Humans maintain a constant cell number throughout their lifespan. This equilibrium of cell number is accomplished when cell proliferation and cell death are kept balanced, achieving a steady-state cell number. Abnormalities in cell growth or cell death can lead to an overabundance of cells known as neoplasm or tumours. While the perception of cancer is often that of an uncontrollable rate of cell growth or increased proliferation, a decrease in cell death can also lead to tumour formation. Most cells when detached from their normal tissue die. However, cancer cells evade cell death, tipping the balance to an overabundance of cell number. Therefore, overcoming this resistance to cell death is a decisive factor in the treatment of cancer. Ion channels play a critical role in cancer in regards to cell proliferation, malignant angiogenesis, migration and metastasis. Additionally, ion channels are also known to be critical components of apoptosis. In this review, we discuss the modes of cell death focusing on the ability of cancer cells to evade apoptosis. Specifically, we focus on the role ion channels play in controlling and regulating life/death decisions and how they can be used to overcome resistance to apoptosis in the treatment of cancer.

1. Introduction

Cancer is not just a single disease, but can be classified into several broad categories based on the cancer cells site of origination such as carcinoma (skin or tissues lining the internal organs), sarcoma (bone, cartilage, connective or support tissues), leukaemia (blood-forming tissue) and lymphoma or myeloma (immune system). Cancer is usually considered an uncontrollable replication of abnormal cells that are capable of invading surrounding or distant tissues. Within a tissue, the close proximity of cells to one another allows for essential paracrine and endocrine signalling that are required for survival. Cells that release or detach from a primary site or tissue lose this vital network signalling and typically undergo apoptosis, whereas malignant cells can cope with their new environment and survive.

2. Apoptosis versus necrosis

Dead cells found in excess of normal cell turnover have been traditionally considered necrotic, signalling an abnormality or deviation in normal tissue homeostasis. Historically, necrosis has been a term used to describe an accidental mode of cell death resulting from chemical damage, blunt toxic insults or physical injury. This passive cell death process is primarily characterized by its distinct swollen cell morphology that results from an early loss of energy [1,2]. This catastrophic cell death resulting from ATP depletion lacks the organized breakdown of cellular contents observed in other more programmed modes of cell death. In addition to cell swelling, necrotic cells randomly degrade their DNA, RNA and proteins, have a massive calcium influx, lose membrane integrity, thus triggering an inflammatory response in the area surrounding the dying cell.

In the early 1970s, the initial morphological observations of Kerr et al. [3] describing a cell’s ability to implode and disintegrate led to the concept of an active, inherently controlled cell death process now known as apoptosis. This physiological, and more importantly, non-inflammatory mode of cell death, was also noted to occur in tissues of healthy animals [4–6], in untreated malignant neoplasms [7], and in organ atrophy upon addition or withdrawal of...
hormones [5,8]. Thus, a mode of cell death was described where balanced cell division provides a mechanism for the body to maintain adult cellular homeostasis.

Apoptosis is known to be an organized cell death and has been shown to play an important role in embryogenesis, tissue and organ development and in diverse pathological states, for example cancer. Apoptosis is characterized by a unique set of morphological and biochemical features that have set it apart from other modes of death. These characteristics include cell shrinkage, nuclear condensation, the cleavage of DNA at the linker region of adjacent nucleosomes and membrane blebbing [9]. Other biochemical characteristics were noted to occur that defined apoptosis, such as externalization of the membrane phosphotidylserine, release of cytochrome c from the mitochondria and activation of a specific family of proteases known as caspases [2,9,10]. Apoptotic cells are eliminated from the body in a timely and orderly manner, via phagocytosis, that results in the absence of an inflammatory response. While not all characteristics that classify apoptosis are observed under every condition, the idea of a precise, internally coded, programmed cell death process remains constant.

Cancer cells evade apoptosis upon detachment from neighbouring cells, spread to other parts of the body through the lymphatic or vascular systems, resulting in the development of metastases. The term anoikis has been used to describe apoptosis that occurs from detachment of anchorage-dependent cells and plays a major role in tumorigenesis, upsetting the balance between cell proliferation and cell death. Considering the numerous ways a cell can die, overcoming resistance to apoptosis or activation of the apoptotic programme would be the most beneficial means for removing malignant cells from the body.

