TOPICAL REVIEW

Mechanisms of cardiac potassium channel trafficking

David F. Steele, Jodene Eldstrom and David Fedida

Department of Anaesthesiology, Pharmacology and Therapeutics, University of British Columbia, 2350 Health Sciences Mall, Vancouver, British Columbia, Canada V6T 1Z3

The regulation of ion channels involves more than just modulation of their synthesis and kinetics, as controls on their trafficking and localization are also important. Although the body of knowledge is fairly large, the entire trafficking pathway is not known for any one channel. This review summarizes current knowledge on the trafficking of potassium channels that are expressed in the heart. Our knowledge of channel assembly, trafficking through the Golgi apparatus and on to the surface is covered, as are controls on channel surface retention and endocytosis.

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Corresponding author D. Fedida: Department of Physiology, University of British Columbia, 2146 Health Sciences Mall, Vancouver, British Columbia, Canada V6T 1Z3. Email: fedida@interchange.ubc.ca

The intracellular trafficking of membrane proteins such as ion channels is complex. These molecules must be synthesized in the endoplasmic reticulum, assembled and processed appropriately, then trafficked and targeted to the membrane or membrane subdomains where they will function. Involved are ER resident proteins like chaperones and glycosylases, microtubules and their associated motors, transport vesicle and Golgi apparatus components, the actin cytoskeleton, myosins, anchoring proteins and more. The specific roles of these various components in the trafficking of ion channels are only beginning to be elucidated, and the entire trafficking pathway is not known for any single channel. This review will examine our knowledge of the trafficking of potassium channels that are expressed in the heart in the context of our knowledge of trafficking mechanisms in general. The generalized path of a channel travelling through a cardiac myocyte will be described from channel synthesis to recycling. Specific knowledge will be highlighted as will many of the gaps in that knowledge. While some results have been confirmed in cardiomyocytes, most work has been conducted using heterologous cells such as HEK293 cells and *Xenopus* oocytes.

Early events in the endoplasmic reticulum

A channel's life begins in the endoplasmic reticulum. As demonstrated for Kv1.3 – and probably true for most channels – assembly begins concurrently with synthesis on the rough ER (Kosolapov & Deutsch, 2003; Kosolapov *et al.* 2004; Robinson & Deutsch, 2005; Lu & Deutsch, 2005). Of course, not every nascent channel will assemble properly and quality control checks exist to ensure that only properly folded and assembled channels are exported from the ER. These checks as well as forward trafficking and/or retention signals are incorporated within the channel primary sequences and have profound influences on the fates of the newly synthesized channels. The simplest control on channel fate may relate to the inappropriate exposure of hydrophobic residues to solvent upon misfolding. Such a channel may be retained in the ER simply because it aggregates there with other misfolded proteins. Similarly, hydrophobic exposure to solvent probably promotes degradation of misfolded channels by the proteosome (Asher *et al.* 2006). This mechanism has been well explored in human ether-à-go-go-related protein (hERG) mutants that are defective in trafficking (Furutani *et al.* 1999; Gong *et al.* 2005; Gong *et al.* 2006; Anderson *et al.* 2006), some of which, interestingly, can be rescued by hERG-binding drugs (Zhou *et al.* 1999; Ficker *et al.* 2002; Paulussen *et al.* 2002; Gong *et al.* 2005; Rossenbacker *et al.* 2005) and/or chemical chaperones (Zhou *et al.* 1999; Anderson *et al.* 2006).

