CHAPTER ELEVEN

Cell Volume Regulatory Ion Channels in Cell Proliferation and Cell Death

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Contents

Abstract

Alterations of cell volume are key events during both cell proliferation and apoptotic cell death. Cell proliferation eventually requires an increase of cell volume, and apoptosis is typically paralleled by cell shrinkage. Alterations of cell volume require the participation of ion transport across the cell membrane, including appropriate activity of Cl^- and K^+ channels. Cl^- channels modify cytosolic Cl^- activity and mediate osmolyte flux, and thus influence cell volume. Most Cl^- channels allow exit of HCO_3^-, leading to cytosolic acidification, which in turn inhibits cell proliferation and favors apoptosis. K^+ exit through K^+ channels decreases cytosolic K^+ concentration, which may sensitize the cell for apoptotic cell death. K^+ channel activity further maintains the cell membrane potential, a critical determinant of Ca^{2+} entry through Ca^{2+} channels. Ca^{2+} may, in addition, enter through Ca^{2+}-permeable cation channels, which, in some cells, are activated by hyperosmotic shock. Increases of cytosolic Ca^{2+} activity may trigger both mechanisms required for cell proliferation and mechanisms, leading to apoptosis. Thereby cell proliferation and apoptosis

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depend on magnitude and temporal organization of Ca^{2+} entry, as well as activity of other signaling pathways. Accordingly, the same ion channels may participate in the stimulation of both cell proliferation and apoptosis. Specific ion channel blockers may thus abrogate both cellular mechanisms, depending on cell type and condition.

1. Introduction

The adjustment of cell number to functional needs requires an adequate balance between formation of new cells by cell proliferation and their elimination by cell death. Suicidal cell death eliminates abundant and potentially harmful cells (Green and Reed, 1998; Gulbins *et al.*, 2000), which need to be replaced by cell proliferation.

Cell proliferation is stimulated by growth factors (Adams *et al.*, 2004; Bikfalvi *et al.*, 1998; Tallquist and Kazlauskas, 2004), apoptosis by a wide variety of mechanisms, including activation of CD95 (Fillon *et al.*, 2002; Gulbins *et al.*, 2000; Lang *et al.*, 1998b, 1999), somatostatin receptor (Teijeiro *et al.*, 2002), or TNFα receptor (Lang *et al.*, 2002a), by thyroid hormones (Alisi *et al.*, 2005), by lack of growth factors (Sturm *et al.*, 2004), by cell density (Long *et al.*, 2003), by cell adhesion (Davies, 2003; Walsh *et al.*, 2003), or by stressors such as oxidants (Rosette and Karin, 1996), radiation (Rosette and Karin, 1996), inhibition of glutaminase (Rotoli *et al.*, 2005), chemotherapeutics (Cariers *et al.*, 2002; Wieder *et al.*, 2001), energy depletion (Pozzi *et al.*, 2002), choline deficiency (Albright *et al.*, 2005), or osmotic shock (Bortner and Cidlowski, 1998, 1999; Lang *et al.*, 1998a, 2000b; Maeno *et al.*, 2000; Michea *et al.*, 2000; Rosette and Karin, 1996).

To eventually generate daughter cells of similar size as parent cells, cell proliferation needs at some point an increase of cell volume (Lang *et al.*, 1998a). Hallmarks of apoptosis include cell shrinkage (Lang *et al.*, 1998a) and breakdown of phosphatidylserine asymmetry of the plasma membrane (Green and Reed, 1998).

Suicidal cell death is not limited to nucleated cells but may similarly affect erythrocytes (Barvitenko *et al.*, 2005; Rice and Alfrey, 2005). The apoptosis-like death of mature erythrocytes (eryptosis) is characterized by cell shrinkage and breakdown of phosphatidylserine asymmetry, both typical features of apoptosis in nucleated cells (Lang *et al.*, 2003b,c,e).

Cell proliferation and apoptosis both involve and require activation of Cl^- channels, K^+ channels, and Ca^{2+} channels. Ample evidence points to an active role of those channels in the triggering of those two fundamental cellular functions. The following short synopsis compiles evidence for the participation of ion channels in cell proliferation and suicidal cell

death. Special emphasis will be placed on cell proliferation of ras oncogene-expressing cells, apoptosis of CD95-triggered Jurkat lymphocytes, and eryptosis of osmotically shrunken erythrocytes.

2. Anion Channels, Osmolyte Transport, and pH Regulation

Anion channels may be activated during cell proliferation (Nilius and Droogmans, 2001; Shen *et al.*, 2000; Varela *et al.*, 2004) and anion channel blockers may interfere with cell proliferation (Jiang *et al.*, 2004; Pappas and Ritchie, 1998; Phipps *et al.*, 1996; Rouzaire-Dubois *et al.*, 2000; Shen *et al.*, 2000; Wondergem *et al.*, 2001). Moreover, cell proliferation may be impaired in cells lacking functional ClC-3 Cl^- channels (Wang *et al.*, 2002). The signaling of cell proliferation may require transient cell shrinkage at some stage, which may be accomplished by activation of Cl^- channels. As intracellular Cl^- activity is usually above electrochemical equilibrium, activation of Cl^- channels leads to Cl^- exit and thus depolarization. If K^+ channels are simultaneously active, the Cl^- exit is paralleled by the exit of K^+. The loss of KCl and osmotically obliged water then leads to cell shrinkage (Lang *et al.*, 1998a). In ras oncogene-expressing cells (Ritter *et al.*, 1993), cell shrinkage is required for the initiation of cytosolic Ca^{2+} oscillations, which are in turn needed for the stimulation of cell proliferation. The initial cell shrinkage is reversed into a later cell swelling, a result of a shifting cell volume regulatory set point toward greater volumes and a subsequent stimulation of Na^+/H^+ exchange and/or Na^+,K^+,2Cl^- cotransport. Activation of Cl^- channels at this later stage may impede cell proliferation.

Activation of Cl^- channels parallels the 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). Cl^- channels activated during CD95-induced apoptosis are the same as those activated by osmotic cell swelling and participating in regulatory cell volume decrease (Lepple-Wienhues *et al.*, 1998). During both cell swelling (Lepple-Wienhues *et al.*, 1998) and CD95-induced apoptosis (Szabo *et al.*, 1998), the activation of Cl^- channels requires the Src-like kinase Lck^{56}. The kinase is in turn activated by ceramide (Gulbins *et al.*, 1997). In lymphocytes from patients with cystic fibrosis the Cl^- channels cannot be opened by protein kinase A but are activated by cell swelling and Lck^{56} (Lepple-Wienhues *et al.*, 2001).

Cl^- channel inhibitors may blunt or even disrupt 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 and Schnellmann, 1993), GABA-induced

enhancement of excitotoxic cell death of rat cerebral neurons (Erdo *et al.*, 1991), cardiomyocyte apoptosis (Takahashi *et al.*, 2005), and eryptosis (Takahashi *et al.*, 2005).

Activation of Cl^- channels leads to cellular loss of KCl and osmotically obliged water and thus to cell shrinkage. Some anion channels further allow exit of organic osmolytes such as taurine (Lang *et al.*, 1998b,e; Moran *et al.*, 2000), an effect contributing to cell shrinkage (Lang *et al.*, 1998a). As organic osmolytes stabilize cellular proteins (Lang *et al.*, 1998a), their loss could destabilize proteins. Inhibition of inositol uptake has indeed been shown to induce renal failure, presumably because of apoptotic death of renal tubular cells (Kitamura *et al.*, 1998).

Many Cl^- channels further allow HCO_3^- exit, leading to cytosolic acidification, a typical feature of cells entering into apoptosis (Lang *et al.*, 2002a; Wenzel and Daniel, 2004). As the DNA-degrading enzyme DNase type II has its pH optimum in the acidic range (for review, see Shrode *et al.*, 1997), acidification is expected to enhance DNA fragmentation. CD95-induced apoptosis is indeed accelerated by the inhibition of Na^+/H^+ exchange (Lang *et al.*, 2000a).

