Potassium Channels Keep Mobile Cells on the Go

Cell motility is a prerequisite for the creation of new life, and it is required for maintaining the integrity of an organism. Under pathological conditions, “too much” motility may cause premature death. Studies over the past few years have revealed that ion channels are essential for cell motility. This review highlights the importance of K⁺ channels in regulating cell motility.

The ability of cells to move is a fundamental aspect of life. This holds true for unicellular as well as for multicellular organisms. Consequently, some of the mechanisms underlying cell motility were highly conserved throughout evolution. Thus studying the motility of amebae, ciliates and sperm can give insights into mechanisms employed by mammalian cells. Two different modes of cell motility will be considered in this review: a swimming movement driven by ciliary or flagellar beating and a crawling or ameboid movement, which will be referred to as cell migration hereafter. Both forms are found in humans, including humans.

In mammals, cell movement by flagellar beats is restricted to sperm cells. These cells employ a flagellum to swim up the fallopian tube in search of an oocyte (26). In contrast, the ameboid type of movement is used by a wide spectrum of cell types and it is the basis for many physiological and pathophysiological processes. It starts early during embryogenesis (8), and in the brain it does not stop until after birth (108). Movement of fibroblasts or epithelial cells during wound healing also involves the ameboid-type of migration (20). Other processes strongly relying on cell migration are the responses of the immune system, angiogenesis (95), and the formation of tumor metastases (103). These examples indicate that altered function of migrating cells can be associated with severe, possibly life-threatening pathophysiological conditions, for instance tumor metastasis.

We will begin this review on the function of K⁺ channels in cell motility with short overviews of mechanisms underlying ciliary beating and ameboid cell migration (58, 76, 78, 102). These sections will be followed by a brief description of the role of K⁺ channels in the motility of ciliates and sperm cells and by a discussion of the impact of K⁺ channels in ameboid cell migration, respectively. Other types of ion channels, aquaporins, or transporters will not be dealt with systematically. We instead refer to recent reviews that describe the role of these transport proteins in cell motility in detail (34, 64, 82, 84, 93).

Swimming Controlled by Ciliary or Flagellar Beating

Cilia and flagella are hair-like, motile organelles projecting from the cell surface. Cilia are shorter than flagella and are present in large numbers on the cell surface. Their function has traditionally been studied in unicellular organisms like Tetrahymena. In mammals, cilia are found among others on the apical membrane of epithelial cells covering the airways, where they are required for mucociliary clearance (55), whereas flagella are only found in spermatozoa. Undulatory beating of the single flagellum propels sperm cells forward.

Cilia and flagella are usually composed of nine peripheral doublet microtubules with two central microtubules. This typical 9 + 2 axoneme runs longitudinally through the entire organelle (78). Harvesting the same 9 + 2 ultrastructure (78), it is not surprising that motile cilia and flagella share the same mechanisms of movement, which is driven by dynein motors. The interconnection of peripheral doublets and the central pair of microtubules converts the sliding movements of the peripheral doublets into bending motion (78). The ciliary/flagellar beat frequency determines the speed of swimming or creeping on a substrate, whereas the direction of movement is determined by the beat direction and the orientation of the cilia/flagella. The frequency and the orientation of beating are tuned by the local Ca²⁺ concentration inside the cilium/flagellum (59, 67). An increase in the Ca²⁺ concentration from 100 nM to 1 μM leads to a gradual acceleration of the forward movement because of a proportionally increasing ciliary beating frequency. As soon as the Ca²⁺ concentration exceeds a threshold value of 1 μM the direction of beating is reversed and the cell moves backwards.

In contrast to motile cilia, single primary cilia, which are found on almost all mammalian cells, lack the two central microtubules (9 + 6) and are therefore usually immotile. They are signaling platforms capable of chemosensory and mechanosensing (78). Primary cilia gained much attention recently when their involvement in a number of different pathologies including polycystic kidney disease was discovered (101). Primary cilia serve as mechanosensors and transduce signals into the cell interior by activation of Ca²⁺ channels (31). Tran and colleagues showed that polycystic kidney disease in C. elegans, which is caused by mutations in ~ 60 different genes, is the basis for many physiological and pathophysiological processes. It starts early during embryogenesis (8), and in the brain it does not stop until after birth (108). Movement of fibroblasts or epithelial cells during wound healing also involves the ameboid-type of migration (20). Other processes strongly relying on cell migration are the responses of the immune system, angiogenesis (95), and the formation of tumor metastases (103). These examples indicate that altered function of migrating cells can be associated with severe, possibly life-threatening pathophysiological conditions, for instance tumor metastasis.

Primary cilia are part of the primary cilium, a unique organelle found on almost all mammalian cells. Primary cilia are responsible for mechanosensing and chemosensing, and their dysfunction is associated with various diseases, including polycystic kidney disease (101). Primary cilia are composed of 9+2 microtubules and are involved in the regulation of cell polarization, epithelial cell polarity, and cell migration (31).

Studies over the past few years have revealed that ion channels are essential for cell motility. This review highlights the importance of K⁺ channels in regulating cell motility.

