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Ion Channels in Cell Proliferation and Apoptotic Cell Death

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Abstract. Cell proliferation and apoptosis are paralleled by altered regulation of ion channels that play an active part in the signaling of those fundamental cellular mechanisms. Cell proliferation must - at some time point - increase cell volume and apoptosis is typically paralleled by cell shrinkage. Cell volume changes require the participation of ion transport across the cell membrane, including appropriate activity of Cl^- and K^+ channels. Besides regulating cytosolic Cl^- activity, osmolyte flux and, thus, cell volume, most Cl^- channels allow HCO_3^- exit and cytosolic acidification, which inhibits cell proliferation and favors apoptosis. K^+ exit through K^+ channels may decrease intracellular K^+ concentration, which in turn favors apoptotic cell death. K^+ channel activity further maintains the cell membrane potential, a critical determinant of Ca^{2+} entry through Ca^{2+} channels. Cytosolic Ca^{2+} may trigger mechanisms required for cell proliferation and stimulate enzymes executing apoptosis. The switch between cell proliferation and apoptosis apparently depends on the magnitude and temporal organization of Ca^{2+} entry and on the functional state of the cell. Due to complex interaction with other signaling pathways, a given ion channel may play a dual role in both cell proliferation and apoptosis. Thus, specific ion channel blockers may abrogate both fundamental cellular mechanisms, depending on cell type, regulatory environment and condition of the cell. Clearly, considerable further experimental effort is required to fully understand the complex interplay between ion channels, cell proliferation and apoptosis.

Key words: CD95/Fas — Scramblase — PGE2 — Cell volume — Lymphocytes — Erythrocytes

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Introduction

Cell homeostasis requires a delicate balance between formation of new cells by cell proliferation and their elimination by apoptosis. Apoptosis eliminates abundant and potentially harmful cells (Green & Reed, 1998). The maintenance of an adequate cell number requires the replacement of apoptotic cells or formation of additional cells by cell proliferation.

Cell proliferation is stimulated by growth factors (Bikfalvi et al., 1998; Adams et al., 2004; Tallquist & Kazlauskas, 2004), apoptosis is triggered by stimulation of respective receptors, such as CD95 (Lang et al., 1998b, 1999; Gulbins et al., 2000; Fillon et al., 2002), somatostatin receptor (Teijeiro et al., 2002) or TNFα receptor (Lang et al., 2002a), by cell density (Long et al., 2003), lack of growth factors (Sturm et al., 2004) thyroid hormones (Alia et al., 2005), or adhesion (Davies, 2003; Walsh et al., 2003), by choline deficiency (Albright et al., 2005), DNA damage (Kohn & Pommier, 2005), or by exposing cells to genotoxic or other stressors such as radiation (Rosette & Karin, 1996), chemotherapeutics (Cariers et al., 2002; Wieder et al., 2001), oxidants (Rosette & Karin, 1996), inhibition of glutaminase (Rotoli et al., 2005), energy depletion (Pozzi et al., 2002) or osmotic shock (Bortner & Cidlowski, 1998, 1999; Lang et al., 1998a, 2000b; Maeno et al., 2000; Michea et al., 2000; Rosette & Karin, 1996).

If cell proliferation is to generate cells similar to the parent cells, it obviously requires the duplication of all cell components, such as DNA, cytoskeleton, mitochondria, etc. To generate cells of similar size as the parent cells, cell proliferation must at some point lead to cell volume increase (Lang et al., 1998a).

Hallmarks of apoptosis include nuclear condensation, DNA fragmentation, mitochondrial depolarization, cell shrinkage and breakdown of

phosphatidylserine asymmetry of the plasma membrane (Green & Reed, 1998). The exposure of phosphatidylserine at the cell surface results from the activation of a scramblase (Zhou et al., 2002), which is activated by increase of cytosolic Ca^{2+} activity (Woon et al., 1999; Dekkers et al., 2002). As macrophages are equipped with receptors specific for phosphatidylserine (Fadok et al., 2000; Henson et al., 2001), cells or cellular fragments exposing phosphatidylserine at their surface will be rapidly recognized, engulfed and degraded (Boas et al., 1998). Cell shrinkage facilitates the engulfment of the dying cells by phagocytes (Boas et al., 1998). Thus, apoptosis allows the elimination of the cells without release of intracellular proteins, which would otherwise cause inflammation (Gulbins et al., 2000).