3. Ca^{2+} and Unselective Cation Channels

Cytosolic Ca^{2+} activity plays a decisive role in the regulation of cell proliferation (Berridge *et al.*, 1998, 2000, 2003; Parekh and Penner, 1997; Santella, 1998; Santella *et al.*, 1998; Whitfield *et al.*, 1995). Growth factors stimulate Ca^{2+} release through activated Ca^{2+} channel I_{CRAC} (Qian and Weiss, 1997), which mediates Ca^{2+} entry, thus triggering and maintaining pulsatile Ca^{2+} release from intracellular stores yielding oscillations of cytosolic Ca^{2+} activity. Those oscillations govern a wide variety of cellular functions (Berridge *et al.*, 1998, 2000, 2003; Parekh and Penner, 1997), including depolymerization of actin filaments (Dartsch *et al.*, 1995; Lang *et al.*, 1992, 2000c; Ritter *et al.*, 1997). The depolymerization of actin filaments results in disinhibition of Na^+/H^+ exchanger and/or $Na^+,K^+,2Cl^-$ cotransporter, which both accumulate ions and osmotically obliged water and thus increase cell volume (Lang *et al.*, 1998a). Activation of I_{CRAC}, Ca^{2+} oscillations, and depolymerization of the actin filament network are prerequisites for the stimulation of cell proliferation (Dartsch *et al.*, 1995; Lang *et al.*, 1992, 2000c; Ritter *et al.*, 1997).

CD95 receptor triggering is paralleled by inhibition of I_{CRAC} in Jurkat T lymphocytes (Dangel *et al.*, 2005; Lepple-Wienhues *et al.*, 1999). Inhibition of I_{CRAC} prevents activation and proliferation of lymphocytes but does not necessarily lead to apoptotic cell death. At a later stage, CD95 stimulation may, in some cells, lead to a sustained increase of cytosolic Ca^{2+} activity, which has been shown to trigger apoptosis in a variety of nucleated cells

(Berridge *et al.*, 2000; Green and Reed, 1998; Liu *et al.*, 2005; Parekh and Penner, 1997; Parekh and Putney, 2005; Spassova *et al.*, 2004). Furthermore, Ca^{2+}-permeable cation channels trigger apoptosis-like suicidal death of erythrocytes (eryptosis) (Brand *et al.*, 2003; Lang *et al.*, 2002b, 2003b). Accordingly, eryptosis is elicited 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 erythrocyte cation channels are activated by 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* (Duranton *et al.*, 2003; Lang *et al.*, 2003b, 2004a). Energy depletion is presumably effective through impairment of GSH replenishment, thus weakening the antioxidative defense of the erythrocytes (Bilmen *et al.*, 2001; Mavelli *et al.*, 1984). The erythrocyte cation channels are inhibited by Cl^- and are activated by replacement of Cl^- with gluconate (Duranton *et al.*, 2002; Huber *et al.*, 2001). Similar or identical cation channels are activated by incubation of human erythrocytes in low ionic strength (Bernhardt *et al.*, 1991; Jones and Knauf, 1985; LaCelle and Rothsteto, 1966) or by depolarization (Bennekou, 1993; Christophersen and Bennekou, 1991; Kaestner *et al.*, 1999).

Increased cytosolic Ca^{2+} concentrations somehow trigger the scrambling of the erythrocyte cell membrane (Zhou *et al.*, 2002) with breakdown of phosphatidylserine asymmetry and phosphatidylserine exposure at the cell surface (Lang *et al.*, 2003b). The cation channels are activated by prostaglandin E_2, which is released upon osmotic shock (Lang *et al.*, 2005a). The cation channel blockers amiloride (Lang *et al.*, 2003b) and ethylisopropylamiloride (Lang *et al.*, 2003c) blunt the phosphatidylserine exposure following osmotic shock.

Cell volume-sensitive cation channels are similarly expressed in nucleated cells, such as airway epithelia cells (Chan *et al.*, 1992), vascular smooth muscle, colon carcinoma and neuroblastoma cells (Koch and Korbmacher, 1999), cortical collecting duct cells (Volk *et al.*, 1995), hepatocytes (Wehner *et al.*, 1995, 2000), mast cells (Cabado *et al.*, 1994), and macrophages (Gamper *et al.*, 2000). Cation channels activated by Cl^- removal are expressed in salivary and lung epithelial cells (Dinudom *et al.*, 1995; Marunaka *et al.*, 1994; Tohda *et al.*, 1994). Whether or not those channels participate in the stimulation of apoptosis remains elusive.

4. K^+ CHANNELS

Several K^+ channels participate in the regulation of cell proliferation (Patel and Lazdunski, 2004; Wang, 2004). Growth factors activate K^+ channels (Enomoto *et al.*, 1986; Faehling *et al.*, 2001; Lang *et al.*, 1991;

Liu *et al.*, 2001; O'Lague *et al.*, 1985; Sanders *et al.*, 1996; Wiecha *et al.*, 1998), and enhanced K^+ channel activity is observed in tumor cells (DeCoursey *et al.*, 1984; Mauro *et al.*, 1997; Nilius and Wohlrab, 1992; Pappas and Ritchie, 1998; Pappone and Ortiz-Miranda, 1993; Patel and Lazdunski, 2004; Skryma *et al.*, 1997; Strobl *et al.*, 1995; Wang, 2004; Zhou *et al.*, 2003). In ras oncogene-expressing cells, repetitive activation of Ca^{2+}-sensitive K^+ channels by oscillating cytosolic Ca^{2+} activity leads to oscillations of cell membrane potential (Lang *et al.*, 1991). Several K^+ channel inhibitors disrupt cell proliferation (for review, see Wang 2004). K^+ channel activation is apparently important for the early G1 phase of the cell cycle (Wang *et al.*, 1998; Wonderlin and Strobl, 1996). The maintenance of cell membrane potential by K^+ channels provides the electrical driving force for Ca^{2+} entry through I_{CRAC} (Parekh and Penner, 1997), which is required for stimulation of cell proliferation.

The role of K^+ channels in apoptosis is less obvious. In some cells, inhibition of K^+ channels participates in the stimulation of apoptosis (Bankers-Fulbright *et al.*, 1998; Chin *et al.*, 1997; Han *et al.*, 2004; Miki *et al.*, 1997; Pal *et al.*, 2004; Patel and Lazdunski, 2004), and activation of K^+ channels inhibits apoptosis (Jakob and Krieglstein, 1997; Lauritzen *et al.*, 1997). Along those lines, extensive neuronal cell death is observed in mice carrying a mutation of G-coupled inward rectifier K^+ channels (*Weaver* mice) (Harrison and Roffler-Tarlov, 1998; Migheli *et al.*, 1995, 1997; Murtomaki *et al.*, 1995; Oo *et al.*, 1996).

However, in other cells apoptosis is stimulated by activation of K^+ channels (Wei *et al.*, 2004; Yu *et al.*, 1997) and inhibited by increase of extracellular K^+ concentration (Colom *et al.*, 1998; Lang *et al.*, 2003e; Prehn *et al.*, 1997) or K^+ channel blockade (Gantner *et al.*, 1995; Lang *et al.*, 2003e). Cellular loss of K^+ apparently favors apoptosis in a wide variety of cells (Beauvais *et al.*, 1995; Benson *et al.*, 1996; Bortner and Cidlowski, 1999, 2004; Bortner *et al.*, 1997; Gomez-Angelats *et al.*, 2000; Hughes and Cidlowski, 1999; Hughes *et al.*, 1997; Maeno *et al.*, 2000; Montague *et al.*, 1999; Perez *et al.*, 2000; Yurinskaya *et al.*, 2005a,b). Moreover, activation of K^+ channels hyperpolarizes the cell membrane, thus increasing the electrical driving force for Cl^- exit. Depending on Cl^- channel activity, K^+ channel activity leads to cellular loss of KCl with osmotically obliged water and hence to apoptotic cell shrinkage (Lang *et al.*, 1998a).