3. Other modes of cell death

While distinct characteristics clearly delinate apoptosis from necrosis (table 1), increasing evidence suggests that these two modes of cell death represent the extreme ends of a wide range of programmable deaths, with numerous variations of dying cells lying in between (figure 1). Recent studies have suggested a programmable type of necrosis that is far from random in its mode of action [11–13]. This variation of necrosis, termed programmed necrosis, caspase-independent cell death or necroptosis, occurs by death receptor or viral infection, in the absence of caspase activation [14]. Necrotic cells exhibit several hallmarks of necrosis; including cell swelling, organelle dysfunction and cell lysis, but these events appear to occur in a more ordered manner. Similarly, a passive mode of cell death known as oncosis or ‘ischaemic cell death’ is triggered by chemical, thermal or radiation damage that goes beyond the point of cellular repair [15]. Oncosis is defined by swelling of mitochondria, nucleus and cytoplasm, along with cytoplasmic vacuolization, and is thought to involve the failure of ionic pumps on the plasma membrane prior to the loss of membrane integrity (figure 1). Pyroptosis, a programmed form of cell death, is associated with anti-microbial responses during inflammation and requires specific caspase activation [16]. Observed only in macrophages and dendritic cells compromised with microbial pathogens, NOD-like receptors on these cells recognize intracytoplasmic pathogen-associated molecular patterns to promote the assembly on the pyroptosome, also known as an inflammasome, a multi-protein complex that recruits and activates caspase-1 (figure 1 and table 1). Finally, autophagy is an evolutionarily conserved catabolic process that plays a role not only in the death of a cell, but also in cell survival [17,18]. As a cell survival mechanism, autophagy attempts to maintain intracellular homeostasis during periods of starvation by recycling cellular components (figure 1 and table 1). However, in several disease states, including Alzheimer’s and Parkinson’s disease, autophagic cells are frequently observed [19,20], suggesting that autophagy can also be considered as a suicide programme. Clearly, there are many ways a cell can die, thus activating or repressing apoptosis in cancer cells would be beneficial for cancer treatment owing to the conserved membrane integrity, apoptotic body formation and lack of an inflammatory response (table 1).

4. Activation and repression of apoptosis

In general, two cellular pathways lead to the activation of apoptosis. The first is a receptor-mediated pathway known as the extrinsic pathway, where cell surface death receptors signal the apoptotic machinery to promote the activation of specific proteases, known as caspases, which leads to cellular degradation and eventual apoptotic body formation [21].

<table>
<thead>
<tr>
<th></th>
<th>apoptosis</th>
<th>pyroptosis</th>
<th>autophagy</th>
<th>oncosis</th>
<th>necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>cellular morphology</td>
<td>shrunk</td>
<td>swelling</td>
<td>no change</td>
<td>swelling</td>
<td>swelling</td>
</tr>
<tr>
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<td>no</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>pore formation (plasma membrane)</td>
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<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>DNA degradation</td>
<td>internucleosomal</td>
<td>random</td>
<td>none</td>
<td>random</td>
<td>random</td>
</tr>
<tr>
<td>caspase activity</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>annexin V staining</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>membrane blebbing</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
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<tr>
<td>inflammatory response</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>
proteins and include TNF-receptor 1 (TNF-R1, p55, CD120a), Fas (CD95, APO-1) and TNF-related apoptosis-inducing ligand receptors (TRAIL-R1, DR4; TRAIL-R2, DR5, APO-2). The core of this signalling pathway involves the formation of the death-inducing signalling complex (DISC) comprising a death receptor, the adapter protein FADD and an initiator caspase [22]. The activation of these initiator caspases at the level of the DISC leads to the further activation of downstream or effector caspases subsequent to apoptosis.