In contrast to motile cilia, single primary cilia, which are found on almost all mammalian cells, lack the two central microtubules (9 + 6) and are therefore usually immotile. They are signaling platforms capable of chemosensory and mechanosensing (78). Primary cilia gained much attention recently when their involvement in a number of different pathologies including polycystic kidney disease was discovered (101). Primary cilia serve as mechanosensors and transduce signals into the cell interior by activation of Ca²⁺ channels (31).

Swimming Controlled by Ciliary or Flagellar Beating

Cilia and flagella are hair-like, motile organelles projecting from the cell surface. Cilia are shorter than flagella and are present in large numbers on the cell surface. Their function has traditionally been studied in unicellular organisms like Tetrahymena. In mammals, cilia are found among others on the apical membrane of epithelial cells covering the airways, where they are required for mucociliary clearance (55), whereas flagella are only found in spermatozoa. Undulatory beating of the single flagellum propels sperm cells forward.

Cilia and flagella are usually composed of nine peripheral doublet microtubules with two central microtubules. This typical 9 + 2 axoneme runs longitudinally through the entire organelle (78). Harvesting the same 9 + 2 ultrastructure (78), it is not surprising that motile cilia and flagella share the same mechanisms of movement, which is driven by dynein motors. The interconnection of peripheral doublets and the central pair of microtubules converts the sliding movements of the peripheral doublets into bending motion (78). The ciliary/flagellar beat frequency determines the speed of swimming or creeping on a substrate, whereas the direction of movement is determined by the beat direction and the orientation of the cilia/flagella. The frequency and the orientation of beating are tuned by the local Ca²⁺ concentration inside the cilium/flagellum (59, 67). An increase in the Ca²⁺ concentration from 100 nM to 1 μM leads to a gradual acceleration of the forward movement because of a proportionally increasing ciliary beating frequency. As soon as the Ca²⁺ concentration exceeds a threshold value of 1 μM the direction of beating is reversed and the cell moves backwards.

In contrast to motile cilia, single primary cilia, which are found on almost all mammalian cells, lack the two central microtubules (9 + 6) and are therefore usually immotile. They are signaling platforms capable of chemosensory and mechanosensing (78). Primary cilia gained much attention recently when their involvement in a number of different pathologies including polycystic kidney disease was discovered (101). Primary cilia serve as mechanosensors and transduce signals into the cell interior by activation of Ca²⁺ channels (31). Tran and colleagues showed that polycystic kidney disease in C. elegans, which is caused by mutations in ~ 60 different genes, is the basis for many physiological and pathophysiological processes. It starts early during embryogenesis (8), and in the brain it does not stop until after birth (108). Movement of fibroblasts or epithelial cells during wound healing also involves the ameboid-type of migration (20). Other processes strongly relying on cell migration are the responses of the immune system, angiogenesis (95), and the formation of tumor metastases (103). These examples indicate that altered function of migrating cells can be associated with severe, possibly life-threatening pathophysiological conditions, for instance tumor metastasis.

Primary cilia are part of the primary cilium, a unique organelle found on almost all mammalian cells. Primary cilia are composed of 9+2 microtubules and are involved in the regulation of cell polarization, epithelial cell polarity, and cell migration (31).
Primary cilia respond to mechanical stimulation such as bending by inducing an increase of the intracellular Ca\(^{2+}\) concentration. This mechanical response is mediated by TRPP2 channels that are located in the ciliary membrane (71). So far, it is unknown whether ion channels located within the membrane of primary cilia or activated by the mechanosensory function of primary cilia also affect cell motility.

**Potassium Channels Modulate the Motility of Ciliates**

It has been known for more than 30 years that the membrane potential is crucial in controlling the motility of ciliated or flagellated cells (24). The membrane potential of ciliates can be modified among other means by mechanical (40), chemical (90), or temperature stimuli (91). A sequence of events elicited by mechanical stimuli, such as the indentation of the plasma membrane or cell/cell collisions, is shown in FIGURE 1. The activation of mechanosensitive Ca\(^{2+}\) channels (40) induces a depolarization, thereby activating voltage-gated L-type Ca\(^{2+}\) channels in the ciliary/flagellar membrane (41) and eventually eliciting an increase of the intracellular Ca\(^{2+}\) concentration. This in turn initiates accelerated forward or even backward movement. In many ciliated cells, the rise of the intracellular Ca\(^{2+}\) concentration also activates Ca\(^{2+}\)-sensitive K\(^+\) channels. The ensuing repolarization of the membrane potential marks the termination of the accelerated forward or backward movement (4). The K\(^+\) conductance of ciliates is affected by chemosensitants and pheromones and can, via activation or deactivation of voltage-gated Ca\(^{2+}\) channels, induce characteristic motility patterns that range from moving rapidly back and forth to remaining on the spot (90). So far, there are only few reports on the molecular identification of K\(^+\) channels in ciliates. Apparently, Paramecium expresses a large number of different K\(^+\) channels that are related to the mammalian K\(^+\) channels (31). Transgenic expression of two of them, PAK11 and PAK11J, led to the reduction of two separate Ca\(^{2+}\)-dependent K\(^+\) currents and to a modulated swimming behavior (46).