In Jurkat lymphocytes, CD95 activation is followed within a few minutes by inhibition of Kv1.3 K^+ channels (Szabo *et al.*, 1996, 1997, 2004), the cell volume regulatory K^+ channel of those cells (Deutsch and Chen, 1993). CD95 triggering leads to tyrosine phosphorylation of the Kv1.3 channel protein (Gulbins *et al.*, 1997; Szabo *et al.*, 1996). Accordingly, CD95-induced inhibition of Kv1.3 requires Lck^{56} (Gulbins *et al.*, 1997; Szabo *et al.*, 1996). The inhibitory effect of CD95 triggering is mimicked by the sphingomyelinase product ceramide, which similarly induces apoptosis

(Gulbins *et al.*, 1997). In other cells, Kv1.3 is similarly regulated by tyrosine phosphorylation (Holmes *et al.*, 1996). Moreover, Kv1.3 is upregulated by the serum and glucocorticoid-inducible kinase (Lang *et al.*, 2003a), which similarly inhibits apoptosis (Aoyama *et al.*, 2005). Following CD95 activation, the early inhibition of Kv1.3 is followed by late activation of Kv1.3 (Storey *et al.*, 2003). Early inhibition of Kv1.3 channels in CD95-activated cells may serve to prevent premature cell shrinkage which otherwise may interfere with 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).

In suicidal erythrocytes, Ca^{2+}-sensitive K^+ channels (GARDOS channels) are activated by increased cytosolic Ca^{2+} activity (Brugnara *et al.*, 1993; Del Carlo *et al.*, 2002; Dunn, 1998; Gardos, 1958; Grygorczyk and Schwarz, 1983; Leinders *et al.*, 1992; Pellegrino and Pellegrini, 1998; Shindo *et al.*, 2000). Activation of GARDOS channels hyperpolarizes the cell membrane and, because of high erythrocyte Cl^- permeability, leads to parallel exit of K^+ and Cl^-. The cellular loss of KCl and osmotically obliged water leads to cell shrinkage, which in turn favors phosphatidylserine exposure (Lang *et al.*, 2003d). An increase of extracellular K^+ or a pharmacological inhibition of GARDOS channels blunts cell shrinkage and has a moderate inhibitory effect on phosphatidylserine scrambling following exposure to the Ca^{2+} ionophore ionomycin (Lang *et al.*, 2003d). Erythrocyte shrinkage stimulates formation of the platelet-activating factor, which in turn activates a sphingomyelinase (Lang *et al.*, 2005b). The ceramide generated by the sphingomyelinase then sensitizes the cell for the scrambling effect of Ca^{2+} (Lang *et al.*, 2004b, 2005b).

5. Switching from Cell Proliferation to Suicidal Cell Death

The same or similar channels could participate in the stimulation of both cell proliferation and apoptosis. The effect of channel activation depends on further properties of the cell. For instance, it may depend on the activity of other channels. Activation of K^+ channels without parallel activity of electrogenic anion transporters or Cl^- channels, for instance, hyperpolarizes the cell membrane but does not shrink the cell (Lang *et al.*, 1998a). Moreover, activation of K^+ channels may increase Ca^{2+} entry and cytosolic Ca^{2+} activity only in the presence of active Ca^{2+} channels.

The effect may further depend on the temporal pattern of channel activation. The oscillating K^+ channel activity typical of proliferating cells (Lang *et al.*, 1991; Pandiella *et al.*, 1989) has different effects as sustained K^+ channel activation typical of apoptotic cells (Lang *et al.*, 2003d). Oscillations of

Ca^{2+} channel activity lead to fluctuations of cytosolic Ca^{2+} concentration, which depolymerize the cytoskeleton (Dartsch *et al.*, 1995; Lang *et al.*, 1992, 2000c; Ritter *et al.*, 1997), whereas permanent opening of Ca^{2+} channels leads to sustained increases of cytosolic Ca^{2+} activity, which may activate caspases (Whitfield *et al.*, 1995) or trigger scrambling of the cell membrane (Dekkers *et al.*, 2002; Woon *et al.*, 1999).

The outcome further depends on the amplitude of channel activity. The amplitude of TASK-3 K^+ channel activity during apoptosis is one order of magnitude higher than in tumor cells (Patel and Lazdunski, 2004; Wang, 2004), and the Ca^{2+} entry required for stimulation of mitogenic transcription factors may remain well below the Ca^{2+} entry required for the triggering of suicidal cell death (Whitfield *et al.*, 1995).

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REFERENCES

Adams, T. E., McKern, N. M., and Ward, C. W. (2004). Signalling by the type 1 insulin-like growth factor receptor: Interplay with the epidermal growth factor receptor. *Growth Factors* **22,** 89–95.

Albright, C. D., da Costa, K. A., Craciunescu, C. N., Klem, E., Mar, M. H., and Zeisel, S. H. (2005). Regulation of choline deficiency apoptosis by epidermal growth factor in CWSV-1 rat hepatocytes. *Cell. Physiol. Biochem.* **15,** 59–68.

Alisi, A., Demori, I., Spagnuolo, S., Pierantozzi, E., Fugassa, E., and Leoni, S. (2005). Thyroid status affects rat liver regeneration after partial hepatectomy by regulating cell cycle and apoptosis. *Cell. Physiol. Biochem.* **15,** 69–76.

Aoyama, T., Matsui, T., Novikov, M., Park, J., Hemmings, B., and Rosenzweig, A. (2005). Serum and glucocorticoid-responsive kinase-1 regulates cardiomyocyte survival and hypertrophic response. *Circulation* **111,** 1652–1659.

Bankers-Fulbright, J. L., Kephart, G. M., Loegering, D. A., Bradford, A. L., Okada, S., Kita, H., and Gleich, G. J. (1998). Sulfonylureas inhibit cytokine-induced eosinophil survival and activation. *J. Immunol.* **160,** 5546–5553.

Barvitenko, N. N., Adragna, N. C., and Weber, R. E. (2005). Erythrocyte signal transduction pathways, their oxygenation dependence and functional significance. *Cell. Physiol. Biochem.* **15,** 1–18.

Beauvais, F., Michel, L., and Dubertret, L. (1995). Human eosinophils in culture undergo a striking and rapid shrinkage during apoptosis: Role of K+ channels. *J. Leukocyte Biol.* **57,** 851–855.

Bennekou, P. (1993). The voltage-gated non-selective cation channel from human red cells is sensitive to acetylcholine. *Biochim. Biophys. Acta* **1147,** 165–167.

Benson, R. S., Heer, S., Dive, C., and Watson, A. J. (1996). Characterization of cell volume loss in CEM-C7A cells during dexamethasone-induced apoptosis. *Am. J. Physiol.* **270,** C1190–C1203.

Berg, C. P., Engels, I. H., Rothbart, A., Lauber, K., Renz, A., Schlosser, S. F., Schulze-Osthoff, K., and Wesselborg, S. (2001). Human mature red blood cells express caspase-3 and caspase-8, but are devoid of mitochondrial regulators of apoptosis. *Cell Death Differ.* **8,** 1197–1206.

Bernhardt, I., Hall, A. C., and Ellory, J. C. (1991). Effects of low ionic strength media on passive human red cell monovalent cation transport. *J. Physiol.* **434,** 489–506.

Berridge, M. J., Bootman, M. D., and Lipp, P. (1998). Calcium: A life and death signal. *Nature* **395,** 645–648.

Berridge, M. J., Bootman, M. D., and Roderick, H. L. (2003). Calcium signalling: Dynamics, homeostasis and remodelling. *Nat. Rev. Mol. Cell. Biol.* **4,** 517–529.

Berridge, M. J., Lipp, P., and Bootman, M. D. (2000). The versatility and universality of calcium signalling. *Nat. Rev. Mol. Cell. Biol.* **1,** 11–21.

Bikfalvi, A., Savona, C., Perollet, C., and Javerzat, S. (1998). New insights in the biology of fibroblast growth factor-2. *Angiogenesis* **1,** 155–173.

Bilmen, S., Aksu, T. A., Gumuslu, S., Korgun, D. K., and Canatan, D. (2001). Antioxidant capacity of G-6-PD-deficient erythrocytes. *Clin. Chim. Acta* **303,** 83–86.

