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Review article

Ion-channel mRNA-expression profiling: Insights into cardiac remodeling and arrhythmic substrates

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ABSTRACT

Membrane ion channels and transporters are key determinants of cardiac electrical function. Their expression is affected by cardiac region, hemodynamic properties, heart-rate changes, neurohormones and cardiac disease. One of the important determinants of ion-channel function is the level of ion-channel subunit mRNA expression, which governs the production of ion-channel proteins that traffic to the cell-membrane to form functional ion-channels. Ion-channel mRNA-expression profiling can be performed with cDNA microarrays or high-throughput reverse transcription/polymerase chain reaction (PCR) methods. Expression profiling has been applied to evaluate the dependence of ion-channel expression on cardiac region, revealing the molecular basis of regionally-controlled electrical properties as well as the molecular determinants of specialized electrical functions like pacemaking activity. Ion-channel remodeling occurs with cardiac diseases like heart failure, congenital repolarization abnormalities, and atrial fibrillation, and expression profiling has provided insights into the mechanisms by which these conditions affect cardiac electrical stability. Expression profiling has also shown how hormonal changes, antiarrhythmic drugs, cardiac development and altered heart rate affect ion-channel expression patterns to modify cardiac electrical function and sometimes to produce cardiac rhythm disturbances. This article reviews the information obtained to date with the application of cardiac ion-channel expression profiling. With increasing availability and efficiency of high-throughput PCR methods for ion-channel subunit mRNA-expression characterization, it is likely that the application of ion-channel expression profiling will increase and that it will provide important new insights into the determinants of cardiac electrical function in both physiological and pathological situations.

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1. Introduction

Specialized cardiac electrical properties are determined by characteristic expression profiles of cardiac ion channels and transporters. Cardiac disease importantly alters ion-channel expression in ways that promote arrhythmogenesis and contractile dysfunction [1,2]. Ion-channel function has been characterized for a wide range of pathologies. A comprehensive description is beyond the scope of the present paper — the interested reader is referred to several detailed reviews [2–5]. Expression profiling refers to the analysis of gene-expression patterns under varying conditions to obtain mechanistic insights. Here, we focus on the use of expression profiling to better understand the molecular basis of cardiac electrical function and dysfunction.

Initially expression profiling was accomplished with high-density mRNA-expression microarrays. Pangenomic arrays proved to have low sensitivity for ion-channels, and custom-made arrays for ion-channel profiling were developed [6]. Subsequently, high-throughput quantitative polymerase-chain reaction (PCR) methods were developed that allow for precise and definitive quantification of a large number of ion-channel subunit mRNAs [6]. This paper will not deal with technical aspects of expression profiling: for these, the reader is referred to relevant review articles [6–8]. We have organized this review thematically according to aspects of cardiac physiology and pathophysiology that have been elucidated by ion-channel/transporter expression profiling.

2. Cardiac regional differences

Different regions of the heart have highly-specialized electrical functions based on distinct ion-channel properties [9]. Differences in ion-channel subunit mRNA and protein expression generally parallel ionic-current properties that account for the cellular (action potential) and macroscopic (conduction and refractoriness) electrical features of each region [9]. Expression profiling has allowed for examination of the potential role of a broad range of subunits in regional function.

2.1. Transmural differences

Characteristic action-potential properties in the different transmural myocardial layers are crucial for normal physiological function and central to certain forms of arrhythmia [9,10]. Rosati et al. used pangenomic arrays to compare transcript-expression patterns in rat left-ventricular epicardium versus endocardium [11]. Of approximately 8000 genes surveyed, only 36 were differentially-expressed. Of particular interest were KCND2 (Kv4.2), which was expressed 17-fold more strongly in epicardium, SCN5A (Nav1.5), expressed 1.5-fold more strongly in endocardium, and the transcription-factor genes IRX3 and IRX5, which were 18 and 29-fold more concentrated in endocardium than epicardium respectively [11]. Larger epicardial than endocardial I_{to} is a feature strongly-conserved across species [9,10] and in murine hearts due to stronger epicardial KCND2-expression [12]. The Iroquois homeobox-gene product IRX5 is a transcription factor that appears to be crucial to the production of the transmural I_{to} gradient by down-regulating KCND2-expression in the mouse heart [13].