Programmed cell death is not limited to nucleated cells but could similarly affect erythrocytes (Barvitenko et al., 2005; Bosman & Willekens, 2005; Rice & Alfrey, 2005). Recently, the term "eryptosis" has been coined (Lang et al., 2005a) to describe apoptosis-like death of mature erythrocytes, which is characterized by cell shrinkage and breakdown of phosphatidylserine asymmetry, both typical features of apoptosis in nucleated cells (Lang et al., 2003a, b, c, e).

Both cell proliferation and apoptosis involve at some point activation of Cl^- channels, K^+ channels and Ca^{2+} channels. As the respective channel inhibitors have been reported to interfere with both cell proliferation and apoptosis, the channels appear to play an active role in the machinery leading to duplication or death of a given cell.

The Role of Ca^{2+} and Nonselective Cation Channels in Cell Proliferation and Apoptosis

Overwhelming evidence points to a critical role of cytosolic Ca^{2+} activity in the regulation of cell proliferation (Whitfield et al., 1995; Parekh & Penner, 1997; Berridge et al., 1998, 2000, 2003; Santella 1998; Santella et al., 1998). Growth factors are known to stimulate Ca^{2+} release-activated calcium channels I_{CRAC} (Qian & Weiss, 1997), which has in turn been shown to trigger Ca^{2+} entry into and subsequent Ca^{2+} oscillations in proliferating cells. The Ca^{2+} oscillations trigger a wide variety of cellular functions (Berridge et al., 1998, 2000, 2003; Parekh & Penner, 1997), including the depolymerization of the actin filaments (Lang et al., 1992, 2000c; Dartsch et al., 1995; Ritter et al., 1997). The depolymerization of the actin filaments leads to disinhibition of the Na^+/H^+ exchanger and/or the Na^+, K^+, $2Cl^-$ cotransporter (Fig. 1) and thus leads to increase of cell volume (Lang et al., 1998a). Activation of I_{CRAC}, Ca^{2+} oscillations and depolymerization of the actin filament network all have been shown to be prerequisites of cell proliferation (Dartsch et al., 1995; Lang et al., 1992, 2000c; Ritter et al., 1997).

Conversely, the lymphocyte apoptosis following CD95 receptor triggering is paralleled by inhibition of I_{CRAC} (Lepple-Wienhues et al., 1999; Dangel et al., 2005) (Fig. 2). Inhibition of I_{CRAC} presumably serves to abrogate activation and proliferation of lymphocytes and does not necessarily foster apoptotic cell death. Whether or not cytosolic Ca^{2+} activity increases at a later stage following CD95 triggering, remains uncertain. In any case, increase of cytosolic Ca^{2+} is not an early event in CD95-induced cell death.

On the other hand, sustained increase of cytosolic Ca^{2+} activity has been shown to trigger apoptosis in a variety of nucleated cells (Parekh & Penner, 1997; Green & Reed, 1998; Berridge et al., 2000; Spassova et al., 2004; Liu et al., 2005; Parekh & Putney, Jr., 2005). Moreover, as illustrated in Fig. 3, Ca^{2+}-permeable cation channels play a decisive role in apoptosis-like death of erythrocytes (eryptosis) (Brand et al., 2003; Lang et al., 2002b; Lang et al., 2003b).