The second pathway for apoptotic activation is known as the intrinsic pathway that involves the release of apoptotic factors such as cytochrome \(c\), apoptosis-inducing factor and second mitochondria-derived activator of caspase from the mitochondria [23]. Death signals converge at the level of the mitochondria to release these factors during the onset of apoptosis. The core of this signalling pathway involves the formation of the apoptosome comprising pro-caspase-9, the adapter protein Apaf-1 and cytochrome \(c\) [24,25]. However, the extrinsic and intrinsic pathways of apoptosis are not mutually exclusive as caspase 8 activated via the extrinsic pathway can cleave the pro-apoptotic protein BID to elicit the activation of components of the intrinsic apoptotic pathway [26,27].

Several cellular mechanisms and proteins have been identified that function at numerous levels of the cell death process to prevent or inhibit apoptosis [28]. Caspase activity can be inhibited by the expression of viral proteins Cp-IAP and Op-IAP that define a family of inhibitors of apoptosis proteins (IAPs) [29–31]. IAPs are thought to function by directly binding caspases during apoptosis, where specific IAP family members interacting with specific caspases to prevent apoptosis. Additionally, anti-apoptotic members of the Bcl-2 family of proteins (Bcl-X\(_L\), Bcl-w and Mcl-1) reside on the outer mitochondrial membrane and inhibit apoptosis by preventing the activation of a subfamily of pro-apoptotic BH3-only proteins, such as Bax and Bak [32]. Through the interaction of the anti-apoptotic proteins with Bax and Bak, pro-apoptotic factors are held in check and not released from the mitochondria [33]. Additionally, the down-regulation of the expression of these pro-apoptotic factors can also contribute to apoptotic resistance. Finally, maintaining a high intracellular ionic strength is known to prevent apoptosis by inhibiting the release of cytochrome \(c\) and the formation of the apoptosome [34,35].

5. Ions and apoptosis

Regardless of the specific route cells may employ to undergo apoptosis, in general both the extrinsic and intrinsic pathways lead to analogous events including cell shrinkage, internucleosomal DNA fragmentation and apoptotic body formation. One hallmark of apoptosis is the loss of cell volume or cell shrinkage [36–38], termed apoptotic volume decrease (AVD) [39]. The loss of cell volume or AVD during apoptosis has been shown to result from changes in intracellular ions, with the loss of intracellular potassium playing a critical role in the downstream activation of the apoptotic machinery [34,35,40,41]. The decrease in cell
volume is a result of a decrease in overall intracellular ionic strength that allows caspase activation, apoptosome formation and apoptotic nuclease activity. While a loss of intracellular potassium has been well documented in many apoptotic model systems, the exact mechanism by which this potassium depletion occurs is not fully resolved. Numerous potassium channels, including voltage-gated, delayed rectifier and inward rectifier potassium channels, have been described as playing a role during the activation of apoptosis [37,38,42], and direct inhibition of potassium channels using tetraethylammonium, tetrapentylammonium or quinine, can protect cells from cell death [43–45]. These data suggest that distinct potassium channels are involved in apoptosis depending on the cell type or cell death stimulus. Sodium and chloride also participate during apoptosis. Specifically, an increase in intracellular sodium has been reported early in the cell death process [46–49]. Inhibition of this intracellular sodium increase prevents apoptosis. In studies where sodium has been removed from the extracellular environment, apoptosis has been shown to occur in the absence of cell shrinkage [48,49], suggesting that sodium flux during apoptosis plays an important role in controlling cell size. Chloride flux has also been reported during apoptosis [50–52]. Chloride flux modulation was shown to impair the intrinsic pathway of apoptotic induction, while having no effect on the extrinsic pathway [51]. Recently, a volume-sensitive outwardly rectifying (VSOR) chloride channel has also been proposed as a primary anionic conductance during apoptosis [53].

Clearly, ion channels and transporters play a central role controlling cell volume to prevent cell death. Cell volume and its regulation also play a critical role in a number of molecular and cellular functions including proliferation, migration, hormone release and gene expression [54,55]. These findings suggest that cells have developed essential protective mechanisms to keep the balance of intracellular and extracellular ions controlled in response to changes in their extracellular environment, which are collectively known as volume regulatory responses [54,56]. In regard to apoptosis, the absence of volume regulation in human lymphocytes contributes to the rapid, stimulus-independent activation of apoptosis [57]. Additionally, deregulation of the inherent cell volume regulatory mechanisms may contribute to AVD [39], and inhibition of hypertonicity-induced cation channels can sensitize HeLa cells to undergo apoptosis [58]. Thus, a cell’s ability to control its cell volume and its ionic homeostasis plays a critical role in the activation and repression of apoptosis.

