A pproximately one decade after the cloning of the first potassium channel, potassium channel genes of amazing diversity have emerged, many of them expressed in the heart. A magnitude of α subunits forming homotetramers or heterotetramers, multiple regulatory sub-units, and alternative splicing of genes adds up to a seemingly endless diversity of potassium channels. Considering the relative uniformity of the major cardiac inward currents, most of the heterogeneity in action potential waveforms among different species and anatomical regions seems to be related to differences in potassium channel expression. Recent attention has focused on electrical heterogeneity within atrial and ventricular myocardium, which also seems predominantly to reflect differences in potassium channel expression. Most of these studies have been done on a functional level; now information about molecular substrates of regional electrical heterogeneity is emerging.

Because of the essential importance for identification of potential targets for therapeutic interventions, much attention has recently focused on 2 aspects: elucidation of the molecular identity of cardiac potassium channels and their correlation to currents, including regional heterogeneity, and identification of regulatory pathways relevant to ion channel expression under normal and pathological conditions.

**Molecular Correlates of Potassium Currents in the Heart**

Molecular identification of potassium channels has been guided by macroscopic current characteristics, single-channel analysis, and pharmacological tools, comparing native currents to currents of candidate genes expressed in heterologous expression systems. In addition, the relative abundance of potassium channel transcripts detected in tissue samples of the anatomical region studied was taken into account. Awareness of regional electrical heterogeneity resulted in tissue sampling from areas considered electrically homogenous to assure that measurements with in situ mRNA detection methods would require coordination of electrophysiological measurements with in situ mRNA detection methods.1

This concept has been addressed by Schultz et al2 in this issue of *Circulation Research.* In rat ventricular myocytes from midmyocardial layers, measurements of potassium currents were combined with qualitative assessments of the presence or absence of Kv2.1 and Kv4.3 mRNA transcripts by a single-cell reverse transcriptase–polymerase chain reaction (RT-PCR) technique. In contrast to the good correlation between the transient outward current (Iₒ) and the presence of Kv4.3 mRNA, a large discrepancy was observed between tetraethylammonium (TEA)-sensitive delayed rectifier currents and the presence of Kv2.1 mRNA transcripts, which is thought to contribute a major part of the TEA-sensitive delayed rectifier current in rat ventricle.3 In fact, there was no difference in mean size or decay time of the TEA-sensitive currents between cells positive and negative for Kv2.1 mRNA transcripts.

How can this finding be interpreted? Of course, there are technical concerns in that the RT-PCR technique may have missed Kv2.1 transcripts present in a cell. However, recovery of Kv4.3 mRNA was consistently successful, and the technique has been proven useful for correlating ion currents to mRNA transcripts in neurons. Moreover, the usual worry with PCR, given the extreme sensitivity of the technique, is false-positives rather than false-negatives. Thus, the conclusion seems to justify that at the level of Kv2.1 mRNA, significant cell-to-cell variability exists, with transcripts present in only 40% to 50% of the myocytes. However, the presence of Kv2.1 mRNA does not warrant functional protein, in which case the uniformly observed TEA-sensitive current would be encoded by different genes. Although this cannot be definitively excluded, the most likely interpretation of the data is that potassium channel expression within these cells is heterogeneous, with other potassium channel α subunits contributing to the TEA-sensitive current in cells negative for Kv2.1 mRNA, possibly Kv1.2, Kv1.5, Kv3.1, Kv3.2, or yet another unidentified potassium channel gene. Earlier findings support this view, demonstrating significant cell-to-cell variability within identified anatomical regions by in situ hybridization.1

This study marks a first step toward high-resolution correlation of molecular substrates to native ion currents in the heart.
heart; probing for additional potassium channel α subunits and a pharmacological profile of the TEA-sensitive current seems useful. However, to accomplish a more definitive identification between K⁺ channel genes and native currents, several other approaches should be considered, including immunohistochemistry with subunit-specific antibodies to confirm the localization of the subunits in the membrane of the cells, specific antibodies that alter channel function to confirm the identity of the current studied, and elimination of responsible genes or transcripts by a transgenic or antisense approach to eliminate the current considered related to the gene.⁴,⁵

Regional and genetic diversity of potassium channels makes correlation of native ion channels with genes a difficult task. However, it also holds great promise: the multitude of α and β subunits being expressed may provide many more targets for rationally designed therapeutic interventions than presently perceived, some of which may have the potential for regional specificity.