Apoptosis-like erythrocyte death could be triggered by exposure to the Ca^{2+} ionophore ionomycin (Berg et al., 2001; Bratosin et al., 2001; Daugas et al., 2001; Lang et al., 2002b, 2003b) and blunted in the nominal absence of Ca^{2+} (Lang et al., 2003b). The Ca^{2+}-permeable cation channels could be activated by exposure of erythrocytes to osmotic shock (Huber et al., 2001), oxidative stress (Duranton et al., 2002), energy depletion (Lang et al., 2003b) and infection with the malaria pathogen *Plasmodium falciparum* (Brand et al., 2003; Duranton et al., 2003; Lang et al., 2004a). Energy depletion presumably impairs the replenishment of GSH and thus weakens the antioxidative defense of the erythrocytes (Mavelli et al., 1984; Bilmen et al., 2001). The cation channels are further activated by removal of intracellular and extracellular Cl^- (Huber et al., 2001; Duranton et al., 2002). The suicidal cation channels are probably identical to the Na^+ and K^+ permeability activated by incubation of human erythrocytes in low ionic strength (LaCelle & Rothsteto, 1966; Jones & Knauf, 1985; Bernhardt et al., 1991). Similar if not identical nonselective cation channels are activated by depolarization (Christophersen & Bennekou, 1991; Bennekou, 1993; Kaestner et al., 1999).

Elevated cytosolic Ca^{2+} concentrations then stimulate the erythrocyte scramblase (Zhou et al., 2002), thus leading to the breakdown of phosphatidylserine asymmetry (Lang et al., 2003b). The phosphatidylserine exposure following osmotic shock is blunted by amiloride (Lang et al., 2003b) and ethylisopropylamiloride (EIPA) (Lang et al., 2003a), both putative inhibitors of the cation channel (Lang et al., 2003b, c). The suicidal erythrocyte cation channels are activated by prostaglandin E_2 (PGE_2), which is released upon osmotic shock (Lang et al., 2005b).

Cell volume-sensitive cation channels are expressed in a wide variety of nucleated cells, such as airway epithelia cells (Chan et al., 1992), mast cells