2.2. Mapping regional expression profiles in the human heart

Gaborit et al. used tissue samples from non-diseased human hearts to obtain a detailed portrait of regional ion-channel expression with high-throughput PCR [14]. One analysis approach that they used is two-way hierarchical clustering, a method that addresses expression similarities and differences among samples from different groups across a large gene-set. The results for all genes from a single sample are represented in one dimension and the individual-gene expression data for each sample are aligned along the other dimension. Results are presented as heat-maps, often with the most strongly-expressed genes shown in bright red, the most weakly-expressed in bright green, and intermediate in black. Samples with similar expression patterns are grouped together, with the most different samples placed furthest apart. Genes with the most similar expression patterns across samples are grouped closely together.

An example of hierarchical-clustering analysis of the ion-channel expression patterns of human cardiac tissues is shown in Fig. 1. Data for individual atrial, ventricular and Purkinje-fiber tissue samples are shown as single columns. The results were grouped together by tissue-type, indicating that the expression-variance due to inter-sample differences was outweighed by the variance due to consistent differences among these regions. In contrast, no distinct clusterings occurred for right versus left-sided chambers (Fig. 1) nor for ventricular endocardium versus epicardium. Characteristic expression patterns were seen for genes separating Purkinje fiber from working myocardium (clusters A and C in the figure) and for atrial–ventricular differences (cluster B). Well-established distinct repolarizing-current properties of Purkinje fibers [15,16] were reflected in higher expression levels of the K^+-channel subunits Kv4.3, MiRP1, and Kvβ3, and much lower levels of KChIP2. Lower-level contractile and metabolic activity was reflected in reduced Purkinje-fiber expression of calsequestrin, sarcoplasmic-reticulum ATPase and Na^+/K^+-ATPase. Subunits of potential relevance to arrhythmogenesis not previously recognized to be differential include inositol–trisphosphate receptors (IP_3R) and calmodulin. Several subunits of poorly-resolved function clustered to Purkinje-fiber tissue, including 3 Cl^--channels (ClC2, ClC6 and ClC7), the putative K^+-channel β-subunit KChAP and the two-pore 4 transmembrane-domain K^+-channel TASK2. Atrial–ventricular differences included such well-known atrial-predominant subunits as Kv1.5, Kir3.1, Cav3.1 and connexin40 [2,18], along with subunits of less-well appreciated differential function like TASK-1, TWIK-1, the Ca^{2+}-channel β-subunit Cavα2δ2 and MiRP3 (KCNE4). Ellinghaus et al. used pangenomic arrays to compare atrial with ventricular gene-expression, and similarly noted stronger expression of Kv1.5, TWIK-1 and TASK-1 in atria, along with stronger expression of Kir2.1 in ventricles [17].

The agreement of certain findings with previously-established important distribution characteristics supports the validity of the analysis and the identification of novel differences points to hypotheses for subsequent functional investigation. The results in Fig. 1 pertain only to relative mRNA levels but not to absolute transcript-expression. However, quantitative PCR allows for absolute expression levels to be obtained, which were used to create expression-profile maps indicating differentially-expressed subunits according to the absolute level of gene-expression [14]. These data are potentially useful to guide subunit selection for follow-up study.

2.3. Pacemaker activity

Marionneau et al. examined regional ion-channel subunit expression in the mouse heart with high-throughput PCR, paying particular attention to the properties of pacemaking tissues like the sinoatrial (SAN) and atrioventricular (AVN) nodes [19]. Hierarchical analysis

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