Quality control

To deal with problems beyond this probably non-specific aggregation, potassium channels incorporate very specific quality control systems. One such mechanism involves RXR motifs first identified in the K_{ATP} channel (Zerangue *et al.* 1999) and later shown to be functional also in Kir2.1, the major cardiomyocyte inward rectifier (Ma *et al.* 2001), as well as in hERG (Kupershmidt *et al.* 2002) and other channels (Chang *et al.* 1999; Margeta-Mitrovic *et al.* 2000; Standley *et al.* 2000). These motifs are hidden in properly folded and assembled channels but promote

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retention in the ER when they are exposed on the channel surface. RXR motifs are also present in many voltage-gated (Kv) channels, although, with the exception of hERG (Kupershmidt *et al.* 2002), their functions there have yet to be established. Other motifs, such as dilysine repeats (Harter & Wieland, 1998; Zerangue *et al.* 2001) also serve to inhibit trafficking out of the ER. The mechanisms by which these motifs prevent export from the endoplasmic reticulum have yet to be established, but some intriguing clues exist.

RXR motifs bind 14-3-3 proteins (Yuan *et al.* 2003), a family of molecules with diverse functions, thought to promote surface expression of membrane proteins (Shikano *et al.* 2006). While at first glance this seems inconsistent with a retention role for the RXR motifs, Yuan *et al.* (2003) have shown that the affinity of the 14-3-3 proteins for the RXR motifs is dramatically higher for tetrameric rather than monomeric constructs. Thus, one possibility is that 14-3-3 proteins promote the export of properly assembled channels. Interestingly, COPI, a component involved in recycling from the Golgi to the ER (Aoe *et al.* 1998; Nufer & Hauri, 2003), competed with 14-3-3 for RXR perhaps indicating that misassembled channels, with lower 14-3-3 affinity, are returned to the ER by COPI (Yuan *et al.* 2003). C-terminal dilysine repeats, which also function as ER retention signals (Cosson & Letourneur, 1994), have been shown to bind COPI (Mellman & Warren, 2000; Shikano & Li, 2003) and binding of COPI to a dibasic motif in the twin-pore KCNK3 potassium channel is inhibited by 14-3-3β (O'Kelly *et al.* 2002). In this case, the competition is indirect; 14-3-3 binding to an adjacent 'release site' drives dissociation of the COP protein from the channel (O'Kelly *et al.* 2002). Another ER retention signal, KDEL (Zerangue *et al.* 1999), binds to the KDEL receptor in the transport vesicles, and this also targets proteins for Golgi-to-ER recycling (Zhou *et al.* 2002; Cabrera *et al.* 2003).

Forward trafficking signals – On to the Golgi

In addition to ER retention/recycling signals, potassium channels harbour forward trafficking signals that promote export from the ER. This is again via ER-to-Golgi transport, a complex and GTP-dependent process, involving COPI and COPII, additional Sec proteins, as well as a pair of Rab proteins and SarI (Lee *et al.* 2004; Murshid & Presley, 2004). COPII concentrates cargo in the transitional ER and COPI is recruited to the newly formed transport vesicles from where it retrieves recycling, escaped ER- and misfolded proteins back to the ER. Transport is conducted along microtubules and is dependent on the dynein motor (Presley *et al.* 1997).

Forward trafficking signals in potassium channels are quite diverse. FYCENE serves such a function in Kir2.1 (Ma *et al.* 2001; Stockklausner *et al.* 2001), Kv1.4 harbours a VXXSL signal, and Kv1.5 harbours a similar but less effective VXXSN (Zhu *et al.* 2003; Li *et al.* 2000). The cyclic nucleotide-binding domains of hERG, ERG3 and HCN2 may also act as forward-trafficking signals (Akhavan *et al.* 2005) and the Kv1.4 pore appears to harbour a pore-based forward trafficking determinant (Watanabe *et al.* 2004). The evidence for the latter, though, is consistent also with the absence of a retention motif in Kv1.4 that is present in Kv1.1. It has been suggested that these forward trafficking motifs may interact directly or indirectly with COPII (Ma & January, 2002). Certainly dileucine motifs, which are ubiquitously present in potassium channels and which function as forward trafficking motifs in other membrane proteins, bind to COPII (Nufer *et al.* 2002). Of course, the diversity in export signals in the various channels implies that a complex scenario is probably operating, leading to differential regulation of channel trafficking. Whether all forward trafficking signals function by promoting ER-to-Golgi transport remains to be established. Also, of course, forward trafficking signals are not the sole promoters of exit from the ER.