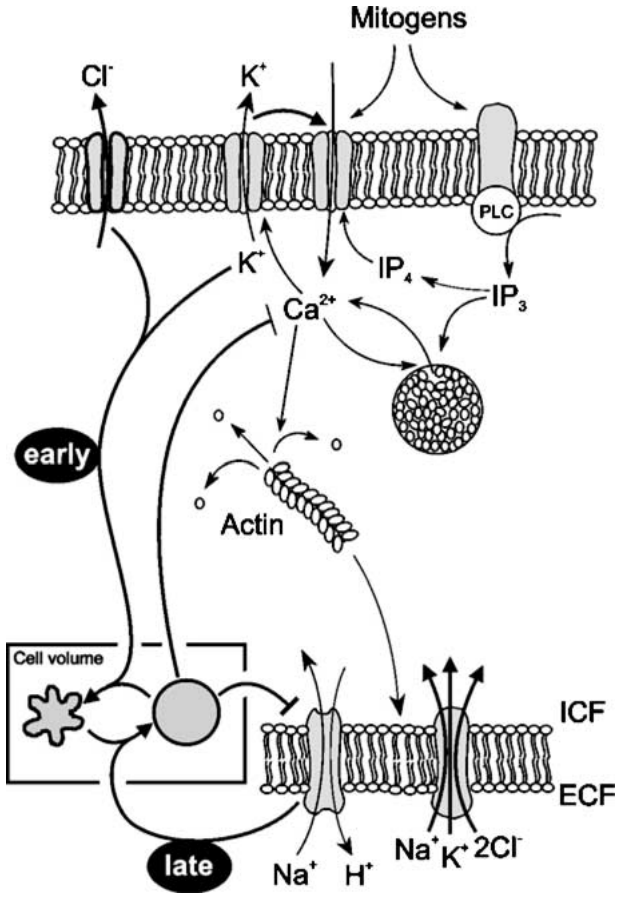

Fig. 1. Involvement of channels in the activation of cell proliferation by ras oncogene. In ras oncogene-expressing cells the mitogen bradykinin triggers the formation of inositol-(1,4,5) trisphosphate (IP_3) with subsequent stimulation of intracellular Ca^{2+} release. The subsequent activation of the Ca^{2+} release-activated Ca^{2+} channel I_{CRAC} leads to Ca^{2+} entry. Ca^{2+} activates Ca^{2+}-sensitive K^+ channels leading to K^+ exit, hyperpolarization, and Cl^- exit through Cl^- channels. The subsequent cell shrinkage is required for the initial triggering of Ca^{2+} and cell membrane potential oscillations due to repetitive Ca^{2+} and K^+ channel activation. The oscillations of Ca^{2+} lead to depolymerization of the cell actin filaments, which disinhibits the Na^+/H^+ exchanger and the Na^+, K^+, $2Cl^-$ cotransporter. Electrolyte accumulation by these carriers eventually leads to cell swelling.

(Cabado et al., 1994), macrophages (Gamper et al., 2000), vascular smooth muscle, colon carcinoma and neuroblastoma cells (Koch & Korbmacher, 1999), cortical collecting duct cells (Volk et al., 1995), and hepatocytes (Wehner et al., 1995, 2000). Cation channels activated by Cl^- removal were identified in salivary and lung epithelial cells (Marunaka et al., 1994; Tohda et al., 1994; Dinudom et al., 1995). It has been shown that Cl^- influences the channels via a pertussis toxin-sensitive G-protein (Dinudom et al., 1995). At present, we do not know the molecular identity of those channels nor do we know whether or not they participate in Ca^{2+} entry and apoptosis.

The Role of K^+ Channels in Cell Proliferation and Apoptosis

A variety of K^+ channels have been implicated in the regulation of cell proliferation (Patel & Lazdunski, 2004; Wang, 2004). Growth factors have been shown to activate K^+ channels (O'Lague et al., 1985; Enomoto et al., 1986; Lang et al., 1991; Sanders et al., 1996; Wiecha et al., 1998; Liu et al., 2001; Faehling et al., 2001;), and enhanced K^+ channel activity has been observed in a wide variety of tumor cells (DeCoursey et al., 1984; Nilius & Wohlrab, 1992; Pappone & Ortiz-Miranda, 1993; Strobl et al., 1995; Mauro et al., 1997; Skryma et al., 1997; Pappas & Ritchie, 1998; Zhou et al., 2003; Patel & Lazdunski, 2004; Wang, 2004). As illustrated in Fig. 1, repetitive activation of Ca^{2+}-sensitive K^+ channels by oscillating cytosolic Ca^{2+} activity leads to oscillations of cell membrane potential in ras oncogene-expressing cells (Lang et al., 1991). Several K^+ channel inhibitors have been shown to disrupt cell proliferation (for review, *see* Wang, 2004)). K^+ channel activation appears to be particularly important for the early G1 phase of the cell cycle (Wonderlin & Strobl, 1996; Wang et al., 1998). The maintenance of cell membrane potential by K^+