6. Overcoming resistance to apoptosis in cancer cells

Resistance to apoptosis can come in numerous forms, and each individual type of cancer can use a different mechanism to obtain this insensitivity to cell death. Thus, the ability to overcome resistance to apoptosis in tumour cells is the goal of most cancer therapies. A major question is how to overcome these molecular blocks that resistant cells use to escape this inherent cell death process. Inhibition of both the extrinsic and intrinsic apoptotic pathways is known to occur in tumour metastasis cancer cells [59], and overcoming this resistance has been one focus of tumour therapy [60]. For example, studies have shown that recombinant human Apo2L/TRAIL can induce apoptosis in various cancer cell types while sparing most normal cells [61,62]. While not effective on all types of cancer, this strategy bypasses the common mutation in the p53 tumour-suppressor gene, as death receptor signalling functions independent of p53 [63]. Additionally, the intrinsic pathway has also been a target in anti-cancer therapy where Bcl-2 family members have been studied for biological modulation to overcome resistance to apoptosis [64,65]. These modulations have included the use of Bcl-2 antisense oligonucleotides [66], BH3-mimetics [67], small molecule inhibitors of anti-apoptotic Bcl-2 proteins [68]. However, targeting-specific apoptotic machinery such as death receptors, anti-apoptotic Bcl-2 members or even caspases would only be beneficial for cancer cells employing these specific components. Thus, one approach to overcome resistance to apoptosis in cancer cells would be to target a common cell death event involved with both the extrinsic and intrinsic pathways. As ion channels play a major role in both apoptotic pathways, targeting ion channels to overcome resistance to apoptosis should have great promise in treatment of cancer cells regardless of a specific cell death pathway.

7. Potassium channels as targets for apoptotic cell death in cancer cells

Clearly, ion channels play a fundamental role in many hallmarks of cancer [69], including in all six pathophysiological phenotypes of malignant growth [70]. For example, potassium channels are known to play a critical role in cell proliferation [71,72]. Early studies of viral infection and H-ras-transformed cells resulting in oncogenic alterations were reported to have enhanced potassium channel activity [73,74], and cell migration depends on potassium channel activity [75,76]. Extensive analysis of breast cancer tissue microarrays, the a-subunit of the large-conductance voltage and calcium-activated potassium channel (KCNA1) showed enhanced expression that may contribute to a high proliferation rate and malignancy [77]. Surprisingly, only recently have ion channels been explored as targets to sensitize apoptotic-resistant cancer cells because of their unique role in the activation of the cell death programme [78–81]. One difficulty in targeting individual ion channels in cancer therapy is determining which channels are involved for a specific cell type and apoptotic pathway. Several excellent reviews on ion channels and cancer, including those in this monograph, have focused on their role at different stages of tumour progression including cell growth and proliferation, motility and invasion, and/or their role in different types of tumours [82–84]. Here, we focus on ion channels in overcoming resistance to apoptosis in cancer.

Potassium channels are the largest, most diverse and well-studied family of ion channels and have been a major focus for cancer therapy owing to their role in cell proliferation, differentiation, regulating cell volume and maintaining membrane potential. An exhaustive array of potassium channels exists, and the expression of these channels differs not only by cell type, but also from normal to metastatic cells of the same cell type [85]. Several voltage-gated potassium channels, including Kv1.1, Kv1.3, Kv1.5, Kv2.1 and Kv11.1, are known to play a critical role during apoptosis [86], with Kv1.3 and Kv1.5 receiving the most attention owing to their
known involvement in cell-cycle progression and calcium signalling [87,88]. In addition to voltage-gated ion channels, other potassium channel family members have the potential to have a role in apoptosis. Table 2 provides a list of potassium channels that are known to play a role during apoptosis in cancer cells.