Chaperones like Hsp70/Hsc70, Hsp90 and calnexin have been shown to facilitate ER exit of hERG (Ficker *et al.* 2003; Gong *et al.* 2006) and Kv1.2 (Manganas & Trimmer, 2004). Very probably, these do so not via an active forward trafficking role but rather by promoting proper folding/assembly of the channels, although, in the case of Hsp70/Hsc70, there may be a role in facilitating vesicular trafficking and membrane fusion as well (Zinsmaier & Bronk, 2001; Clay & Kuzirian, 2002). β-subunits, KChIPs, KChAP and other accessory proteins also bind to their target channels in this locale, promoting forward trafficking via chaperone-like activities (Shi *et al.* 1996; Wible *et al.* 1998; Pongs *et al.* 1999; Kuryshev *et al.* 2000; Bahring *et al.* 2001). This is in addition to their roles, in the cases of KChIPs and the β-subunits, as modifiers of channel kinetics (Wible *et al.* 1998; An *et al.* 2000; Hanlon & Wallace, 2002; Nerbonne & Guo, 2002; Aimond *et al.* 2005).

Interestingly, KChIP was recently reported to traffic from the ER to Golgi in vesicles lacking COPII (Hasdemir *et al.* 2005). Sar1 activity, essential for most ER-to-Golgi traffic (Yoshihisa *et al.* 1993; Kuge *et al.* 1994; Gurkan *et al.* 2006) was not required. That promotion of Kv4.2 expression by the neuron-specific KChIP3 is modulated by GRKs and calcineurin (Ruiz-Gomez *et al.* 2007) strongly suggests that KChIPs also function downstream of ER-to-Golgi transport and as more than mere chaperones. It will be very interesting to learn what pathway(s) are employed for this trafficking, how it is regulated and whether other channels are transported similarly. Figure 1 summarizes some of the major features of ER-to-Golgi trafficking.

Through the Golgi and on to the sarcolemma

The sorting and targeting of cardiac potassium channels has barely been explored. Nevertheless, it is highly likely that this sorting, like that of other newly synthesized secretory and plasma membrane proteins, begins in the Golgi apparatus (Gu *et al.* 2001). Glycosylation is completed in the Golgi apparatus, a step important for the surface expression of channels such as EagI (Napp *et al.* 2005), K_{ATP} (Conti *et al.* 2002), Kv1.4 (Watanabe *et al.* 2004) and other Kv1-type channels (Khanna *et al.* 2001; Folco *et al.* 2004), although the degree to which cardiac potassium channels are sensitive to interference with glycosylation is variable. While the stability of glycosylation-defective hERG channels at the membrane is reduced, glycosylation is not required for hERG expression in heterologous cells (Gong *et al.* 2002).

Basic sorting to the sarcolemma or to intracellular organelles certainly occurs in the Golgi (specifically, the *trans*-Golgi network) (Gu *et al.* 2001), but it is likely that targeting to specific sarcolemma subdomains is effected mainly downstream of this organelle (Cereijido *et al.* 2003; Mogelsvang & Howell, 2006). We know that Kir2.1 and other inward rectifiers require an intact N-terminal signal for exit from the Golgi when expressed in heterologous cells (Stockklausner & Klocker, 2003), but whether this is a bona fide sorting event is unclear.

In neurons, the targeting of potassium channels is highly specific. Kv4.2, for example, is generally targeted to the distal regions of dendrites, whereas in myelinated neurons, Kv1 channels localize to juxtaparanodal regions (reviewed in Trimmer & Rhodes (2004)). Known to involve various motor proteins, the actin and microtubule cytoskeletons, scaffolding proteins and accessory subunits, just how these various components work together to achieve directed targeting is very poorly understood (reviewed in Lai & January (2006). Similarly, while specific targeting clearly occurs in cardiac myocytes (see below), we have little insight into the mechanism(s) by which this is effected. Nevertheless, some progress has been made in identifying proteins that enhance forward trafficking and targeting of cardiac potassium channels.

