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Transmural gradients in ion channel and auxiliary subunit expression

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ABSTRACT

Evolution has acted to shape the action potential in different regions of the heart in order to produce a maximally stable and efficient pump. This has been achieved by creating regional differences in ion channel expression levels within the heart as well as differences between equivalent cardiac tissues in different species. These region- and species-dependent differences in channel expression are established by regulatory evolution, evolution of the regulatory mechanisms that control channel expression levels. Ion channel auxiliary subunits are obvious targets for regulatory evolution, in order to change channel expression levels and/or modify channel function. This review focuses on the transmural gradients of ion channel expression in the heart and the role that regulation of auxiliary subunit expression plays in generating and shaping these gradients.

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Abbreviations: Epi, epicardium; Mid, mid-myocardium; Endo, endocardium.

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The level at which different ion channels are expressed in electrically excitable cells is tightly regulated by natural selection, just as the functional properties of the channels are subject to selection (Rosati et al., 2008; Rosati and McKinnon, 2009). Even modest changes in expression levels can have large effects on cellular electrophysiological function and/or the calcium metabolism of cardiac myocytes which, in turn, affects overall organ function (Rosati et al., 2008). Large differences in ion channel expression levels are observed, both between different regions of the heart (Barth et al., 2005; Gaborit et al., 2007; Marionneau et al., 2005; Rosati et al., 2003, 2006; Szentadrassy et al., 2005) as well as between equivalent cardiac tissues in different species (Rosati et al., 2008). These species- and region-dependent differences in channel expression are established by regulatory evolution.

Regulatory evolution is a broad category that encompasses the evolution of all the various mechanisms that can affect expression of a given protein. Regulatory evolution establishes the baseline expression levels of the different ion channels in each differentiated compartment of the heart. Evolution of a given gene's promoter and of the various cis-regulatory modules that modulate the function of that promoter is known, more specifically, as cis-regulatory evolution. Baseline expression of ion channels in heart appears to be predominantly determined at the level of transcription (Abd Allah et al., 2012; Chandler et al., 2009; Gaborit et al., 2007; Marionneau et al., 2005; Rosati and McKinnon, 2004). Consequently, it is likely that cis-regulatory evolution will be a major factor determining tissue specific channel expression levels in the heart and there is experimental evidence to support this hypothesis (Yan et al., 2012). This does not preclude the possibility that virtually any aspect of the channel biosynthesis pathway, intracellular transport and signaling pathway regulation could also evolve to modify channel expression levels.

Ion channel auxiliary subunits can be important modifiers of all these processes and are obvious targets for regulatory evolution in order to change functional channel expression levels (Yan et al., 2012). Exactly which proteins qualify as bona fide channel auxiliary subunits eludes a simple definition. There are a plethora of proteins that can interact transiently with a given channel during its biosynthesis and transport within the cell (Vandenberg et al., 2012). Many of these are general purpose proteins, chaperones, co-chaperones, cytoskeletal proteins, etc., for which there is currently no evidence that they directly contribute to differential expression of channels within the heart. For the purposes of this review we rely on a functional definition, addressing only those proteins generally understood to be channel auxiliary subunits in the literature (Table 1). In general, these proteins are bound to the pore-forming subunit of the channel when it is located in the cell membrane, although they may first combine with the channel at much earlier stages of channel synthesis/transport.

Channel expression levels will tend to fall to the lowest levels consistent with the positive selection criteria acting on a given electrophysiological system during the course of evolution (Kim et al., 2015). This is because mutations generally erode regulatory function over time and regulatory function will only be maintained if there is some opposing positive selective pressure. For example, there will be strong positive selection for efficient action potential conduction and electrical stability, resulting in the maintenance of stable sodium channel expression levels over long periods of evolutionary time in a given species. Purifying selection will eliminate mutant alleles that reduce channel expression below this baseline level. Mutations in the human sodium channel promoter that reduce transcriptional function result in an increased risk of arrhythmia (Bezzina et al., 2006; Yang et al., 2008). Individuals carrying these mutations will have an increased mortality rate and, therefore, a reduced reproductive potential. Eventually these mutations will be eliminated from the population, albeit somewhat slowly.

Evolution has acted to shape the action potential in different regions of the heart in order to maximize electrical stability as well as to shape calcium influx (contraction timing and strength) to produce a maximally stable and efficient pump. In part, this has required establishing region specific patterns of ion channel expression, such as differential expression of channels within the ventricle wall. In the hearts of large mammals, the transient outward current (I_{to}) is expressed in a large transmural gradient across the ventricle walls. The relatively high expression of this channel in the epicardium and mid-myocardium of the ventricle wall can be interpreted in a similar way to the sodium channel there is positive selection for expression of the channel at relatively high levels in these tissues. Purifying selection maintains this expression level in the face of any mutations that might reduce or eliminate expression of this channel in these species. The relative absence of expression of the I_{to} in the endocardium can be explained in one of two ways. The simplest explanation is that there is no positive selection for I_{to} expression in the endocardium and the corresponding regulatory mechanisms have either eroded over time due to mutation or were never selected for in the first place. Alternatively, expression of the I_{to} channel in the endocardium could somehow reduce fitness, resulting in selection against high I_{to} expression levels in this tissue. In this case, competing constraints may exist, so that in addition to positive selection for I_{to} expression in the endocardium there is also negative selection, which dominates the overall fitness function for this particular tissue. It is difficult to distinguish between these two possibilities. The absence or reduced expression of a given current in a particular tissue compartment does not necessarily imply anything beyond the absence of positive selective pressure, since this is the default state, due to the cumulative effect of mutations on regulatory function (Kim et al., 2015). The constraints acting on the evolution of channel expression in the heart are complex and it can be difficult to make definitive conclusions about the necessity for particular channel expression levels in a specific species, although broad patterns can be discerned (Rosati et al., 2008).

1. Role of auxiliary subunits in controlling functional channel expression levels

Most channel forming subunits are associated with auxiliary subunits (Table 1) (Abriel et al., 2015). These subunits have a diverse set of functions including facilitating transport from the ER to the Golgi or from the Golgi to the plasma membrane, modification of channel kinetic properties, connection to cytoskeletal elements, targeting to specific membrane compartments, connection to regulatory scaffolds and mediation of cell signaling pathways (Abbott, 2014; Trimmer, 1998; Vacher and Trimmer, 2011). Unlike the