A comprehensive understanding of potassium channels in the context of a variety of apoptotic pathways is of primary importance to restore cell death sensitivity in tumour cells. For example, a recent report using human glioblastoma cells showed that staurosporine-induced apoptosis (intrinsic pathway) occurred via intermediate-conductance calcium-activated potassium (IK) channels, while TRAIL-induced cell death (extrinsic pathway) used large-conductance BKCa channels [104]. Therefore, clotrimazole and TRAM-34 (IK blockers) were effective in preventing staurosporine-induced apoptosis, while paclitaxel (BK blocker) was completely ineffective. Developing appropriate therapeutic treatments to prevent the growth of cancer requires an in-depth understanding of the complexity of ion channel for a given cell type, as well as the signalling mechanisms provided by the chemotherapy agent employed.

As indicated earlier, an efflux of intracellular potassium, the dominant intracellular cation, occurs during apoptosis resulting in the loss of cell volume (AVD) and activation of the apoptotic machinery. For example, a cancer cell may evade apoptosis by simply downregulating these potassium channels. Interestingly, Kv1.3 and Kv1.5 are expressed at reduced levels in many types of human cancers [105], suggesting that these ion channels may contribute to apoptotic resistance. Thus, targeted overexpression of voltage-gated potassium channels may result in a pro-apoptotic response by providing a mechanism to lower the overall intracellular ionic strength that is important in overcoming apoptotic resistance.

Additionally, the expression of proteins that modulate ion channels may also be beneficial in restoring apoptotic sensitivity. For example, the potassium channel modulatory protein KChAP when overexpressed in a prostate cancer cell line, LNCaP cells, resulted in increased potassium channel expression, a decrease in average cell size that enhanced AVD, and promoted spontaneous apoptosis [106]. Repetitive overexpression of KChAP in LNCaP or DU-2145 xenografts significantly suppressed tumour growth owing to increased apoptosis. While overexpression of KChAP in LNCaP cells also resulted in a G0/G1 cell-cycle arrest through the activation of p53, DU-2145 cells express a mutated, non-functional p53, thus ruling out p53 as the reason for cell death. As both cell lines showed increased apoptosis, the action of the KChAP modulatory protein was determined to result from the direct interaction with the potassium channel.

While direct intervention at the level of ion channels can be beneficial, indirect consequences of channel inhibition can also sensitize tumour cells to apoptosis. Indirect inhibition of large-conductance Ca2+-activated potassium channels (BK channels) in HeLa and A2780 cancer cells induced tumour cell apoptosis [107]. Although counterintuitive to the efflux of intracellular potassium, the mechanism of apoptotic activation via potassium channel inhibition in these cells occurred via increased p53, p21 and Bax expression. Thus, intervention at the level of ion channels can also have indirect beneficial effects that result in activation of apoptosis.

Ion channels located on intracellular membranes can also have a functional role during apoptosis. Kv1.3 is expressed in the mitochondria of lymphocytes [108], where its location on the inner mitochondrial membrane allows a direct interaction with Bax, a pro-apoptotic protein [109]. Inhibition of mtKv1.3 through Bax binding results in hyperpolarization of the mitochondria membrane potential, the release of cytochrome c and the production of reactive oxygen species; which lead to apoptosis. The presence of mtKv1.3 has also been reported in the prostate cancer and breast cancer cell lines, PC3 and MCF-7, respectively [110]. Interestingly, pharmacological inhibition of mtKv1.3 with membrane-permeant drugs induced apoptosis in a variety of cancer cell lines in a Bax/Bak-independent manner and reduced the tumour size by

Table 2. Potassium channels: their role in apoptosis and cancer.