Involvement of MAGUK proteins

The membrane-associated guanylate kinase (MAGUK) protein CASK has been implicated in the targeting of Kir2 channels (Leonoudakis *et al.* 2004) in heart and brain,

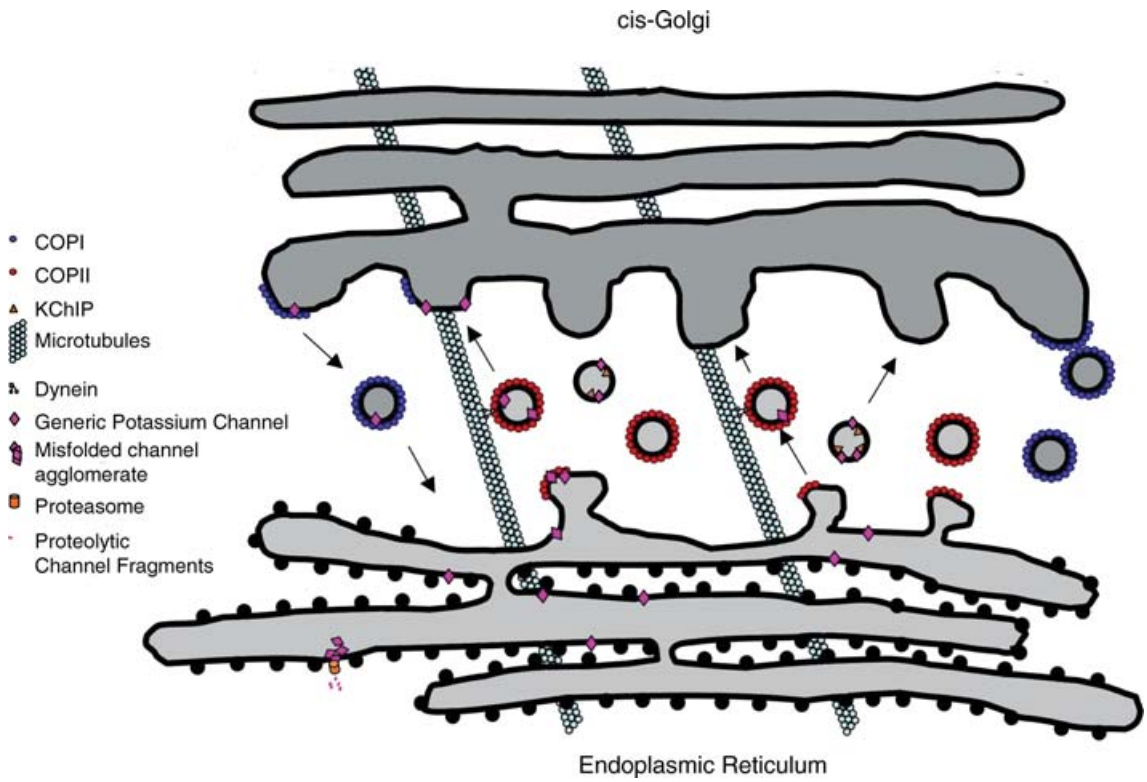

Figure 1. ER to Golgi trafficking of cardiac potassium channels
Following synthesis on the rough ER, channels which make their way to the transitional ER are recruited into COPII-coated vesicles. They then traffic along microtubules to the *cis*-Golgi in a dynein-dependent manner. At the *cis*-Golgi, properly assembled channels are sent on through the organelle. KChIP, accompanied by Kv4.2, is shown trafficking to the Golgi in vesicles lacking COPII. Misassembled channels or those with 'ER-retention motifs' are illustrated returning from Golgi apparatus in COPI-coated vesicles. Also illustrated are agglomerated misfolded channels being degraded by a proteasome after translocation out of the ER.