Bortner, C. D., and Cidlowski, J. A. (1998). A necessary role for cell shrinkage in apoptosis. *Biochem. Pharmacol.* **56,** 1549–1559.

Bortner, C. D., and Cidlowski, J. A. (1999). Caspase independent/dependent regulation of K(+), cell shrinkage, and mitochondrial membrane potential during lymphocyte apoptosis. *J. Biol. Chem.* **274,** 21953–21962.

Bortner, C. D., and Cidlowski, J. A. (2004). The role of apoptotic volume decrease and ionic homeostasis in the activation and repression of apoptosis. *Pflüg. Arch.* **448,** 313–318.

Bortner, C. D., Hughes, F. M., Jr., and Cidlowski, J. A. (1997). A primary role for K+ and Na+ efflux in the activation of apoptosis. *J. Biol. Chem.* **272,** 32436–32442.

Brand, V. B., Sandu, C. D., Duranton, C., Tanneur, V., Lang, K. S., Huber, S. M., and Lang, F. (2003). Dependence of *Plasmodium falciparum in vitro* growth on the cation permeability of the human host erythrocyte. *Cell. Physiol. Biochem.* **13,** 347–356.

Bratosin, D., Leszczynski, S., Sartiaux, C., Fontaine, O., Descamps, J., Huart, J. J., Poplineau, J., Goudaliez, F., Aminoff, D., and Montreuil, J. (2001). Improved storage of erythrocytes by prior leukodepletion: Flow cytometric evaluation of stored erythrocytes. *Cytometry* **46,** 351–356.

Brugnara, C., de Franceschi, L., and Alper, S. L. (1993). Inhibition of Ca(2+)-dependent K+ transport and cell dehydration in sickle erythrocytes by clotrimazole and other imidazole derivatives. *J. Clin. Invest.* **92,** 520–526.

Cabado, A. G., Vieytes, M. R., and Botana, L. M. (1994). Effect of ion composition on the changes in membrane potential induced with several stimuli in rat mast cells. *J. Cell. Physiol.* **158,** 309–316.

Cariers, A., Reinehr, R., Fischer, R., Warskulat, U., and Haussinger, D. (2002). c-Jun-N-terminal kinase dependent membrane targeting of CD95 in rat hepatic stellate cells. *Cell. Physiol. Biochem.* **12,** 179–186.

Chan, H. C., Goldstein, J., and Nelson, D. J. (1992). Alternate pathways for chloride conductance activation in normal and cystic fibrosis airway epithelial cells. *Am. J. Physiol.* **262,** C1273–C1283.

Chin, L. S., Park, C. C., Zitnay, K. M., Sinha, M., DiPatri, A. J., Jr., Perillan, P., and Simard, J. M. (1997). 4-Aminopyridine causes apoptosis and blocks an outward rectifier K+ channel in malignant astrocytoma cell lines. *J. Neurosci. Res.* **48,** 122–127.

Christophersen, P., and Bennekou, P. (1991). Evidence for a voltage-gated, non-selective cation channel in the human red cell membrane. *Biochim. Biophys. Acta* **1065,** 103–106.
Colom, L. V., Diaz, M. E., Beers, D. R., Neely, A., Xie, W. J., and Appel, S. H. (1998). Role of potassium channels in amyloid-induced cell death. *J. Neurochem.* **70,** 1925–1934.
Dangel, G. R., Lang, F., and Lepple-Wienhues, A. (2005). Effect of sphingosine on Ca2+ entry and mitochondrial potential of Jurkat T cells: Interaction with Bcl2. *Cell. Physiol. Biochem.* **16,** 9–14.
Dartsch, P. C., Ritter, M., Gschwentner, M., Lang, H. J., and Lang, F. (1995). Effects of calcium channel blockers on NIH 3T3 fibroblasts expressing the Ha-ras oncogene. *Eur. J. Cell Biol.* **67,** 372–378.
Daugas, E., Cande, C., and Kroemer, G. (2001). Erythrocytes: Death of a mummy. *Cell Death Differ.* **8,** 1131–1133.
Davies, A. M. (2003). Regulation of neuronal survival and death by extracellular signals during development. *EMBO J.* **22,** 2537–2545.
DeCoursey, T. E., Chandy, K. G., Gupta, S., and Cahalan, M. D. (1984). Voltage-gated K+ channels in human T lymphocytes: A role in mitogenesis? *Nature* **307,** 465–468.
Dekkers, D. W., Comfurius, P., Bevers, E. M., and Zwaal, R. F. (2002). Comparison between Ca2+-induced scrambling of various fluorescently labelled lipid analogues in red blood cells. *Biochem. J.* **362,** 741–747.
Del Carlo, B., Pellegrini, M., and Pellegrino, M. (2002). Calmodulin antagonists do not inhibit IK(Ca) channels of human erythrocytes. *Biochim. Biophys. Acta* **1558,** 133–141.
Deutsch, C., and Chen, L. Q. (1993). Heterologous expression of specific K+ channels in T lymphocytes: Functional consequences for volume regulation. *Proc. Natl. Acad. Sci. USA* **90,** 10036–10040.
Dinudom, A., Komwatana, P., Young, J. A., and Cook, D. I. (1995). Control of the amiloride-sensitive Na+ current in mouse salivary ducts by intracellular anions is mediated by a G protein. *J. Physiol.* **487**(Pt. 3), 549–555.
Dunn, P. M. (1998). The action of blocking agents applied to the inner face of Ca(2+)-activated K+ channels from human erythrocytes. *J. Membr. Biol.* **165,** 133–143.
Duranton, C., Huber, S., Tanneur, V., Lang, K., Brand, V., Sandu, C., and Lang, F. (2003). Electrophysiological properties of the *Plasmodium falciparum*-induced cation conductance of human erythrocytes. *Cell. Physiol. Biochem.* **13,** 189–198.
Duranton, C., Huber, S. M., and Lang, F. (2002). Oxidation induces a Cl(−)-dependent cation conductance in human red blood cells. *J. Physiol.* **539,** 847–855.
Enomoto, K., Cossu, M. F., Edwards, C., and Oka, T. (1986). Induction of distinct types of spontaneous electrical activities in mammary epithelial cells by epidermal growth factor and insulin. *Proc. Natl. Acad. Sci. USA* **83,** 4754–4758.
Erdo, S., Michler, A., and Wolff, J. R. (1991). GABA accelerates excitotoxic cell death in cortical cultures: Protection by blockers of GABA-gated chloride channels. *Brain Res.* **542,** 254–258.
Faehling, M., Koch, E. D., Raithel, J., Trischler, G., and Waltenberger, J. (2001). Vascular endothelial growth factor-A activates $Ca2^{+}$-activated K+ channels in human endothelial cells in culture. *Int. J. Biochem. Cell Biol.* **33,** 337–346.
Fillon, S., Klingel, K., Warntges, S., Sauter, M., Gabrysch, S., Pestel, S., Tanneur, V., Waldegger, S., Zipfel, A., Viebahn, R., Haussinger, D., Broer, S., Kandolf, R., and Lang, F. (2002). Expression of the serine/threonine kinase hSGK1 in chronic viral hepatitis. *Cell. Physiol. Biochem.* **12,** 47–54.
Gamper, N., Huber, S. M., Badawi, K., and Lang, F. (2000). Cell volume-sensitive sodium channels upregulated by glucocorticoids in U937 macrophages. *Pflüg. Arch.* **441,** 281–286.
Gantner, F., Uhlig, S., and Wendel, A. (1995). Quinine inhibits release of tumor necrosis factor, apoptosis, necrosis and mortality in a murine model of septic liver failure. *Eur. J. Pharmacol.* **294,** 353–355.

Gardos, G. (1958). The function of calcium in the potassium permeability of human erythrocytes. *Biochim. Biophys. Acta* **30,** 653–654.

