be used to identify potential therapies for long QT syndrome as well as compounds that induce QT prolongation as a side effect—a problem that has derailed many drug development programs.

Of the 12 subtypes of long QT syndrome, the two most common—LQT1 and LQT2—are caused by mutations in potassium channel proteins that normally help maintain the regular electrical activity of the heart. Other long QT subtypes are associated with mutations in additional proteins, including calcium channels, sodium channels and ankyrin 2 (ANK2).

In response to stress, excitement and high doses of some drugs, long QT patients can experience palpitations, fainting and even sudden death due to a life-threatening form of ventricular tachycardia known as *torsades de pointes* (TdP).

Although the genetic underpinnings of many forms of long QT syndrome have been elucidated, a dearth of preclinical models has slowed the development of therapies. For example, the physiological differences in mouse and human hearts limit the usefulness of transgenic mice that carry long QT-associated mutations.

To address this problem, the two groups took a similar approach to the development of patient-specific models of long QT syndrome. In both cases, the researchers began with fibroblasts isolated from patients.

The Technion group obtained fibroblasts from a 28-year-old woman with the LQT2 disease subtype. The Stanford researchers isolated fibroblasts from two patients with Timothy syndrome, an LQT8 disease phenotype that is characterized by a single mutation in calcium channel voltage-dependent L type- α 1C subunit (CACNA1C; Cav1.2).

Next, the fibroblasts were reprogrammed to generate patient-specific induced pluripotent stem (iPS) cell clones, which were then differentiated into lineages of cardiomyocytes that expressed the patients' original long QT syndrome mutation.

In vitro analysis of the iPS cell-derived cardiomyocytes revealed significant prolongation of their action potentials and dysregulated potassium or calcium currents compared with healthy control cells, confirming that the new cells exhibited the original long QT phenotypes.

The iPS cell-derived cardiomyocytes were used to evaluate the potency of compounds that targeted ion channels and were known to improve or worsen the long QT phenotype.

In the Technion study, potassium channel blockers worsened the disease phenotype, whereas calcium and sodium channel blockers improved the phenotype. The Stanford group found that a calcium channel modulator restored the electrical activity of Timothy syndrome cardiomyocytes.

The Israeli group was led by Lior Gepstein, professor of cardiology and physiology at Technion. The American team was led by Ricardo Dolmetsch, professor of neurobiology at Stanford.

“Our study illustrates the ability of human iPS technology to model the abnormal functional phenotype of an inherited cardiac disorder and to identify potential new therapeutic agents,” the Technion authors wrote in their paper published in *Nature*.

Indeed, an iPS cell-derived cell model provides “...new opportunities for studying the molecular and cellular mechanisms of cardiac arrhythmias in humans, and provides a robust assay for developing new drugs to treat the diseases,” wrote the Stanford researchers in their paper, which was also published in *Nature*.

“Development of a patient- and disease-specific human heart cell model, which displays an abnormal patient-specific phenotype, represents a paradigm shift from conventional preclinical models for understanding disease mechanisms and developing personalized medicine,” corresponding author Gepstein told *SciBX*.

A key advantage the stem cell model may have over animal models of long QT syndrome “is that the cells have the same genetic background as human patients. This is useful because the cells can potentially be used to model cardiac arrhythmias that were caused by multiple mutations in multiple genes. In contrast, it is very difficult to generate mice with more than two or three mutations,” said Dolmetsch, corresponding author on the Stanford paper.

Gepstein said he wants to use the model to develop and test new therapeutics for long QT syndrome. Moreover, he plans “to extend the same iPS cell-based approach to studying other inherited cardiac disorders.”

Dolmetsch said he also wants to use the cardiac stem cells to “develop models of other types of cardiac defects.” He added that his team is already “generating better models of the human heart that embody the complex relationship between the different types of myocytes in the heart.”

Gepstein pointed out that the iPS cell-derived model “could also have implications for studying and identifying acquired forms of long QT syndrome that result from cardiac disease states or the side effects of drugs. Indeed, drug-induced QT prolongation is one of the single most important reasons why an approved drug is withdrawn from the market,” he said.

Over the past 15 years, at least 9 structurally unrelated drugs marketed in the U.S. for a range of cardiovascular indications have been removed from the market or had their access restricted because of toxicity resulting from QT prolongation.³

Gepstein said the findings are covered by patents. He declined to disclose the licensing status of that IP.

Dolmetsch said his group's findings are covered by patents, which are available for licensing.

Fulmer, T. *SciBX* 4(6); doi:10.1038/scibx.2011.153

Published online Feb. 10, 2011

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COMPANIES AND INSTITUTIONS MENTIONED

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