where it forms complexes with other PDZ proteins, i.e. SAP97, Veli-1, Veli-3 and Mint1. Expression of a dominant negative CASK mutant disrupts basolateral targeting of these channels in polarized epithelial cells (Leonoudakis *et al.* 2004); Kir2.2 localizes non-specifically to both the basolateral and the apical membrane, instead. While CASK may indeed be intimately involved in directing potassium channels to their ultimate destinations in the cell, MAGUKs are more generally thought to serve as scaffolding proteins that anchor proteins at their targeted locations (Carnegie & Scott, 2003) rather than targeting the channels, per se. Given that MAGUK complexes associate with motor proteins (Hanada *et al.* 2000; Naisbitt *et al.* 2000; Wu *et al.* 2002), though, the importance of proteins like CASK and SAP97 in intracellular trafficking may be greater than thought.

SAP97 has been implicated in the trafficking of other potassium channels, as well. In heterologous expression systems, Kv1.5 has been reported to interact with SAP97 (Murata *et al.* 2001; Godreau *et al.* 2002; Godreau *et al.* 2003) and to localize to lipid rafts (Martens *et al.* 2000; Martens *et al.* 2001) where it forms a tripartite complex with caveolin-3 and SAP97 (Folco *et al.* 2004). However, in rat and canine cardiac myocytes no evidence of lipid raft localization or of Kv1.5 binding to either SAP97 (Eldstrom *et al.* 2003) or caveolin-3 could be found (Eldstrom *et al.* 2006). The interaction of Kv1.5 in heterologous cells may be an artifact of transient overexpression (Mathur *et al.* 2006), although, if so, the artifact is an interesting one, occurring only in transiently transfected cells and not in stable lines. Nevertheless, SAP97 overexpression increases the levels of Kv1.5 at the cell surface. The mechanism by which this occurs has yet to be elucidated.

Other Kv channels have also been shown to interact with SAP97 (Tiffany *et al.* 2000) and to do so directly with the closely related PSD95 (Kim *et al.* 1995; Imamura *et al.* 2002), although the latter is not expressed in heart (Seeber *et al.* 2000). Unlike its effect on Kv1.5 though, SAP97 co-expression down-regulates these other Kv channels (Tiffany *et al.* 2000). While conceivably also an artifact of overexpression, it is certainly possible that SAP97 plays a role in regulating the forward trafficking of these channels as well.

Cytoskeletal players

SAP97 has been shown to bind myosin VI (Wu *et al.* 2002), a molecular motor implicated in secretion, endoyctosis and submembrane vesicular trafficking along the actin cytoskeleton (Lister *et al.* 2004). Myosins, tracking along the actin cytoskeleton, are involved mainly in trafficking near the cell surface and it has been long known that disruption of the actin cytoskeleton can have profound effects on potassium channel functional expression (Calaghan *et al.* 2004). Such disruption dramatically increases the expression of Kv1.5 (Maruoka *et al.* 2000; Cukovic *et al.* 2001; Mason *et al.* 2002) and Kv4.2 (Wang *et al.* 2004) in both heterologous cells and cardiomyocytes. Similarly, disruption of the microtubule cytoskeleton increases Kv1.5 surface expression (Choi *et al.* 2005), although microtubule disruption did not affect Kv2.1 expression in heterologous cells (Martens *et al.* 2000). Long-range vesicular transport generally involves the microtubule cytoskeleton and the kinesin and dynein motors (Karcher *et al.* 2002).