Gomez-Angelats, M., Bortner, C. D., and Cidlowski, J. A. (2000). Protein kinase C (PKC) inhibits fas receptor-induced apoptosis through modulation of the loss of K+ and cell shrinkage: A role for PKC upstream of caspases. *J. Biol. Chem.* **275,** 19609–19619.

Green, D. R., and Reed, J. C. (1998). Mitochondria and apoptosis. *Science* **281,** 1309–1312.

Grygorczyk, R., and Schwarz, W. (1983). Properties of the CA2+-activated K+ conductance of human red cells as revealed by the patch-clamp technique. *Cell Calcium* **4,** 499–510.

Gulbins, E., Jekle, A., Ferlinz, K., Grassme, H., and Lang, F. (2000). Physiology of apoptosis. *Am. J. Physiol. Renal Physiol.* **279,** F605–F615.

Gulbins, E., Szabo, I., Baltzer, K., and Lang, F. (1997). Ceramide-induced inhibition of T lymphocyte voltage-gated potassium channel is mediated by tyrosine kinases. *Proc. Natl. Acad. Sci. USA* **94,** 7661–7666.

Han, H., Wang, J., Zhang, Y., Long, H., Wang, H., Xu, D., and Wang, Z. (2004). HERG K channel conductance promotes H_2O_2-induced apoptosis in HEK293 cells: Cellular mechanisms. *Cell. Physiol. Biochem.* **14,** 121–134.

Harrison, S. M., and Roffler-Tarlov, S. K. (1998). Cell death during development of testis and cerebellum in the mutant mouse weaver. *Dev. Biol.* **195,** 174–186.

Holmes, T. C., Fadool, D. A., and Levitan, I. B. (1996). Tyrosine phosphorylation of the Kv1.3 potassium channel. *J. Neurosci.* **16,** 1581–1590.

Huber, S. M., Gamper, N., and Lang, F. (2001). Chloride conductance and volume-regulatory nonselective cation conductance in human red blood cell ghosts. *Pflüg. Arch.* **441,** 551–558.

Hughes, F. M., Jr., Bortner, C. D., Purdy, G. D., and Cidlowski, J. A. (1997). Intracellular K+ suppresses the activation of apoptosis in lymphocytes. *J. Biol. Chem.* **272,** 30567–30576.

Hughes, F. M., Jr., and Cidlowski, J. A. (1999). Potassium is a critical regulator of apoptotic enzymes *in vitro* and *in vivo*. *Adv. Enzyme Regul.* **39,** 157–171.

Jakob, R., and Krieglstein, J. (1997). Influence of flupirtine on a G-protein coupled inwardly rectifying potassium current in hippocampal neurones. *Br. J. Pharmacol.* **122,** 1333–1338.

Jiang, B., Hattori, N., Liu, B., Nakayama, Y., Kitagawa, K., and Inagaki, C. (2004). Suppression of cell proliferation with induction of p21 by Cl(−) channel blockers in human leukemic cells. *Eur. J. Pharmacol.* **488,** 27–34.

Jones, G. S., and Knauf, P. A. (1985). Mechanism of the increase in cation permeability of human erythrocytes in low-chloride media: Involvement of the anion transport protein capnophorin. *J. Gen. Physiol.* **86,** 721–738.

Kaestner, L., Bollensdorff, C., and Bernhardt, I. (1999). Non-selective voltage-activated cation channel in the human red blood cell membrane. *Biochim. Biophys. Acta* **1417,** 9–15.

Kitamura, H., Yamauchi, A., Sugiura, T., Matsuoka, Y., Horio, M., Tohyama, M., Shimada, S., Imai, E., and Hori, M. (1998). Inhibition of myo-inositol transport causes acute renal failure with selective medullary injury in the rat. *Kidney Int.* **53,** 146–153.

Koch, J., and Korbmacher, C. (1999). Osmotic shrinkage activates nonselective cation (NSC) channels in various cell types. *J. Membr. Biol.* **168,** 131–139.

LaCelle, P. L., and Rothsteto, A. (1966). The passive permeability of the red blood cell in cations. *J. Gen. Physiol.* **50,** 171–188.

Lang, F., Busch, G. L., Ritter, M., Volkl, H., Waldegger, S., Gulbins, E., and Haussinger, D. (1998a). Functional significance of cell volume regulatory mechanisms. *Physiol. Rev.* **78,** 247–306.

Lang, F., Friedrich, F., Kahn, E., Woll, E., Hammerer, M., Waldegger, S., Maly, K., and Grunicke, H. (1991). Bradykinin-induced oscillations of cell membrane potential in cells expressing the Ha-ras oncogene. *J. Biol. Chem.* **266,** 4938–4942.

Lang, F., Henke, G., Embark, H. M., Waldegger, S., Palmada, M., Bohmer, C., and Vallon, V. (2003a). Regulation of channels by the serum and glucocorticoid-inducible kinase: Implications for transport, excitability and cell proliferation. *Cell. Physiol. Biochem.* **13,** 41–50.

Lang, F., Lang, P. A., Lang, K. S., Brand, V., Tanneur, V., Duranton, C., Wieder, T., and Huber, S. M. (2004a). Channel-induced apoptosis of infected host cells-the case of malaria. *Pflüg. Arch.* **448,** 319–324.

Lang, F., Madlung, J., Bock, J., Lukewille, U., Kaltenbach, S., Lang, K. S., Belka, C., Wagner, C. A., Lang, H. J., Gulbins, E., and Lepple-Wienhues, A. (2000a). Inhibition of Jurkat-T-lymphocyte Na+/H+-exchanger by CD95(Fas/Apo-1)-receptor stimulation. *Pflüg. Arch.* **440,** 902–907.

Lang, F., Madlung, J., Siemen, D., Ellory, C., Lepple-Wienhues, A., and Gulbins, E. (2000b). The involvement of caspases in the CD95(Fas/Apo-1)- but not swelling-induced cellular taurine release from Jurkat T-lymphocytes. *Pflüg. Arch.* **440,** 93–99.

Lang, F., Madlung, J., Uhlemann, A. C., Risler, T., and Gulbins, E. (1998b). Cellular taurine release triggered by stimulation of the Fas(CD95) receptor in Jurkat lymphocytes. *Pflüg. Arch.* **436,** 377–383.

Lang, F., Ritter, M., Gamper, N., Huber, S., Fillon, S., Tanneur, V., Lepple-Wienhues, A., Szabo, I., and Gulbins, E. (2000c). Cell volume in the regulation of cell proliferation and apoptotic cell death. *Cell. Physiol. Biochem.* **10,** 417–428.

Lang, F., Szabo, I., Lepple-Wienhues, A., Siemen, D., and Gulbins, E. (1999). Physiology of receptor-mediated lymphocyte apoptosis. *News Physiol. Sci.* **14,** 194–200.

Lang, F., Waldegger, S., Woell, E., Ritter, M., Maly, K., and Grunicke, H. (1992). Effects of inhibitors and ion substitutions on oscillations of cell membrane potential in cells expressing the RAS oncogene. *Pflüg. Arch.* **421,** 416–424.

Lang, K. S., Duranton, C., Poehlmann, H., Myssina, S., Bauer, C., Lang, F., Wieder, T., and Huber, S. M. (2003b). Cation channels trigger apoptotic death of erythrocytes. *Cell Death Differ.* **10,** 249–256.

Lang, K. S., Fillon, S., Schneider, D., Rammensee, H. G., and Lang, F. (2002a). Stimulation of TNF alpha expression by hyperosmotic stress. *Pflüg. Arch.* **443,** 798–803.

Lang, K. S., Myssina, S., Brand, V., Sandu, C., Lang, P. A., Berchtold, S., Huber, S. M., Lang, F., and Wieder, T. (2004b). Involvement of ceramide in hyperosmotic shock-induced death of erythrocytes. *Cell Death Differ.* **11,** 231–243.

Lang, K. S., Myssina, S., Tanneur, V., Wieder, T., Huber, S. M., Lang, F., and Duranton, C. (2003c). Inhibition of erythrocyte cation channels and apoptosis by ethylisopropylamiloride. *Naunyn Schmiedebergs Arch. Pharmacol.* **367,** 391–396.