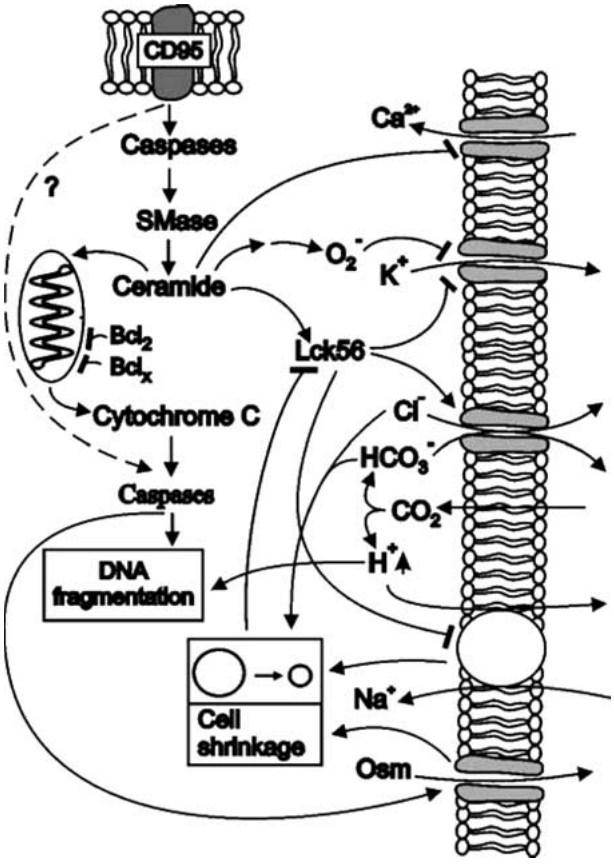

Fig. 2. Regulation of transport mechanisms in Jurkat T cells following stimulation of the CD95 receptor. CD95 stimulation is followed by activation of anion channels (ORCC) and, with delay, of cellular osmolyte release channels, as well as inhibition of Na^+/H^+ exchange, the K^+ channel Kv1.3 and the Ca^{2+} channels I_{CRAC}.

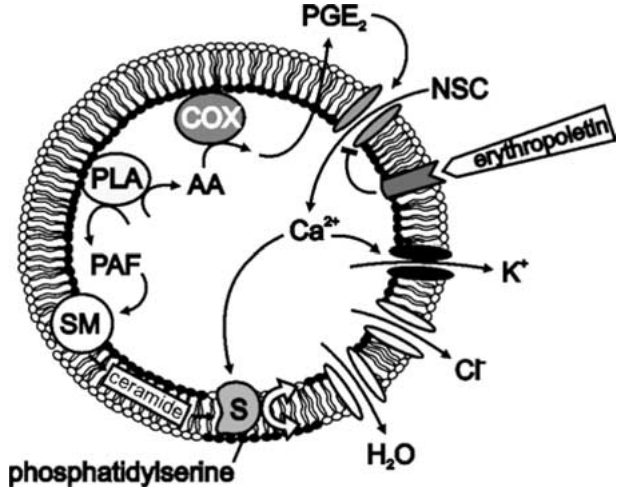

Fig. 3. Channel regulation in eryptosis. Several triggers of eryptosis (e.g., osmotic shock) stimulate the release of PGE_2 which activates Ca^{2+} permeable cation channels. The subsequent increase of cytosolic Ca^{2+} activates Ca^{2+} sensitive K^+ channels, which lead to cell shrinkage due to loss of K^+, hyperpolarization and Cl^- exit through Cl^- channels. Ca^{2+} in addition activates a scramblase, which breaks down the phosphatidylserine asymmetry of the cell membrane. Cell shrinkage activates a phospholipase leading to formation of platelet-activating factor, sphingomyelinase activation, ceramide formation and further scramblase activation.

channels is a prerequisite for Ca^{2+} entry through I_{CRAC} (Parekh & Penner, 1997). As discussed above, I_{CRAC} activation has been shown to be required for stimulation of cell proliferation.