Kinesins, which track along the microtubule cytoskeleton, have recently been directly implicated in the trafficking of Kv4.2. The neuron-specific kinesin isoform Kif17 was shown to interact with Kv4.2 in brain lysates and dissociated cortical neurons (Chu *et al.* 2006); expression of a dominant negative Kif17 construct in the neurons blocked surface expression of the channel. Deletion of a previously identified dileucine targeting domain from the channel, though, did not prevent Kv4.2 trafficking but, rather than being restricted to the dendritic tree, these channels were mistargeted and appeared widely throughout the neurons. While Kif17 is not expressed in heart (Setou *et al.* 2000), it is reasonable to expect that another kinesin isoform is involved in Kv4.2 transport in cardiomyocytes.

Plasma membrane insertion

Whatever the route by which a channel makes its way to the cell surface, it must insert into the sarcolemma once there. Membrane insertion appears to be a conserved process and while the specifics for most channels are unknown, the process is essentially certain to involve SNARE-mediated fusion of exocytotic vesicles with the sarcolemma (Hong, 2005; Jahn & Scheller, 2006). SNAREs are thought to deform membranes, disturbing the hydrophobic–hydrophilic boundary and directly causing fusion (Jahn & Scheller, 2006). Indeed, the exocytotic fusion SNARE proteins SNAP25 and Syntaxin 1A have been implicated in Kv1.1 and Kv2.1 plasma membrane integration (Fili *et al.* 2001; Ji *et al.* 2002; MacDonald *et al.* 2002; Michaelevski *et al.* 2002; Leung *et al.* 2003).

Localization, surface retention, recycling and degradation

Potassium channels don't merely traffic non-specifically to the sarcolemma. Instead, individual channel types localize to specific cell surface domains. ERG1 localizes to the transverse tubular network in rat atrial and ventricular myocytes whereas KCNQ1 (KvLQT1) is found in the peripheral sarcolemma and in T-tubules (Rasmussen *et al.* 2004). Kv4.2, Kir2.1 and TASK-1 are also localized at least in part to T-tubules (Takeuchi *et al.* 2000; Clark *et al.* 2001; Jones *et al.* 2002) and Kv1.5 is highly

enriched at the intercalated disk of rat and canine atrial and ventricular myocytes (Mays *et al.* 1995; Eldstrom *et al.* 2006), as, in part, is Kv4.2 (Barry *et al.* 1995) and Nav1.5 (Maier *et al.* 2002; Kucera *et al.* 2002). In ventricular myocytes, Kv1.5 is found also in proximity to the Z-lines (Eldstrom *et al.* 2006). Even in heterologous systems, potassium channels sometimes segregate into distinct cell surface microdomains (O'Connell & Tamkun, 2005). These distinct localizations may result from specific trafficking (see above) or from specialized anchoring in the cell membrane.

A number of candidates exist for mediators of specific targeting/retention of cardiac potassium channel isoforms. In addition to SAP97, caveolin and syntaxin 1A (see above), actin-binding proteins like α-actinin-2 and filamin have been at least circumstantially implicated in channel targeting and anchoring. α-Actinin-2, a molecule that links to the actin cytoskeleton, has been shown to directly bind Kv1.5 (Maruoka *et al.* 2000; Cukovic *et al.* 2001). Given that α-actinin-2 antisense RNA increases Kv1.5 surface expression (Maruoka *et al.* 2000) and the involvement of the actin cytoskeleton in early endosomal trafficking (Jeng & Welch, 2001), it is quite possible that actinin is involved in Kv1.5 endocytosis and/or in maintaining pools of Kv1.5 in vesicles just below the cell surface. Filamin, another molecule that binds the actin cytoskeleton, has been shown to interact with Kv4.2 (Petrecca *et al.* 2000). Kv4.2 expression is increased by filamin overexpression, suggesting that filamin's role may well be to anchor the channel at the membrane. Yet another actin-binding protein, cortactin, interacts with Kv1.2 (Hattan *et al.* 2002). Kv1.2 channels defective for cortactin binding express much more poorly in HEK293 cells than do their wild-type equivalents, suggesting a role in channel stabilization at the surface for this protein, as well.