Lang, K. S., Roll, B., Myssina, S., Schittenhelm, M., Scheel-Walter, H. G., Kanz, L., Fritz, J., Lang, F., Huber, S. M., and Wieder, T. (2002b). Enhanced erythrocyte apoptosis in sickle cell anemia, thalassemia and glucose-6-phosphate dehydrogenase deficiency. *Cell. Physiol. Biochem.* **12,** 365–372.

Lang, P. A., Kaiser, S., Myssina, S., Wieder, T., Lang, F., and Huber, S. M. (2003d). Role of Ca2+-activated K+ channels in human erythrocyte apoptosis. *Am. J. Physiol. Cell. Physiol.* **285,** C1553–C1560.

Lang, P. A., Kempe, D. S., Myssina, S., Tanneur, V., Birka, C., Laufer, S., Lang, F., Wieder, T., and Huber, S. M. (2005a). PGE(2) in the regulation of programmed erythrocyte death. *Cell Death Differ.* **12,** 415–428.

Lang, P. A., Kempe, D. S., Tanneur, V., Eisele, K., Klarl, B. A., Myssina, S., Jendrossek, V., Ishii, S., Shimizu, T., Waidmann, M., Hessler, G., Huber, S. M., Lang, F., and Wieder, T. (2005b). Stimulation of erythrocyte ceramide formation by platelet-activating factor. *J. Cell. Sci.* **118,** 1233–1243.

Lang, P. A., Warskulat, U., Heller-Stilb, B., Huang, D. Y., Grenz, A., Myssina, S., Duszenko, M., Lang, F., Haussinger, D., Vallon, V., and Wieder, T. (2003e). Blunted

apoptosis of erythrocytes from taurine transporter deficient mice. *Cell. Physiol. Biochem.* **13,** 337–346.

Lauritzen, I., De Weille, J. R., and Lazdunski, M. (1997). The potassium channel opener (−)-cromakalim prevents glutamate-induced cell death in hippocampal neurons. *J. Neurochem.* **69,** 1570–1579.

Leinders, T., van Kleef, R. G., and Vijverberg, H. P. (1992). Single Ca(2+)-activated K+ channels in human erythrocytes: Ca2+ dependence of opening frequency but not of open lifetimes. *Biochim. Biophys. Acta* **1112,** 67–74.

Lepple-Wienhues, A., Belka, C., Laun, T., Jekle, A., Walter, B., Wieland, U., Welz, M., Heil, L., Kun, J., Busch, G., Weller, M., Bamberg, M., Gulbins, E., and Lang, F. (1999). Stimulation of CD95 (Fas) blocks T lymphocyte calcium channels through sphingomyelinase and sphingolipids. *Proc. Natl. Acad. Sci. USA* **96,** 13795–13800.

Lepple-Wienhues, A., Szabo, I., Laun, T., Kaba, N. K., Gulbins, E., and Lang, F. (1998). The tyrosine kinase p56lck mediates activation of swelling-induced chloride channels in lymphocytes. *J. Cell Biol.* **141,** 281–286.

Lepple-Wienhues, A., Wieland, U., Laun, T., Heil, L., Stern, M., and Lang, F. (2001). A src-like kinase activates outwardly rectifying chloride channels in CFTR-defective lymphocytes. *FASEB J.* **15,** 927–931.

Liu, X. H., Kirschenbaum, A., Yu, K., Yao, S., and Levine, A. C. (2005). Cyclooxygenase-2 suppresses hypoxia-induced apoptosis via a combination of direct and indirect inhibition of p53 activity in a human prostate cancer cell line. *J. Biol. Chem.* **280,** 3817–3823.

Liu, X. M., Tao, M., Han, X. D., Fan, Q., and Lin, J. R. (2001). Gating kinetics of potassium channel and effects of nerve growth factors in PC12 cells analyzed with fractal model. *Acta Pharmacol. Sin* **22,** 103–110.

Long, H., Han, H., Yang, B., and Wang, Z. (2003). Opposite cell density-dependence between spontaneous and oxidative stress-induced apoptosis in mouse fibroblast L-cells. *Cell. Physiol. Biochem.* **13,** 401–414.

Maeno, E., Ishizaki, Y., Kanaseki, T., Hazama, A., and Okada, Y. (2000). Normotonic cell shrinkage because of disordered volume regulation is an early prerequisite to apoptosis. *Proc. Natl. Acad. Sci. USA* **97,** 9487–9492.

Marunaka, Y., Nakahari, T., and Tohda, H. (1994). Cytosolic (Cl-) regulates Na+ absorption in fetal alveolar epithelium?: Roles of cAMP and Cl- channels. *Jpn. J. Physiol.* **44** (Suppl. 2), S281–S288.

Mauro, T., Dixon, D. B., Komuves, L., Hanley, K., and Pappone, P. A. (1997). Keratinocyte K+ channels mediate Ca2+-induced differentiation. *J. Invest. Dermatol.* **108,** 864–870.

Mavelli, I., Ciriolo, M. R., Rossi, L., Meloni, T., Forteleoni, G., De Flora, A., Benatti, U., Morelli, A., and Rotilio, G. (1984). Favism: A hemolytic disease associated with increased superoxide dismutase and decreased glutathione peroxidase activities in red blood cells. *Eur. J. Biochem.* **139,** 13–18.

Michea, L., Ferguson, D. R., Peters, E. M., Andrews, P. M., Kirby, M. R., and Burg, M. B. (2000). Cell cycle delay and apoptosis are induced by high salt and urea in renal medullary cells. *Am. J. Physiol. Renal Physiol.* **278,** F209–F218.

Migheli, A., Attanasio, A., Lee, W. H., Bayer, S. A., and Ghetti, B. (1995). Detection of apoptosis in weaver cerebellum by electron microscopic *in situ* end-labeling of fragmented DNA. *Neurosci. Lett.* **199,** 53–56.

Migheli, A., Piva, R., Wei, J., Attanasio, A., Casolino, S., Hodes, M. E., Dlouhy, S. R., Bayer, S. A., and Ghetti, B. (1997). Diverse cell death pathways result from a single missense mutation in weaver mouse. *Am. J. Pathol.* **151,** 1629–1638.

Miki, T., Tashiro, F., Iwanaga, T., Nagashima, K., Yoshitomi, H., Aihara, H., Nitta, Y., Gonoi, T., Inagaki, N., Miyazaki, J., and Seino, S. (1997). Abnormalities of pancreatic