**Regulatory Pathways of Cardiac Ion Channel Expression**

Differential regional expression of ion channels necessitates regulatory pathways to control the specific pattern. A very characteristic distribution has been recognized for the Ca²⁺-independent transient outward current, Iₒ, which is strongly influenced by location within the ventricular wall, with 5-fold larger currents in epicardial than endocardial layers.⁶ Iₒ seems to be highly regulated, being affected by electrical remodeling in atrial fibrillation and, at the ventricular level, by cardiac hypertrophy and failure, with up to 70% downregulation of the current in these disease states.⁷ Therefore, regulation of Iₒ, encoded mostly by Kv4.3 in human and canine ventricle, seems to be an interesting target. Is control of expression of normal development and regional distribution exerted along the same or different pathways as under pathological conditions? Is regulation of Iₒ attributable to changes in Kv4.3 α subunit expression or rather related to modulatory subunits? Downregulation of Iₒ in human heart failure has been found to correlate with the reduction of Kv4.3 mRNA levels, suggesting that channel expression is at least in part regulated by steady-state accumulation of Kv4.3 mRNA.⁸

Potential mechanisms of Kv4.3 downregulation in cardiac hypertrophy and failure are addressed by Zhang et al.⁹ in this issue of Circulation Research, advancing a novel concept of dual regulatory control of Kv4.3 mRNA accumulation by hypertrophic stimuli. In rat neonatal myocytes, both phenylephrine and angiotensin II caused Kv4.3 mRNA to decrease by ≈50%, but with a notably different time course: decay in response to angiotensin II was much more rapid, with minimal Kv4.3 mRNA levels reached after only 8 hours, much earlier than after exposure to phenylephrine. As turnover measurements revealed that Kv4.3 mRNA was very stable, with a half-life of >20 hours, destabilization of Kv4.3 mRNA was concluded to be the mechanism underlying downregulation of Kv4.3 mRNA in response to angiotensin II. Kv4.3 promoter-reporter constructs confirmed this concept, because angiotensin II had no effect on transcriptional activity, whereas phenylephrine inhibited Kv4.3 promoter activity. Thus, the influence of the hypertrophic stimuli phenylephrine and angiotensin II on Kv4.3 mRNA accumulation is exerted by disparate pathways.

Provided that this finding is applicable to adult tissue, specifically human myocardium, and that steady-state mRNA levels of Kv4.3 translate into functional current, this study might prove to be of utmost importance for understanding expression of ion channels under normal and pathophysiological conditions. Angiotensin II has emerged as a central neurohumoral signal in the pathophysiology of cardiac hypertrophy and failure. In addition to circulating angiotensin II, the hormone is produced locally within the myocardium under normal conditions, with increased activity during cardiac hypertrophy and failure.¹⁰ Therefore, involvement of angiotensin II in the downregulation of Iₒ in heart failure, or, more generally, in cardiac ion channel expression, is an attractive hypothesis. Another perspective offered by this hypothesis is related to findings of increased levels of angiotensinogen in human endocardium.¹¹ Higher levels of angiotensin II in endocardium might decrease Kv4.3 mRNA accumulation and, hence, Iₒ expression, possibly contributing to the transmural gradient of Iₒ. However, caution is warranted: it has not yet been determined whether the gradient in Iₒ is related to a similar transmural expression gradient of Kv4.3 α subunit; other factors, such as distribution of modulatory subunits, could be responsible as well. Canine endocardial and epicardial myocytes, at least, did not reveal any changes in Kv4.3 mRNA abundance after incubation with angiotensin II, suggesting that mechanisms other than altered Kv4.3 mRNA accumulation may be operative.¹²

The electrical homogeneity of myocardium in situ does not seem to reflect electrophysiological homogeneity at a cellular and molecular level, where significant regional and cell-to-cell heterogeneity can be detected, especially related to the diversity of potassium channel expression. Identification of the pathways of ion channel regulation holds great promise for therapeutic interventions if we succeed in unraveling the complexities of ion channel diversity and the relation of that diversity to the electrical stability of the heart.

**References**


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