Interestingly, the interaction of Kv1.2 with cortactin can be modulated by tyrosine phosphorylation; activation of the M1 muscarinic acetylcholine receptor dramatically attenuates the interaction of cortactin with the channel (Hattan *et al.* 2002). Implicating this attenuation with Kv1.2 endocytosis, Nesti *et al.* (2004) have demonstrated that phosphorylation of a specific Kv1.2 N-terminal tyrosine residue results in rapid internalization of that channel. Incubation of the cells with a dynamin-inhibitory peptide blocked this internalization, confirming the role

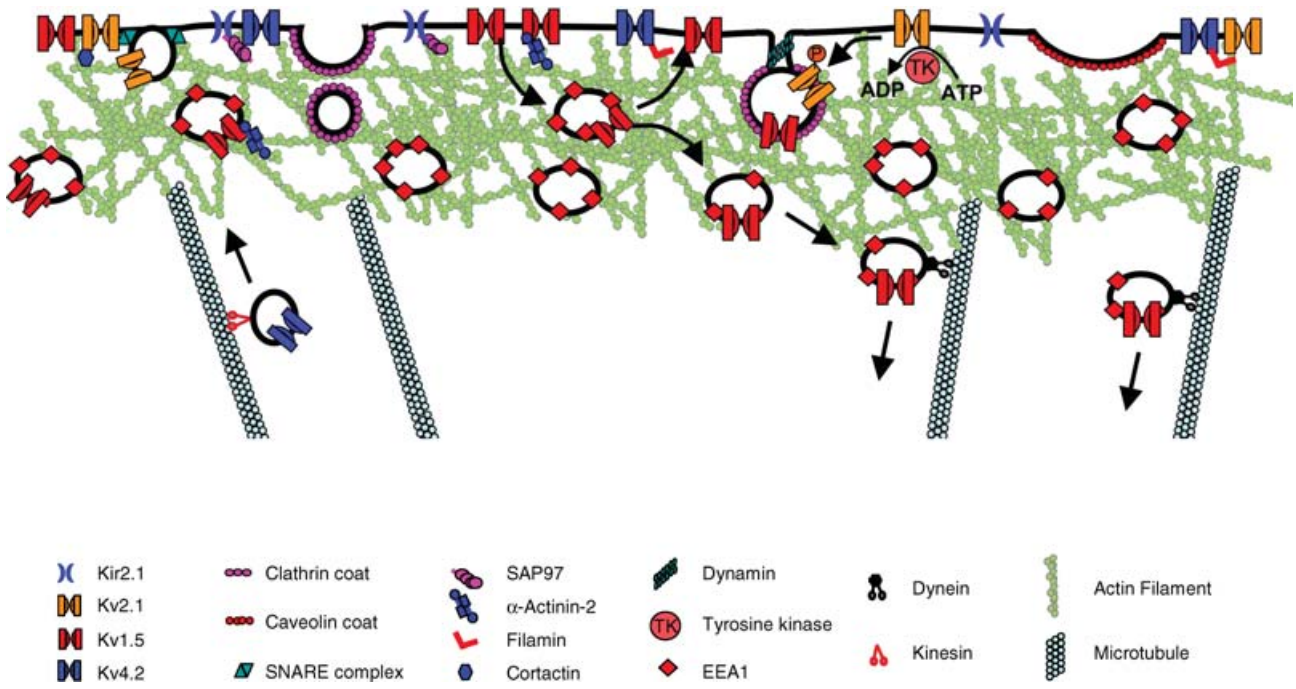

Figure 2. Potassium channel dynamics near the cell surface
Interactions of several cardiac potassium channels with components of the trafficking machinery near the sarcolemma are illustrated. Early endosomes travel through the cortical actin cytoskeleton and are pictured as either recycled to the sarcolemma or transferred to the dynein motor for further internalization. Anterograde trafficking of Kv4.2 is illustrated as involving kinesin based on the known interaction of Kv4.2 with Kif17 in neurons. The involvement of clathrin-coated pits in potassium channel endocytosis is hypothesized on the basis of the ubiquitous presence of dileucine motifs in the channels and the known interaction of Kir2.1 with clathrin. Kv1.5 and Kv2.1 are illustrated in the process of internalization: Kv1.2 in response to tyrosine phosphorylation and Kv1.5 on the basis of the known role for dynamin in its internalization. Other interactions are as described in the text of this review.

of endocytosis in this down-regulation of Kv1.2 functional expression.

Dynamin has been recently implicated also in the regulation of Kv1.5 expression (Choi *et al.* 2005). Dynamin catalyses the scission of endocytic vesicles from the plasma membrane (McClure & Robinson, 1996). It is important for clathrin-dependent and most clathrin-independent endocytosis (Takai *et al.* 2005) and, perhaps, in modulating actin dynamics at the cell surface (reviewed in Schafer, 2004). Suggesting that ongoing endocytosis is important for the maintenance of normal Kv1.5 expression, Kv1.5 currents are increased in heterologous cells treated with dynamin inhibitory peptide. Immunocytochemistry/confocal microscopy showed that Kv1.5 localized to early endosomes as well as to the cell surface and that dynamin inhibition dramatically reduced the number of these Kv1.5-positive endosomes. A proline-rich SH3 binding domain was found to be essential for internalization of this channel, perhaps implicating tyrosine phosphorylation in Kv1.5 endocytosis, as well.

