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Conference report: Building a biological pacemaker

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Physiological pacemaking in the normal heart is the province of the sinus node, in which a family of ionic currents contributes to the pacemaker potential. Of paramount importance in initiating pacemaker function is I_f, an inward current carried by sodium through a family of channels that are hyperpolarization-activated and cyclic nucleotide-gated (HCN channels) (1).

In a variety of settings where physiological pacemaking fails, therapy relies on electronic pacing. Although electronic pacemakers are an excellent therapy, their persistent shortcomings (need for monitoring and replacement, indwelling catheter-electrodes in the heart, possibility of infection, lack of autonomic responsiveness, geometric limitations with respect to pediatric patients) are sufficient to warrant a search for better alternatives(2). The biological pacemaker, a tissue that spontaneously or via engineering confers pacemaker properties to regions of the heart, is one such alternative. A variety of approaches have been taken in attempting to produce biological pacemakers. These can be considered under three major headings: first, the use of viral vectors to deliver genes to regions of the heart such that a pacemaker potential resulting in spontaneous impulse initiation evolves in the region of gene administration(3–7) ;second, the use of embryonic stem cells grown along a cardiac lineage and manifesting the electrophysiologic properties of sinus node cells (8); third, the use of mesenchymal stem cells as platforms to carry pacemaker genes to the heart, relying on gap junctional coupling such that the stem cell and a coupled myocyte form a single functional unit to generate pacemaker function(9).

Generating pacemaker function via any of these approaches depends on increasing inward current and/or decreasing outward current to bring about membrane depolarization and the initiation of a heartbeat. Early approaches to achieve this included beta-2 adrenergic receptor overexpression to increase catecholamine sensitivity(3,4), or engineering a dominant negative viral construct of the inwardly rectifying current, I_{K1}, which served to decrease outward current and increase pacemaker rate(5). However, most approaches at present have evolved in the direction of using the hyperpolarization-activated cyclic nucleotide-gated (HCN) family of channel genes that are responsible for generating the primary pacemaker current of the heart, I_f (6,7,10,11). The isoforms used to date have included HCN1, HCN2 and HCN4, as well as mutant and chimeric channels developed to optimize the rates and rhythms generated(6,7,9–11). In addition attempts have been made to engineer HCN-like genes using other constructs as the base structure (12). Success lasting weeks-months in large animal models has been achieved with both embryonic stem cell and adult human mesenchymal stem cell (hMSC)

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approaches (8,13) and likely will be achieved with lenteviral and adeno-associated viral vectors as well.

Our research employs both the wild-type HCN channels (mainly HCN2) as well as mutant and chimeric channel genes to produce pacemaker currents that both drive the heart at acceptable rates and are responsive to autonomic stimulation. The gene therapy approach uses adenoviral vectors and delivers the pacemaker complex via catheter to the bundle branch system of dogs that have radiofrequency-induced complete heart block 6,7,10,13). The cell therapy approach uses hMSCs as a platform: the hMSCs, which express the gap junctional proteins connexin43 and connexin40 are transfected with HCN via electroporation(9). MSCs overexpressing HCN are then injected into the hearts of dogs in complete heart block. Gap junctional communication is established between the hMSCs and cardiac myocytes, permitting the generation of physiologically acceptable rhythms for study periods that have gone as long as 6 weeks. (9) There is no apparent rejection of the hMSCs during this period (13).

Our current research directions include both optimizing biological pacemaker function via manipulation of channel constructs and using the biological pacemakers in tandem with electronic units (10,14). In this setting the electronic unit tracks the function of the biological pacemaker and provides a fail-safe device, while the biological component provides the lion's share of heartbeats from a site that optimizes contractile efficiency, is autonomically responsive and conserves the battery life of the electronic unit. Such a tandem approach will be essential until the safety and efficacy and duration of efficacy of the biological units can be convincingly demonstrated.

Despite successes to date, many important issues remain to be considered before biological pacemakers are administered to man (2). These include the extent to which the biological approaches used confer any risk of migration, neoplasia, rejection, proarrhythmia. While data here are encouraging, they are not yet definitive.

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