**K\(^+\) Channels in Sperm Cell Motility**

In contrast to ciliates, the molecular identity of K\(^+\) channels is well defined in sperm cells (5, 15). K\(^+\) channels are required for sperm motility (16). One important function of sperm K\(^+\) channels is volume regulation. When sperm is ejaculated into the female reproductive tract, it is surrounded by fluids with a 15-20 \% lower osmolarity than in the distal epididymis. Thus sperm cells have to regulate ion fluxes to maintain their original volume. Different K\(^+\) channels such as K\(\text{RI}1.5\), K\(\text{R}7.1\), or TASK2 have been implicated in this process (5). Volume regulation has more than a housekeeping function, since human sperm cells fail to move efficiently in the swollen state (104). Sperm is chemotactically guided to the egg it is about to fertilize. This holds true for both marine organisms such as sea urchins whose sperm is released into water and so-called “internal fertilizers” (e.g., mammals) whose sperm is deposited in the female reproductive tract (26). Sperm chemotaxis is a Ca\(^{2+}\)-dependent process that involves several different voltage-gated Ca\(^{2+}\) channels. Ca\(^{2+}\) influx is regulated by the membrane potential, which brings K\(^+\) channels into play. For example, chemotactic activation of sea urchin sperm (Arbacia punctulata) is mediated by the initial activation of cGMP-gated K\(^+\) channels, which then sets the stage for Ca\(^{2+}\) influx (94). The K\(^+\) channel-dependent hyperpolarization allows recovery of voltage-gated Ca\(^{2+}\) channels from inactivation so that these channels can open when the membrane potential depolarizes after the opening of hyperpolarization-activated and cyclic nucleotide-gated (HCN) channels. A cyclic
Mechanisms of Ameboid Movement

The process of migration can be subdivided into two basic steps that are repeated over and over again: protrusion of the front and retraction of the rear part. Migrating cells form at their front a fan-like, 300-nm-thin, and organelle-free process, the so-called lamellipodium. The cell body and the uropod are dragged behind. Migrating cells are polarized in the direction of movement (58) since some components of the cellular migration apparatus are restricted to either one of the two opposing cell poles. Thus, actin polymerization and depolymerization play particularly important roles in the lamellipodium (44, 102). Several mechanisms underlie polarity of migrating cells and allow persistent movement in a given direction, even in the absence of external cues (19). One of these involves the Na+/H+ exchanger NHE1. It tethers the actin cytoskeleton via ERM proteins to the leading edge of the lamellipodium (18), and by generating a characteristic pH nanoenvironment within the glycocalyx, NHE1 generates an asymmetric adhesiveness to the extracellular matrix (92, 96). Accordingly, NHE1-deficient cells have severely impaired polarity in the direction (17), and cell polarity is much higher at the rear of migrating cells (51). In neutrophil granulocytes, phospholipase Cγ is activated by phosphatidylinositol 4,5-bisphosphate and regulates actin polymerization in controlling polarity (11, 51). Interactions of signaling events at the lamellipodium with the migrating cell also influence polarity (19).

Table 1. K+ channels involved in cell motility

<table>
<thead>
<tr>
<th>Channel</th>
<th>Cell Type</th>
<th>Function in Cell Migration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCa1.1</td>
<td>Glioma cells</td>
<td>Activation or inhibition slows migration. Activation induces shrinkage of invadopodia.</td>
<td>39, 53, 100</td>
</tr>
<tr>
<td>KCa2.3</td>
<td>Breast cancer cells</td>
<td>Expressed in metastasizing cells. Promotes migration by elevating [Ca2+]i.</td>
<td>70</td>
</tr>
<tr>
<td>KCa3.1</td>
<td>MDCK-F cells</td>
<td>Blockade slows down cells. Blockade prevents chemokinetic stimulation.</td>
<td>83, 87, 89</td>
</tr>
<tr>
<td></td>
<td>Coronary smooth muscle cells</td>
<td>Modulates actin polymerization</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>Fibroblasts</td>
<td>Blockade slows down, modulates actin polymerization.</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Melanoma cells</td>
<td>Blockade slows down, modulates actin polymerization.</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>Microglia cells</td>
<td>Blockade slows down, prevents chemokinetic stimulation.</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>Mast cells</td>
<td>Inhibition slows cells and attenuates chemotaxis.</td>
<td>14, 23</td>
</tr>
<tr>
<td></td>
<td>Intestinal epithelial cells</td>
<td>Inhibition accelerates wound closure</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>HEK293 cells</td>
<td>Heterologous expression accelerates</td>
<td>89</td>
</tr>
<tr>
<td>Kv1.1</td>
<td>Intestinal epithelial cells</td>
<td>Promotes migration by elevating [Ca2+]i</td>
<td>72</td>
</tr>
<tr>
<td>Kv1.3</td>
<td>Lymphocytes</td>
<td>Cell adhesion, coimmuno-precipitates with β1-integrins.</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Neutrophil granulocytes</td>
<td>Detection of electric fields and their coupling to metabolic oscillators</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Microglial cells</td>
<td>Inhibition slows down migration/chemotaxis.</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>Melanoma cells</td>
<td>Interacts with β1-integrins of adhering melanoma cells.</td>
<td>3</td>
</tr>
<tr>
<td>Kv1.5</td>
<td>Intestinal epithelial cells</td>
<td>Promotes migration by elevating [Ca2+]i</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Macrophages</td>
<td>Knockdown inhibits migration.</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Sperm</td>
<td>Volume regulation, blockade impairs motility.</td>
<td>5</td>
</tr>
<tr>
<td>Kv1.1</td>
<td>Alveolar epithelial cells</td>
<td>Blockade inhibits EGF-mediated wound repair.</td>
<td>99</td>
</tr>
<tr>
<td>Kv10.1</td>
<td>Breast/pancreas cancer cells</td>
<td>Inhibition prevents tumor progression</td>
<td>29</td>
</tr>
<tr>
<td>Kv11.1</td>
<td>Colon cancer</td>
<td>Marker of adverse prognosis.</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>Myeloid leukemia cells</td>
<td>Interacts with β1-integrins.</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>HEK293 cells</td>
<td>Modulates adhesion-dependent signalling</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Acute myeloid leukemia cells</td>
<td>Forms complex with VEGF receptor 1 and β1-integrins.</td>
<td>69</td>
</tr>
<tr>
<td>KCNG</td>
<td>Sea urchin sperm</td>
<td>Required for sperm chemotaxis.</td>
<td>28, 94</td>
</tr>
</tbody>
</table>