Once internalized, a channel must eventually be either recycled to the membrane or degraded. In the same study that implicated the SH3 binding domain in Kv1.5 endocytosis, the dynein motor was shown also to profoundly affect Kv1.5 surface expression. Similar to its effects on the ClC-2 chloride channel (Dhani *et al.* 2003), dynein inhibition increased Kv1.5 surface expression as assayed both physically and electrophysiologically (Choi *et al.* 2005). These increases in Kv1.5 functional expression matched those obtained with the dynamin-inhibitory peptide. Dynein is a molecular motor required for retrograde trafficking of cargo along the microtubule cytoskeleton. Very probably, interference with this retrograde trafficking prevented the trafficking of newly formed endosomes and these endosomes, unable to internalize further, either reintegrated into the sarcolemma or interfered with the further endocytosis of the channel, thus increasing Kv1.5 net surface expression.

Fates unknown

Beyond the apparent role of dynein in modulation of Kv1.5 surface expression, little is known about the fate of cardiac potassium channels following internalization. Probably many recycle to the sarcolemma and others are targeted for degradation, perhaps with ubiquitination playing an important role in the determination of a channel's fate (Lin *et al.* 2005; Chapman *et al.* 2005; Kato *et al.* 2005). Future work with Rab proteins, etc., will be necessary to identify the compartments to which various potassium channels segregate, not only after endocytosis, but throughout the trafficking process. A summary of our present knowledge concerning near-cell surface trafficking of cardiac potassium channels is presented in Fig. 2.

Still more questions

Many questions remain about potassium channel trafficking in the heart. Are pathways shared by most potassium channels or are different pathways utilized for each? Is Hsc70 involved in channel endocytosis as well as forward trafficking? What other molecules are involved in trafficking and targeting? How is trafficking regulated? By what mechanisms do drugs that promote or inhibit potassium channel trafficking (Cordes *et al.* 2005; Kuryshev *et al.* 2005; Anderson *et al.* 2006; Gong *et al.* 2006; Rajamani *et al.* 2006; Sun *et al.* 2006) operate? The study of cardiac ion channel trafficking is a young and growing field. Undoubtedly the processes are complex and intertwined. Much is to be gained both intellectually and clinically in deciphering the trafficking of these channels.

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