Reports on the role of K^+ channels in apoptosis are conflicting. In some cells, inhibition of K^+ channels appears to favour (Szabo et al., 1996, 1997, 2004; Chin et al., 1997; Miki et al., 1997; Bankers-Fulbright et al., 1998; Han et al., 2004; Pal et al., 2004; Patel & Lazdunski, 2004) and activation of K^+ channels to inhibit (Jakob & Krieglstein, 1997; Lauritzen et al., 1997) apoptosis. Mice carrying a mutation of a G protein-coupled inward rectifier K^+ channel (*Weaver* mice) suffer from extensive neuronal cell death (Migheli et al., 1995, 1997; Murtomaki et al., 1995; Oo et al., 1996; Harrison & Roffler-Tarlov, 1998). However, in other models, apoptosis has been reported to be stimulated by activation of K^+ channels (Yu et al., 1997; Wei et al., 2004) and to be inhibited by increase of extracellular K^+ concentration (Prehn et al., 1997; Colom et al., 1998; Lang et al., 2003e) or inhibition of K^+ channels (Gantner et al., 1995; Lang et al., 2003e). In any case, cellular loss of K^+ appears to be an important trigger of apoptosis in a wide variety of cells (Beauvais et al., 1995; Benson et al., 1996; Bortner et al., 1997; Hughes, Jr. et al., 1997; Bortner & Cidlowski, 1999, 2004; Hughes, Jr. & Cidlowski, 1999; Montague et al., 1999; Gomez-Angelats et al., 2000; Maeno et al., 2000; Perez et al., 2000; Yurinskaya et al., 2005a, b). Activation of K^+ channels leads to hyperpolarization of the cell membrane, thus increasing the electrical driving force for Cl^- exit into the extracellular space. Thus, if K^+ channel activity is paralleled by Cl^- channel activity, it leads to cellular loss of KCl with osmotically obliged water and hence to cell shrinkage, a hallmark of apoptosis (Lang et al., 1998a).

As illustrated in Fig. 2, ligation of the CD95 receptor in Jurkat lymphocytes has been observed to inhibit Kv1.3 K^+ channels within a few minutes (Szabo et al., 1996, 1997, 2004). Kv1.3 is considered to be the cell volume regulatory K^+ channel of Jurkat lymphocytes (Deutsch & Chen, 1993). The channel protein is tyrosine phosphorylated upon CD95-receptor stimulation (Szabo et al., 1996; Gulbins et al., 1997) and its inhibition requires Lck^{56} (Szabo et al., 1996; Gulbins et al., 1997). Similar to CD95 receptor triggering, the sphingomyelinase product ceramide inhibits Kv1.3 and induces apoptosis (Gulbins et al., 1997). Tyrosine phosphorylation of Kv1.3 has been reported to similarly inhibit channel activity in other systems (Holmes et al., 1996). Kv1.3 is stimulated by the serum- and

glucocorticoid-inducible kinase (Lang et al., 2003a), which in turn inhibits apoptosis (Aoyama et al., 2005). The early inhibition of Kv1.3 is followed by late activation of Kv1.3 upon CD95 ligation (Storey et al., 2003). The early inhibition of Kv1.3 channels following CD95 triggering prevents premature cell shrinkage, which would otherwise interfere with the signaling of apoptosis (Lang et al., 1998a). The late activation of Kv1.3 channels during the execution phase of apoptosis supports apoptotic cell shrinkage (Storey et al., 2003).

As illustrated in Fig. 3, Ca^{2+}-sensitive K^+ channels (Gardos channels) are activated by increased cytosolic Ca^{2+} activity in suicidal erythrocytes (Gardos, 1958; Grygorczyk & Schwarz, 1983; Leinders et al., 1992; Brugnara et al., 1993; Dunn, 1998; Pellegrino & Pellegrini, 1998; Shindo et al., 2000; Del Carlo et al., 2002). The activation of the channels leads to hyperpolarization and due to the high erythrocyte Cl^- permeability, to parallel exit of K^+ and Cl^-. The cellular loss of KCl and subsequent cell shrinkage stimulate eryptosis (Lang et al., 2003d). Accordingly, increase of extracellular K^+ or pharmacological inhibition of the Gardos channels blunts the cell shrinkage and apoptosis following exposure to the Ca^{2+} ionophore ionomycin (Lang et al., 2003d). The cell shrinkage following Gardos channel activation triggers the formation of platelet activating factor PAF and subsequent activation of sphingomyelinase with formation of ceramide (Lang et al., 2005c). Ceramide then potentiates the pro-apoptotic effect of Ca^{2+} (Lang et al., 2004b, 2005c).