islets by targeted expression of a dominant-negative KATP channel. *Proc. Natl. Acad. Sci. USA* **94,** 11969–11973.
Miller, G. W., and Schnellmann, R. G. (1993). Cytoprotection by inhibition of chloride channels: The mechanism of action of glycine and strychnine. *Life Sci.* **53,** 1211–1215.
Montague, J. W., Bortner, C. D., Hughes, F. M., Jr., and Cidlowski, J. A. (1999). A necessary role for reduced intracellular potassium during the DNA degradation phase of apoptosis. *Steroids* **64,** 563–569.
Moran, J., Hernandez-Pech, X., Merchant-Larios, H., and Pasantes-Morales, H. (2000). Release of taurine in apoptotic cerebellar granule neurons in culture. *Pflüg. Arch.* **439,** 271–277.
Murtomaki, S., Trenkner, E., Wright, J. M., Saksela, O., and Liesi, P. (1995). Increased proteolytic activity of the granule neurons may contribute to neuronal death in the weaver mouse cerebellum. *Dev. Biol.* **168,** 635–648.
Nilius, B., and Droogmans, G. (2001). Ion channels and their functional role in vascular endothelium. *Physiol. Rev.* **81,** 1415–1459.
Nilius, B., and Wohlrab, W. (1992). Potassium channels and regulation of proliferation of human melanoma cells. *J. Physiol.* **445,** 537–548.
O'Lague, P. H., Huttner, S. L., Vandenberg, C. A., Morrison-Graham, K., and Horn, R. (1985). Morphological properties and membrane channels of the growth cones induced in PC12 cells by nerve growth factor. *J. Neurosci. Res.* **13,** 301–321.
Okada, Y., Maeno, E., Shimizu, T., Manabe, K., Mori, S., and Nabekura, T. (2004). Dual roles of plasmalemmal chloride channels in induction of cell death. *Pflüg. Arch.* **448,** 287–295.
Oo, T. F., Blazeski, R., Harrison, S. M., Henchcliffe, C., Mason, C. A., Roffler-Tarlov, S. K., and Burke, R. E. (1996). Neuron death in the substantia nigra of weaver mouse occurs late in development and is not apoptotic. *J. Neurosci.* **16,** 6134–6145.
Pal, S., He, K., and Aizenman, E. (2004). Nitrosative stress and potassium channel-mediated neuronal apoptosis: Is zinc the link? *Pflüg. Arch.* **448,** 296–303.
Pandiella, A., Magni, M., Lovisolo, D., and Meldolesi, J. (1989). The effect of epidermal growth factor on membrane potential: Rapid hyperpolarization followed by persistent fluctuations. *J. Biol. Chem.* **264,** 12914–12921.
Pappas, C. A., and Ritchie, J. M. (1998). Effect of specific ion channel blockers on cultured Schwann cell proliferation. *Glia* **22,** 113–120.
Pappone, P. A., and Ortiz-Miranda, S. I. (1993). Blockers of voltage-gated K channels inhibit proliferation of cultured brown fat cells. *Am. J. Physiol.* **264,** C1014–C1019.
Parekh, A. B., and Penner, R. (1997). Store depletion and calcium influx. *Physiol. Rev.* **77,** 901–930.
Parekh, A. B., and Putney, J. W., Jr. (2005). Store-operated calcium channels. *Physiol. Rev.* **85,** 757–810.
Patel, A. J., and Lazdunski, M. (2004). The 2P-domain K+ channels: Role in apoptosis and tumorigenesis. *Pflüg. Arch.* **448,** 261–273.
Pellegrino, M., and Pellegrini, M. (1998). Modulation of $Ca2^{+}$-activated K^{+} channels of human erythrocytes by endogenous cAMP-dependent protein kinase. *Pflüg. Arch.* **436,** 749–756.
Perez, G. I., Maravei, D. V., Trbovich, A. M., Cidlowski, J. A., Tilly, J. L., and Hughes, F. M., Jr. (2000). Identification of potassium-dependent and -independent components of the apoptotic machinery in mouse ovarian germ cells and granulosa cells. *Biol. Reprod.* **63,** 1358–1369.
Phipps, D. J., Branch, D. R., and Schlichter, L. C. (1996). Chloride-channel block inhibits T lymphocyte activation and signalling. *Cell Signal* **8,** 141–149.

Pozzi, S., Malferrari, G., Biunno, I., and Samaja, M. (2002). Low-flow ischemia and hypoxia stimulate apoptosis in perfused hearts independently of reperfusion. *Cell. Physiol. Biochem.* **12,** 39–46.

Prehn, J. H., Jordan, J., Ghadge, G. D., Preis, E., Galindo, M. F., Roos, R. P., Krieglstein, J., and Miller, R. J. (1997). Ca2+ and reactive oxygen species in staurosporine-induced neuronal apoptosis. *J. Neurochem.* **68,** 1679–1685.

Qian, D., and Weiss, A. (1997). T cell antigen receptor signal transduction. *Curr. Opin. Cell Biol.* **9,** 205–212.

Rice, L., and Alfrey, C. P. (2005). The negative regulation of red cell mass by neocytolysis: Physiologic and pathophysiologic manifestations. *Cell. Physiol. Biochem.* **15,** 245–250.

Ritter, M., Woll, E., Haller, T., Dartsch, P. C., Zwierzina, H., and Lang, F. (1997). Activation of Na+/H(+)-exchanger by transforming Ha-ras requires stimulated cellular calcium influx and is associated with rearrangement of the actin cytoskeleton. *Eur. J. Cell Biol.* **72,** 222–228.

Ritter, M., Woll, E., Waldegger, S., Haussinger, D., Lang, H. J., Scholz, W., Scholkens, B., and Lang, F. (1993). Cell shrinkage stimulates bradykinin-induced cell membrane potential oscillations in NIH 3T3 fibroblasts expressing the ras-oncogene. *Pflüg. Arch.* **423,** 221–224.

Rosette, C., and Karin, M. (1996). Ultraviolet light and osmotic stress: Activation of the JNK cascade through multiple growth factor and cytokine receptors. *Science* **274,** 1194–1197.

Rotoli, B. M., Uggeri, J., Dall'Asta, V., Visigalli, R., Barilli, A., Gatti, R., Orlandini, G., Gazzola, G. C., and Bussolati, O. (2005). Inhibition of glutamine synthetase triggers apoptosis in asparaginase-resistant cells. *Cell. Physiol. Biochem.* **15,** 281–292.

Rouzaire-Dubois, B., Milandri, J. B., Bostel, S., and Dubois, J. M. (2000). Control of cell proliferation by cell volume alterations in rat C6 glioma cells. *Pflüg. Arch.* **440,** 881–888.

Sanders, D. A., Fiddes, I., Thompson, D. M., Philpott, M. P., Westgate, G. E., and Kealey, T. (1996). In the absence of streptomycin, minoxidil potentiates the mitogenic effects of fetal calf serum, insulin-like growth factor 1, and platelet-derived growth factor on NIH 3T3 fibroblasts in a K+ channel-dependent fashion. *J. Invest. Dermatol.* **107,** 229–234.

Santella, L. (1998). The role of calcium in the cell cycle: Facts and hypotheses. *Biochem. Biophys. Res. Commun.* **244,** 317–324.

Santella, L., Kyozuka, K., De Riso, L., and Carafoli, E. (1998). Calcium, protease action, and the regulation of the cell cycle. *Cell Calcium* **23,** 123–130.

Shen, M. R., Droogmans, G., Eggermont, J., Voets, T., Ellory, J. C., and Nilius, B. (2000). Differential expression of volume-regulated anion channels during cell cycle progression of human cervical cancer cells. *J. Physiol.* **529**(Pt. 2), 385–394.

Shindo, M., Imai, Y., and Sohma, Y. (2000). A novel type of ATP block on a Ca(2+)-activated K(+) channel from bullfrog erythrocytes. *Biophys. J.* **79,** 287–297.

Shrode, L. D., Tapper, H., and Grinstein, S. (1997). Role of intracellular pH in proliferation, transformation, and apoptosis. *J. Bioenerg. Biomembr.* **29,** 393–399.

Skryma, R. N., Prevarskaya, N. B., Dufy-Barbe, L., Odessa, M. F., Audin, J., and Dufy, B. (1997). Potassium conductance in the androgen-sensitive prostate cancer cell line, LNCaP: Involvement in cell proliferation. *Prostate* **33,** 112–122.

Spassova, M. A., Soboloff, J., He, L. P., Hewavitharana, T., Xu, W., Venkatachalam, K., van Rossum, D. B., Patterson, R. L., and Gill, D. L. (2004). Calcium entry mediated by SOCs and TRP channels: Variations and enigma. *Biochim. Biophys. Acta* **1742,** 9–20.

Storey, N. M., Gomez-Angelats, M., Bortner, C. D., Armstrong, D. L., and Cidlowski, J. A. (2003). Stimulation of Kv1.3 potassium channels by death receptors during apoptosis in Jurkat T lymphocytes. *J. Biol. Chem.* **278,** 33319–33326.

Strobl, J. S., Wonderlin, W. F., and Flynn, D. C. (1995). Mitogenic signal transduction in human breast cancer cells. *Gen. Pharmacol.* **26,** 1643–1649.

Sturm, J. W., Zhang, H., Magdeburg, R., Hasenberg, T., Bonninghoff, R., Oulmi, J., Keese, M., and McCuskey, R. (2004). Altered apoptotic response and different liver structure during liver regeneration in FGF-2-deficient mice. *Cell. Physiol. Biochem.* **14,** 249–260.