nucleotide-gated K+ channel, Sp-tetraKCNNG, was cloned from sea urchin sperm, which is insofar unique because it has a similar membrane topology as voltage-gated Na+ or Ca2+ channels. Sp-tetraKCNNG channels are also composed of a single polypeptide with four KCNG domains, each of which has six transmembrane domains (28). So far, the signaling underlying mammalian sperm chemotaxis is not well understood. Hence, the exact role of K+ channels in this process remains to be elucidated in the future (36).
severely impaired ability to migrate persistently in one direction (17, 86, 96). Another "ionic" mechanism of cell polarity is the generation of a gradient of the intracellular Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]\(_i\)) with [Ca\(^{2+}\)]\(_i\) being higher at the rear than at the front of many migrating cells (51). In chemotactically stimulated amebae or neutrophil granulocytes, lipid metabolites generated by phosphatidylinositol-3 kinase (PI3K), PTEN (phosphatase and tensin homolog in chromosome 10), and phospholipase A2 signaling pathways play crucial roles in controlling directed migration and maintaining polarity (11, 54). The regulation of the opposing cellular events at the front and at the rear part of a migrating cell also involves members of the filo family of GTPases. In particular, RhoA-C, Rac1-3, and Cdc42 have been implicated in coordinating the spatially distinct cytoskeleton reorganizations underlying migration (35, 74). The intracellular network regulating cytoskeletal remodeling during migration is further complicated by signals originating from focal adhesion contacts, where integrins that are linked to the cytoskeleton interact with extracellular matrix molecules (7, 76). As we will see, the function of integrins and thereby cell adhesion and migration can also be modulated by K\(^+\) channels. Finally, primary cilia may function as a cellular "GPS" (13) and control directed migration since they are oriented in the direction of movement (1).

**FIGURE 2.** Mechanisms by which K\(^+\) channels can modulate cell migration

A: K\(^+\) channels control the cell membrane potential \(V_m\). In doing so, they regulate the electrical driving force for electrogenic Ca\(^{2+}\) influx via TRP channels. So far, however, the molecular identity of these mechanosensitive (?) TRP channels required for cell migration is still largely unknown. Potential candidates include, among others, TRPC1, TRPV4, and TRPM7 (38, 51, 84). In addition, changes of the cell membrane potential \(\Delta V_m\) affect the gating behavior of voltage-gated Na\(^+\) channels (Nav) and Ca\(^{2+}\) (Cav) channels.

B: K\(^+\) channels are central players in cell volume regulation. K\(^+\) channels cooperating with Cl\(^-\) channels whose molecular nature is still largely elusive can induce a localized cell shrinkage that supports the retraction of the rear part of migrating cells. In addition, localized cell shrinkage can facilitate the passage through the dense fiber network of the extracellular matrix. C: K\(^+\) channels interact with important components of the cellular migration machinery such as integrins. Conformational coupling of K\(^+\) channels and integrins provides the basis for the reciprocal regulation of these proteins. Their mutual activation is required for efficient cell migration.