The Role of Anion Channels, Osmolyte Transport and pH Regulation in Cell Proliferation and Apoptosis

Anion channels have been shown to be activated during cell proliferation (Shen et al., 2000; Nilius & Droogmans, 2001; Varela et al.2004) and anion channel blockers have been shown to interfere with cell proliferation (Phipps et al., 1996; Pappas & Ritchie, 1998; Rouzaire-Dubois et al., 2000; Shen et al., 2000; Wondergem et al., 2001; Jiang et al., 2004). Moreover, impaired cell proliferation has been observed in ClC_3-deficient cells (Wang et al., 2002). Possibly, the signaling of cell proliferation needs at some stage transient cell shrinkage, which may require the activation of Cl^- channels. Usually, intracellular Cl^- is above electrochemical equilibrium and activation of Cl^- channels leads to Cl^- exit and thus depolarization. As long as K^+ channels are active, the Cl^- exit is paralleled by exit of K^+. The loss of KCl and osmotically obliged water shrinks the cells (Lang et al., 1998a). Cell shrinkage is, for instance, required for the triggering of cytosolic Ca^{2+} oscillations in ras oncogene-expressing cells (Ritter et al., 1993). The Ca^{2+} oscillations are in turn needed for the stimulation of cell proliferation (Fig. 1). At a later stage, proliferating cells swell due to a shift of the cell volume regulatory set point towards greater volumes and subsequent stimulation of Na^+/H^+ exchange and/or $Na^+,K^+,2Cl^-$ cotransport (Fig. 1). At this later stage activation of Cl^- channels either tends to impede cell proliferation or maintains the activity of Na^+/H^+ exchange and/or $Na^+,K^+,2Cl^-$ cotransport by keeping the actual cell volume below the new set point volume.

CD95 induced apoptosis of Jurkat cells (Szabo et al., 1998) and the TNFα- or staurosporine-induced apoptosis of various cell types (Maeno et al., 2000; Okada et al., 2004) is paralleled by activation of Cl^- channels (Fig. 2). In Jurkat cells the same channels are activated by osmotic cell swelling and are required for regulatory cell volume decrease (Lepple-Wienhues et al., 1998). In those cells activation of the Cl^- channels by cell swelling (Lepple-Wienhues et al., 1998) as well as by stimulation of the CD95 receptor (Szabo et al., 1998) requires the Src-like kinase Lck^{56}. The kinase is activated by ceramide (Gulbins et al., 1997), which is released by sphingomyelinase-mediated hydrolysis of sphingomyelin after stimulation of the CD95 receptor. In lymphocytes from patients with cystic fibrosis, outwardly rectifying Cl^- channels (ORCC) are resistant to activation by protein kinase A but could still be activated by cell swelling and Lck^{56} (Lepple-Wienhues et al., 2001).

Activation of Cl^- channels is required for stimulation of apoptosis, which is blunted or even disrupted by Cl^- channel inhibitors. Specifically, the respective Cl^- channel blockers inhibited apoptosis in CD95-induced Jurkat cell apoptosis (Szabo et al., 1998), TNFα- or staurosporine-induced apoptosis of various cell types (Maeno et al., 2000; Okada et al., 2004), apoptotic death of cortical neurons (Wei et al., 2004), antimycin A-induced death of proximal renal tubules (Miller & Schnellmann, 1993). In addition, chloride channel blockers inhibited GABA-induced enhancement of excitotoxic cell death of rat cerebral neurons (Erdo et al., 1991); cardiomyocyte apoptosis (Takahashi et al., 2005) and eryptosis (Myssina et al., 2004).

Activation of Cl^- channels leads to cell shrinkage by triggering cellular loss of KCl (*see* above). Some anion channels further allow the permeation of organic osmolytes such as taurine (Lang et al., 2003e), which are released by cells undergoing apoptosis (Lang et al., 1998b; Moran et al., 2000). The loss of the organic osmolytes then contributes to cell shrinkage (Lang et al., 1998a). Moreover, organic osmolytes stabilize cellular proteins (for review, *see* (Lang et al., 1998a) and their loss could, indeed, destabilize proteins. For instance, inhibition of inositol uptake has been shown to induce renal failure presumably due to apoptotic death of renal tubular cells (Kitamura et al., 1998).