Szabo, I., Gulbins, E., and Lang, F. (1997). Regulation of Kv1.3 during Fas-induced apoptosis. *Cell. Physiol. Biochem.* **7,** 148–158.

Szabo, I., Adams, C., and Gulbins, E. (2004). Ion channels and membrane rafts in apoptosis. *Pflüg. Arch.* **448,** 304–312.

Szabo, I., Gulbins, E., Apfel, H., Zhang, X., Barth, P., Busch, A. E., Schlottmann, K., Pongs, O., and Lang, F. (1996). Tyrosine phosphorylation-dependent suppression of a voltage-gated K+ channel in T lymphocytes upon Fas stimulation. *J. Biol. Chem.* **271,** 20465–20469.

Szabo, I., Lepple-Wienhues, A., Kaba, K. N., Zoratti, M., Gulbins, E., and Lang, F. (1998). Tyrosine kinase-dependent activation of a chloride channel in CD95-induced apoptosis in T lymphocytes. *Proc. Natl. Acad. Sci. USA* **95,** 6169–6174.

Takahashi, N., Wang, X., Tanabe, S., Uramoto, H., Jishage, K., Uchida, S., Sasaki, S., and Okada, Y. (2005). ClC-3-independent sensitivity of apoptosis to Cl- channel blockers in mouse cardiomyocytes. *Cell. Physiol. Biochem.* **15,** 263–270.

Tallquist, M., and Kazlauskas, A. (2004). PDGF signaling in cells and mice. *Cytokine Growth Factor Rev.* **15,** 205–213.

Teijeiro, R., Rios, R., Costoya, J. A., Castro, R., Bello, J. L., Devesa, J., and Arce, V. M. (2002). Activation of human somatostatin receptor 2 promotes apoptosis through a mechanism that is independent from induction of p53. *Cell. Physiol. Biochem.* **12,** 31–38.

Tohda, H., Foskett, J. K., O'Brodovich, H., and Marunaka, Y. (1994). Cl- regulation of a Ca(2+)-activated nonselective cation channel in beta-agonist-treated fetal distal lung epithelium. *Am. J. Physiol.* **266,** C104–C109.

Varela, D., Simon, F., Riveros, A., Jorgensen, F., and Stutzin, A. (2004). NAD(P)H oxidase-derived H(2)O(2) signals chloride channel activation in cell volume regulation and cell proliferation. *J. Biol. Chem.* **279,** 13301–13304.

Volk, T., Fromter, E., and Korbmacher, C. (1995). Hypertonicity activates nonselective cation channels in mouse cortical collecting duct cells. *Proc. Natl. Acad. Sci. USA* **92,** 8478–8482.

Walsh, M. F., Thamilselvan, V., Grotelueschen, R., Farhana, L., and Basson, M. (2003). Absence of adhesion triggers differential FAK and SAPKp38 signals in SW620 human colon cancer cells that may inhibit adhesiveness and lead to cell death. *Cell. Physiol. Biochem.* **13,** 135–146.

Wang, G. L., Wang, X. R., Lin, M. J., He, H., Lan, X. J., and Guan, Y. Y. (2002). Deficiency in ClC-3 chloride channels prevents rat aortic smooth muscle cell proliferation. *Circ. Res.* **91,** E28–E32.

Wang, S., Melkoumian, Z., Woodfork, K. A., Cather, C., Davidson, A. G., Wonderlin, W. F., and Strobl, J. S. (1998). Evidence for an early G1 ionic event necessary for cell cycle progression and survival in the MCF-7 human breast carcinoma cell line. *J. Cell. Physiol.* **176,** 456–464.

Wang, Z. (2004). Roles of K+ channels in regulating tumour cell proliferation and apoptosis. *Pflüg. Arch.* **448,** 274–286.

Wehner, F., Böhmer, C., Heinzinger, H., van den, B. F., and Tinel, H. (2000). The hypertonicity-induced Na(+) conductance of rat hepatocytes: Physiological significance and molecular correlate. *Cell. Physiol. Biochem.* **10,** 335–340.

Wehner, F., Sauer, H., and Kinne, R. K. (1995). Hypertonic stress increases the Na+ conductance of rat hepatocytes in primary culture. *J. Gen. Physiol.* **105,** 507–535.

Wei, L., Xiao, A. Y., Jin, C., Yang, A., Lu, Z. Y., and Yu, S. P. (2004). Effects of chloride and potassium channel blockers on apoptotic cell shrinkage and apoptosis in cortical neurons. *Pflüg. Arch.* **448,** 325–334.

Wenzel, U., and Daniel, H. (2004). Early and late apoptosis events in human transformed and non-transformed colonocytes are independent on intracellular acidification. *Cell. Physiol. Biochem.* **14,** 65–76.

Whitfield, J. F., Bird, R. P., Chakravarthy, B. R., Isaacs, R. J., and Morley, P. (1995). Calcium-cell cycle regulator, differentiator, killer, chemopreventor, and maybe, tumor promoter. *J. Cell Biochem. Suppl.* **22,** 74–91.

Wiecha, J., Reineker, K., Reitmayer, M., Voisard, R., Hannekum, A., Mattfeldt, T., Waltenberger, J., and Hombach, V. (1998). Modulation of Ca2+-activated K+ channels in human vascular cells by insulin and basic fibroblast growth factor. *Growth Horm. IGF Res.* **8,** 175–181.

Wieder, T., Essmann, F., Prokop, A., Schmelz, K., Schulze-Osthoff, K., Beyaert, R., Dorken, B., and Daniel, P. T. (2001). Activation of caspase-8 in drug-induced apoptosis of B-lymphoid cells is independent of CD95/Fas receptor-ligand interaction and occurs downstream of caspase-3. *Blood* **97,** 1378–1387.

Wondergem, R., Gong, W., Monen, S. H., Dooley, S. N., Gonce, J. L., Conner, T. D., Houser, M., Ecay, T. W., and Ferslew, K. E. (2001). Blocking swelling-activated chloride current inhibits mouse liver cell proliferation. *J. Physiol.* **532,** 661–672.

Wonderlin, W. F., and Strobl, J. S. (1996). Potassium channels, proliferation and G1 progression. *J. Membr. Biol.* **154,** 91–107.

Woon, L. A., Holland, J. W., Kable, E. P., and Roufogalis, B. D. (1999). Ca2+ sensitivity of phospholipid scrambling in human red cell ghosts. *Cell Calcium* **25,** 313–320.

Yu, S. P., Yeh, C. H., Sensi, S. L., Gwag, B. J., Canzoniero, L. M., Farhangrazi, Z. S., Ying, H. S., Tian, M., Dugan, L. L., and Choi, D. W. (1997). Mediation of neuronal apoptosis by enhancement of outward potassium current. *Science* **278,** 114–117.

Yurinskaya, V. E., Goryachaya, T. S., Guzhova, T. V., Moshkov, A. V., Rozanov, Y. M., Sakuta, G. A., Shirokova, A. V., Shumilina, E. V., Vassilieva, I. O., Lang, F., and Vereninov, A. A. (2005a). Potassium and sodium balance in U937 cells during apoptosis with and without cell shrinkage. *Cell. Physiol. Biochem.* **16,** 155–162.

Yurinskaya, V. E., Moshkov, A. V., Rozanov, Y.M, Shirokova, A. V., Vassilieva, I. O., Shumilina, E. V., Lang, F., Volgareva, A. A., and Vereninov, A. A. (2005b). Thymocyte K+, Na+ and water balance during dexamethasone and etoposide induced apoptosis. *Cell. Physiol. Biochem.* **16,** 15–22.

Zhou, Q., Kwan, H. Y., Chan, H. C., Jiang, J. L., Tam, S. C., and Yao, X. (2003). Blockage of voltage-gated K+ channels inhibits adhesion and proliferation of hepatocarcinoma cells. *Int. J. Mol. Med.* **11,** 261–266.

Zhou, Q., Zhao, J., Wiedmer, T., and Sims, P. J. (2002). Normal hemostasis but defective hematopoietic response to growth factors in mice deficient in phospholipid scramblase 1. *Blood* **99,** 4030–4038.