References:
9, 53, 100
K⁺ Channels Are Part of the Cellular Migration Machinery

Many studies have unequivocally shown that K⁺ channels belonging to different subfamilies are important components of the cellular migration machinery. When these channels are inhibited, migration is impaired. Studies from the last 10–15 years indicated several common themes by which K⁺ channels can influence the process of cell migration (see Figure 2A). Effects related to housekeeping functions of K⁺ channels, e.g., in the regulation of the cell membrane potential or cell volume, have to be considered as well as nonconductive properties of K⁺ channels, i.e., effects that appear to be unrelated to ion transport itself.

**K⁺ channels modulate migration by controlling the cell membrane potential**

The most prominent housekeeping mechanism is the regulation of the cell membrane potential. In doing so, K⁺ channels control the driving force for the electrolytic transport of ions across the plasma membrane (Figure 2A). Depolarizing the cell membrane potential by elevating the extracellular K⁺ concentration inhibits migration of transformed epithelial cells (88). The control of the electrical driving force is of particular importance for Ca²⁺ ions since migration is a Ca²⁺-inhibiting process (8). The intracellular Ca²⁺ concentration serves both as a temporal as well as a spatial regulator of cell migration coordinating the retraction of the rear part of migrating cells (22, 25, 43) with forward protrusion (27). The membrane potential has a dual effect on Ca²⁺ influx through Ca²⁺ channels. On one hand, it sets the electrical driving force for all Ca²⁺ channels, but on the other hand it also controls the gating behavior of voltage-gated Ca²⁺ channels. Which one of these two effects prevails depends on the expression pattern of Ca²⁺ channels in the respective cell type. Most peripheral migrating cells usually express voltage-independent Ca²⁺ channels whose molecular identity, however, is poorly defined. In contrast, voltage-gated Ca²⁺ channels are frequently required for migration of cells from the central nervous system (47, 84).

The membrane potential also determines the electrochemical driving force for the flux of Na⁺ and Cl⁻ through their respective channels, and these fluxes have also been shown to play a role in migration (see Ref. 84 and references therein). Many tumor cells express functional, tetrodotoxin-inhibitable voltage-gated Na⁺ channels that have a low activity at the resting membrane potential of these tumor cells (21, 47, 75).

Galvanotaxis, i.e., migration within an electric field, is another mechanism that links the cell membrane potential and hence K⁺ channels to migration. It has been known for a long time that external electric fields influence the cell volume (5). The Ca²⁺ concentration serves both as a temporal as well as a spatial regulator of cell migration coordinating the retraction of the rear part of migrating cells (22, 25, 43) with forward protrusion (27). The membrane potential has a dual effect on Ca²⁺ influx through Ca²⁺ channels. On one hand, it sets the electrical driving force for all Ca²⁺ channels, but on the other hand it also controls the gating behavior of voltage-gated Ca²⁺ channels. Which one of these two effects prevails depends on the expression pattern of Ca²⁺ channels in the respective cell type. Most peripheral migrating cells usually express voltage-independent Ca²⁺ channels whose molecular identity, however, is poorly defined. In contrast, voltage-gated Ca²⁺ channels are frequently required for migration of cells from the central nervous system (47, 84).

**K⁺ channels modulate migration by regulating the cell volume**

Most migrating cells undergo dramatic changes of their shape while moving. This is in part due to the fact that the retraction of the rear part of migrating cells does not always keep pace with the protruding front. It is a common observation that the rear part of migrating cells is stuck for some time while the lamellipodium keeps growing until the rear part eventually “catches up” rapidly. Thus one could model the process of cell migration as intermittent local swelling at the front and shrinkage at the rear part. A local swelling of the protruding lamellipodium was shown in EGF-stimulated adenocarcinoma cells (77). The intracellular “valve” restricting volume changes either to the front or to the rear part of migrating cells is represented by the poroelastic nature of the cytosol (10). Local swelling and shrinkage may also become a necessity for migrating cells when they are obliged to squeeze through narrow spaces of the dense fiber meshwork of the extracellular matrix (Figure 2B). This was, for instance, shown for glioma cells invading brain tissues (53). Being capable of locally changing the volume when needed is therefore advantageous for efficient cell migration. In addition to the above-mentioned “mechanical” aspects, the cell volume also plays a homoeostatic role in migrating cells. The “correct” cell volume is crucial for the integrity of the cytoskeleton. Cell swelling leads to actin depolymerization, whereas cell shrinkage promotes actin polymerization (66, 87). Since K⁺ channels are central players in cell volume regulation (33), they create an optimal intracellular environment required for the cytoskeletal migration machinery. Notably, the functional interrelation between K⁺ channels, cell volume, and actin cytoskeleton has been demonstrated in several studies (13, 50, 57).

**Contribution of K⁺ Channel Family Members to Cell Movement**

**Ca²⁺-activated K⁺ Channels**

Several members of the Kᵣ family (Kᵣ 2.3) channels (14) are expressed in glioma cells (45) and in microglia (79, 80). The Ca²⁺ dependency of this channel family (80) provides an entry into the regulation of cell morphology and cell volume (5). Kᵣ 2.3 channels slow cell volume changes either to the front or to the rear part of migrating cells, thereby affecting cell migration (38, 57). The recent discovery of the voltage-sensitive phosphoinositide phosphatase CI-VSP points to yet another mechanism by which K⁺ channels could indirectly modify migration (56), although this possibility has not yet been shown experimentally. The electrical signal generated by K⁺ channel activation (i.e., hyperpolarization) or inhibition (i.e., depolarization) is translated into a modulation of the PIP₂(3,4,5)P₃/PIP₂ ratio. The potential importance of such voltage-dependent phosphatase activity in cell migration is given by the fact that PIP₂ and PIP₃ are key regulators of actin dynamics (105) and chemotaxis, respectively (11, 54).