Many Cl^- channels further allow the passage of HCO_3^- and their activation thus leads to cytosolic acidification, a typical feature of cells entering into apoptosis (Lang et al., 2002a; Wenzel & Daniel, 2004). Acidification may promote DNA fragmentation, as DNase type II has its pH optimum in the acidic range (for review, *see* Shrode et al., 1997). Along those lines, CD95-induced apoptosis is accelerated by inhibition of Na^+/H^+ exchange (Lang et al., 2000a).

The Dual Role of Ion Channels – a Paradox?

At first glance it is surprising that the same or similar channels could stimulate or support both cell proliferation and apoptosis. It should be kept in mind, though, that the effect of channel activation depends on further properties of the cell. For instance, activation of K^+ channels without parallel activity of electrogenic anion transporters or Cl^- channels may hyperpolarize but not shrink the cell (Lang et al., 1998a). The influence of K^+ channel activity and cell membrane potential on cytosolic Ca^{2+} activity depends on the activity of Ca^{2+} channels.

Moreover, the temporal pattern of channel activation may be important. For instance, the functional impact of oscillating K^+ channel activity typical for proliferating cells (Pandiella et al., 1989; Lang et al., 1991) has effects different from sustained K^+ channel activation typical for apoptotic cells (Lang et al., 2003d). Oscillatory Ca^{2+}-channel activity leading to fluctuations of cytosolic Ca^{2+} concentration could depolymerize the cytoskeleton (Lang et al., 1992, 2000c; Dartsch et al., 1995; Ritter et al., 1997) but may be too short-lived to activate caspases (Whitfield et al., 1995) or the scramblase (Woon et al., 1999; Dekkers et al., 2002).

Finally, the amplitude of channel activity may be decisive for the outcome. For instance, the amplitude of TASK-3 K^+ channel activity observed during apoptosis is one order of magnitude higher than the activity of the same channels in tumor cells (Patel & Lazdunski, 2004; Wang, 2004). Similarly, the Ca^{2+} entry required for stimulation of mitogenic transcription factors may remain below the Ca^{2+} entry required for triggering of apoptosis (Whitfield et al., 1995).

Conclusions

Ion channels play an active role in the concerted cellular mechanisms leading to cell proliferation and apoptosis. They participate in the appropriate adjustment of cell volume and influence cytosolic pH and Ca^+ concentrations.

Typically, stimulation of cell proliferation is followed by early cell shrinkage requiring activation of Cl^- and K^+ channel activity, by cytosolic alkalinization (supported by activation of the Na^+/H^+ exchanger and impeded by activation of HCO_3^--permeable Cl^- channels), and by Ca^{2+} oscillations (requiring activation of Ca^{2+} channels). The Ca^{2+} oscillations are maintained by Ca^{2+} entry through Ca^{2+} release-activated channels I_{CRAC}, which in turn require K^+ channel-dependent maintenance of cell membrane polarization. The Ca^{2+} oscillations lead to depolymerization of the actin filament network, with subsequent disinhibition of Na^+/H^+ exchanger and/or Na^+,K^+,2Cl^- resulting in cell swelling.

Typically, apoptosis eventually leads to cell shrinkage due to activation of K^+ and/or Cl^- channels and organic osmolyte release. The activation of Cl^- channels and inhibition of Na^+/H^+ exchangers leads to cytosolic acidification. While I_{CRAC} is inhibited during CD95-induced apoptosis, sustained Ca^{2+} entry through Ca^{2+}-permeable cation channels is able to trigger apoptosis.

Several channels play dual roles in both cell proliferation and apoptosis. The effect of channel activation critically depends on the temporal pattern and amplitude of channel activity as well as the interplay with other channels, transporters and signaling pathways.

Despite the generation of a tremendous body of experimental evidence we are still far from fully understanding the complex interplay between channel activity and signaling of proliferating or dying cells. Clearly, further experimental efforts are needed to address the many open questions.

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