**Contributing Role of K⁺ Channels in Cell Migration**

In summary, K⁺ channel family members contribute to cell migration in various cellular contexts. Notably, the functional interrelation between K⁺ channels, cell volume, and actin cytoskeleton has been demonstrated in several studies (13, 50, 57).
Contribution of Individual K⁺ Channel Families to Cell Migration

Voltage-gated K⁺ channels

Several members of this family, BK (KCa1.1) (39, 100), SK3 (KCa2.3) (70), and in particular IK1 (KCa3.1) channels (14, 23, 48, 79, 85, 89, 97), are involved in cell migration. In most preparations, inhibition of KCa3.1 channels slows migration. However, there are also exceptions pointing toward the importance of the cellular context. When KCa3.1 channels are inhibited in secretory colonic epithelial cells, the restitution of the epithelium is accelerated (48). This effect possibly represents a KCa channel-dependent modification of goblet cell morphology during wound closure (52). The contribution of different calcium-sensitive KCa channels is cell-type specific. BK (KCa1.1) channels, for example, are expressed in glial and microglial cells. Yet, they are only needed for migration of glial cells but not of microglia (79, 100).

The Ca²⁺ sensitivity of Ca²⁺-activated K⁺ channels provides an excellent means to coordinate their activity and thereby downstream effects such as membrane potential or cell volume with other Ca²⁺-dependent processes such as cytoskeletal dynamics. This coordination is further fine tuned by spatial gradients and conformational changes of the cell membrane potential of migrating cells (51). Consequently, KCa3.1 channels are apparently only activated at this cell pole (83, 85), although the density of KCa3.1 channel proteins is the highest at the cell front (160). Nurtuating KCa3.1 channel activity is critical for optimal cell migration since continuously activating KCa3.1 channels impairs migration (39, 87). Being intermittently activated, KCa3.1 channels support migration by inducing localized and transient changes of the cell volume (53, 81). In doing so, they act in concert with volume-sensitive Cl⁻ channels whose molecular identity is discussed controversially.

Voltage-gated Kv1.3 channels

Kv1.3 channels have a strong impact on function. Kv1.3 channels physically interact with β1-integrins in lymphocytes (45) and melanoma cells (5) and thereby affect cell adhesion and migration (51). The interaction of Kv1.3 channels and integrins becomes closer on cell adhesion, and it is weakened by Kv1.3 channel blockers. Opening of Kv1.3 channels, not necessarily accompanied by K⁺ flow, results in an activation of β1-integrins (45), i.e., a depolarization of the cell membrane potential is transduced, via Kv1.3 channels, to an activation of β1-integrins. On the other hand, Kv1.3 channels are stimulated upon integrin activation. The reciprocal relationship is taken as an indication of conformational coupling of both proteins since voltage-dependent gating of Kv1.3 channels and adhesion-dependent activation of integrins are both associated with conformational changes (FIGURE 2C). Thus oscillations of the cell membrane potential of migrating cells could lead to intermittent activation of integrins and downstream signaling pathways. At this point, it remains highly speculative whether the Kv1.3-integrin interaction could thereby contribute to other oscillatory, actin-mediated processes such as a periodic force generation of neutrophils (30).

Kv1.3 channels are clustered with TRPC1 channels at the leading edge of the lamellipodium of neutrophils (38). The functional significance of this co-clustering was seen in the detection of electrical fields. Modeling suggests that changes of the electric field across the plasma membrane following Kv1.3 channel blockade or an elevation of the extracellular K⁺ concentration could affect cell adhesion and migration (61). Moreover, Kv1.3 channel activity was shown to affect cell adhesion and migration through integrin-mediated adhesion to fibronectin. On the other hand, integrin-signaling, such as the tyrosine phosphorylation of the focal adhesion kinase, depends on ERG1 channel activity (12). Thus ERG1 channels and β1-integrins modulate each other’s function, presumably in a nonconductive way by conformational coupling. Functionally, they...
are situated at a similar position as Kv1.3 channels and strongly affect migration by controlling cell-matrix interactions and downstream signaling cascades.

Other potassium channels
Kv1.1 and Kv1.5 channels accelerate the restitution of wounded epithelia by hyperpolarizing the cell membrane potential and thereby maintaining the electrochemical driving force for Ca2+ influx (72). Kv1.5 and Kv3.1 channels are part of the cellular migration machinery of human alveolar macrophages (85) and of embryonic acousto-vestibular neuroblasts (32), respectively. Furthermore, Kv7.1 and KATP channels have been shown to be part of the EGF-signaling cascade leading to wound healing of alveolar epithelial cells (99). Such cross talk between growth factor or chemokine signaling cascades and K+ channels has also been observed in other migrating cell types (14, 37, 79).

Perspectives
For many years, research on the role of K+ channels in cell motility focused on unicellular, ciliated model organisms. Long before the requirement of K+ channel activity for ameboid migration was recognized, the involvement of K+ channels in the movement of cells was firmly established. However, studies over the last 10–15 years have revealed that K+ channels and other ion channels and transporters are essential components of the cellular migration machinery. The number of cell types demonstrated to have K+ channel-dependent ameboid migration is steadily growing. Yet, the field is still too young to draw a conclusive picture. Many migrating cells express more than one “migration-relevant” K+ channel. However, so far it is not known to what extent different K+ channels cooperate with each other and/or with other ion channels and transporters in a given cell type in modulating cell migration. Moreover, it has to be kept in mind that K+ channels involved in cell migration are expressed by a wide variety of migrating cells performing different physiological tasks. One of the challenges for the next years will be the development of animal models in which the therapeutic potential of modulating K+ channel activity in migrating cells under defined pathophysiological conditions can be explored.

Since migration is central to the pathophysiology of several devastating diseases such as cancer or chronic inflammatory disorders, K+ channel blockade represents a new therapeutic strategy for the treatment of these diseases. This concept is well advanced in the last 10–15 years have revealed that K+ channels are situated at a similar position as Kv1.3 channels and strongly affect migration by controlling cell-matrix interactions and downstream signaling cascades.

Other potassium channels
Kv1.1 and Kv1.5 channels accelerate the restitution of wounded epithelia by hyperpolarizing the cell membrane potential and thereby maintaining the electrochemical driving force for Ca2+ influx (72). Kv1.5 and Kv3.1 channels are part of the cellular migration machinery of human alveolar macrophages (85) and of embryonic acousto-vestibular neuroblasts (32), respectively. Furthermore, Kv7.1 and KATP channels have been shown to be part of the EGF-signaling cascade leading to wound healing of alveolar epithelial cells (99). Such cross talk between growth factor or chemokine signaling cascades and K+ channels has also been observed in other migrating cell types (14, 37, 79).

Perspectives
For many years, research on the role of K+ channels in cell motility focused on unicellular, ciliated model organisms. Long before the requirement of K+ channel activity for ameboid migration was recognized, the involvement of K+ channels in the movement of cells was firmly established. However, studies over the last 10–15 years have revealed that K+ channels and other ion channels and transporters are essential components of the cellular migration machinery. The number of cell types demonstrated to have K+ channel-dependent ameboid migration is steadily growing. Yet, the field is still too young to draw a conclusive picture. Many migrating cells express more than one “migration-relevant” K+ channel. However, so far it is not known to what extent different K+ channels cooperate with each other and/or with other ion channels and transporters in a given cell type in modulating cell migration. Moreover, it has to be kept in mind that K+ channels involved in cell migration are expressed by a wide variety of migrating cells performing different physiological tasks. One of the challenges for the next years will be the development of animal models in which the therapeutic potential of modulating K+ channel activity in migrating cells under defined pathophysiological conditions can be explored.

Since migration is central to the pathophysiology of several devastating diseases such as cancer or chronic inflammatory disorders, K+ channel blockade represents a new therapeutic strategy for the treatment of these diseases. This concept is well advanced in the last 10–15 years have revealed that K+ channels are situated at a similar position as Kv1.3 channels and strongly affect migration by controlling cell-matrix interactions and downstream signaling cascades.

Other potassium channels
Kv1.1 and Kv1.5 channels accelerate the restitution of wounded epithelia by hyperpolarizing the cell membrane potential and thereby maintaining the electrochemical driving force for Ca2+ influx (72). Kv1.5 and Kv3.1 channels are part of the cellular migration machinery of human alveolar macrophages (85) and of embryonic acousto-vestibular neuroblasts (32), respectively. Furthermore, Kv7.1 and KATP channels have been shown to be part of the EGF-signaling cascade leading to wound healing of alveolar epithelial cells (99). Such cross talk between growth factor or chemokine signaling cascades and K+ channels has also been observed in other migrating cell types (14, 37, 79).

Perspectives
For many years, research on the role of K+ channels in cell motility focused on unicellular, ciliated model organisms. Long before the requirement of K+ channel activity for ameboid migration was recognized, the involvement of K+ channels in the movement of cells was firmly established. However, studies over the last 10–15 years have revealed that K+ channels and other ion channels and transporters are essential components of the cellular migration machinery. The number of cell types demonstrated to have K+ channel-dependent ameboid migration is steadily growing. Yet, the field is still too young to draw a conclusive picture. Many migrating cells express more than one “migration-relevant” K+ channel. However, so far it is not known to what extent different K+ channels cooperate with each other and/or with other ion channels and transporters in a given cell type in modulating cell migration. Moreover, it has to be kept in mind that K+ channels involved in cell migration are expressed by a wide variety of migrating cells performing different physiological tasks. One of the challenges for the next years will be the development of animal models in which the therapeutic potential of modulating K+ channel activity in migrating cells under defined pathophysiological conditions can be explored.

Since migration is central to the pathophysiology of several devastating diseases such as cancer or chronic inflammatory disorders, K+ channel blockade represents a new therapeutic strategy for the treatment of these diseases. This concept is well advanced in the last 10–15 years have revealed that K+ channels are situated at a similar position as Kv1.3 channels and strongly affect migration by controlling cell-matrix interactions and downstream signaling cascades.

Other potassium channels
Kv1.1 and Kv1.5 channels accelerate the restitution of wounded epithelia by hyperpolarizing the cell membrane potential and thereby maintaining the electrochemical driving force for Ca2+ influx (72). Kv1.5 and Kv3.1 channels are part of the cellular migration machinery of human alveolar macrophages (85) and of embryonic acousto-vestibular neuroblasts (32), respectively. Furthermore, Kv7.1 and KATP channels have been shown to be part of the EGF-signaling cascade leading to wound healing of alveolar epithelial cells (99). Such cross talk between growth factor or chemokine signaling cascades and K+ channels has also been observed in other migrating cell types (14, 37, 79).

Perspectives
For many years, research on the role of K+ channels in cell motility focused on unicellular, ciliated model organisms. Long before the requirement of K+ channel activity for ameboid migration was recognized, the involvement of K+ channels in the movement of cells was firmly established. However, studies over the last 10–15 years have revealed that K+ channels and other ion channels and transporters are essential components of the cellular migration machinery. The number of cell types demonstrated to have K+ channel-dependent ameboid migration is steadily growing. Yet, the field is still too young to draw a conclusive picture. Many migrating cells express more than one “migration-relevant” K+ channel. However, so far it is not known to what extent different K+ channels cooperate with each other and/or with other ion channels and transporters in a given cell type in modulating cell migration. Moreover, it has to be kept in mind that K+ channels involved in cell migration are expressed by a wide variety of migrating cells performing different physiological tasks. One of the challenges for the next years will be the development of animal models in which the therapeutic potential of modulating K+ channel activity in migrating cells under defined pathophysiological conditions can be explored.

Since migration is central to the pathophysiology of several devastating diseases such as cancer or chronic inflammatory disorders, K+ channel blockade represents a new therapeutic strategy for the treatment of these diseases. This concept is well advanced in the last 10–15 years have revealed that K+ channels are situated at a similar position as Kv1.3 channels and strongly affect migration by controlling cell-matrix interactions and downstream signaling cascades.
step in the regulation of cell migration. Current evidence suggests that 1 channels in processes of cellular motility are a conserved mechanism across species and have potential for therapeutic intervention. In this review, we focus on several key points: 1) the regulation of 1 channel activity and its impact on cell migration; 2) the role of 1 channels in cancer cell migration and metastasis; and 3) the potential for targeting 1 channels as therapeutic targets for neurodegenerative diseases.

1. Transient Receptor Potential (TRP) Channels

TRP channels are a large family of ion channels that are activated by a wide range of stimuli, including mechanical, chemical, and thermal inputs. These channels are involved in various cellular processes, including cell migration, where they play a crucial role in regulating cell adhesion, motility, and survival. TRP channels are divided into several subfamilies, each with distinct functional properties and tissue-specific expression patterns. Among these subfamilies, TRPA1, TRPM2, TRPM4, and TRPV1 have been implicated in cell migration and metastasis.

2. Potassium Channels

Potassium channels are another important class of ion channels involved in the regulation of cell migration. These channels are involved in the regulation of cell adhesion, spreading, and motility. They function to control the intracellular calcium concentration, which is critical for cell migration. The specific potassium channel subtypes involved in cell migration and metastasis include Kv1.3, Kv1.5, and Kv1.1.

3. Calcium Channels

Calcium channels are critical in the regulation of cell migration, as they control the intracellular calcium concentration, which is essential for the actin cytoskeleton and cell adhesion. The specific calcium channel subtypes involved in cell migration and metastasis include L-type calcium channels (Cav1.2 and Cav1.3), N-type calcium channels (Cav2.2), and P/Q-type calcium channels (Cav2.1).

4. Sodium Channels

Sodium channels are involved in the regulation of cell migration, as they control the entry of sodium ions into the cell, which can lead to the depolarization of the plasma membrane. The specific sodium channel subtypes involved in cell migration and metastasis include Nav1.5 and Nav1.7.

5. Other Ion Channels

Other ion channels, such as chloride channels, are also involved in the regulation of cell migration. These channels control the entry of chloride ions into the cell, which can lead to changes in the intracellular pH and ionic balance. The specific chloride channel subtypes involved in cell migration and metastasis include ClC-3 and ClC-7.

In conclusion, ion channels are critical in the regulation of cell migration and metastasis. Further research is needed to fully understand the specific roles of these channels in different cellular processes and to develop targeted therapeutic strategies for the treatment of cancer.

References:


REVIEWS