<table>
<thead>
<tr>
<th>channel</th>
<th>role in apoptosis</th>
<th>associated cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kv1.3</td>
<td>inhibition of Kv1.3 by rituximab stimulates FcγRIIB receptor to induce apoptosis</td>
<td>B-cell lymphoma [89]</td>
</tr>
<tr>
<td>Kv1.5</td>
<td>dichloroacetate upregulates Kv1.5 to induce apoptosis</td>
<td>non-small lung [90]</td>
</tr>
<tr>
<td>Kv10.1 (Eag1)</td>
<td>simultaneous knockdown of Eag1 and overexpression of TRAIL-induced apoptosis</td>
<td>osteosarcoma [92]</td>
</tr>
<tr>
<td>Kv10.1 (Eag1)</td>
<td>inhibition of Eag1 with imipramine-induced apoptosis</td>
<td>ovarian [93]</td>
</tr>
<tr>
<td>Kv10.1 (Eag1)</td>
<td>KV10.1 antibody fused to TRAIL-induced apoptosis upon sensitization with cytotoxic drugs</td>
<td>prostate [94]</td>
</tr>
<tr>
<td>Kv11.1 (hERG)</td>
<td>inhibition of Kv11.1 by doxorubicin-induced apoptosis in cells overexpression this channel</td>
<td>prostate, pituitary [95]</td>
</tr>
<tr>
<td>Kv (general)</td>
<td>potassium channel inhibition with 4-AP-induced apoptosis</td>
<td>acute myeloid leukaemia [96]</td>
</tr>
<tr>
<td>TREK-1</td>
<td>inhibition of TREK-1 by curcumin-induced apoptosis</td>
<td>ovarian [97]</td>
</tr>
<tr>
<td>KCa3.1 (IK1)</td>
<td>inhibition of KCa3.1 by TRAM-34 enhanced TRAIL-induced apoptosis</td>
<td>melanoma [98]</td>
</tr>
<tr>
<td>BKCa</td>
<td>increased BKCa activity by zoledronic acid-induced apoptosis</td>
<td>breast cancer [99]</td>
</tr>
<tr>
<td>KATP</td>
<td>inhibition of KATP by glibenclamide or U37883A enhanced TRAIL-induced apoptosis</td>
<td>melanoma [100]</td>
</tr>
<tr>
<td>mitoKv1.3</td>
<td>inhibition of mitoKv1.3 by Psora-4, PAP-1 or clofazimine-induced apoptosis</td>
<td>osteosarcoma and melanoma [101]</td>
</tr>
<tr>
<td>HERG</td>
<td>increased expression of HERG by cisplatin-induced apoptosis</td>
<td>gastric [102]</td>
</tr>
<tr>
<td>hERG1</td>
<td>inhibition of hERG1 with E-4031 enhanced SDF-1-induced apoptosis</td>
<td>acute myeloid leukaemia [103]</td>
</tr>
</tbody>
</table>

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90% in an ophthalmic melanoma mouse model [101], suggesting that targeting of this specific ion channel in tumour cells would be advantageous under conditions of non-functional or inactive pro-apoptotic proteins. Furthermore, it has been reported that Kv1.1 and Kv1.5 also interact with Bax because Kv-deficient lymphocytes transfected with these ion channels restores sensitivity to cell death in apoptosis-resistant CTLL-2 cells [111]. J774 macrophages also express Kv1.3 and Kv1.5 in their mitochondria and siRNA downregulation or pharmacological inhibition of these channels induces apoptosis [111]. These data provide an avenue for the depletion of tumour-associated macrophages known to foster tumour growth.

8. Sodium channels as targets for apoptotic cell death in cancer cells

While a majority of focus has been on potassium channels in metastatic development, the contribution of other ionic channels, including sodium and chloride channels, have not been completely overlooked [81,83,84]. Voltage-gated sodium channels are also thought to play a role in tumour cell proliferation, migration and adhesion and are expressed in several aggressive carcinomas [84]. An increase in intracellular sodium has been observed during the early stage of apoptosis that is coupled to an initial decrease in intracellular potassium [47]. Although Jurkat cells cultured in sodium-free media swell instead of shrink when stimulated to undergo cell death, they still retain other classical characteristics of apoptosis [48]. Reintroduction of sodium resulted in the shrunken, apoptotic morphology. Furthermore, the voltage-gated sodium channel blocker saxitoxin was shown to prevent Fas ligand-induced apoptosis in Jurkat cells [48]. Further studies into the role of sodium during apoptosis are essential, but current evidence suggests that sodium channels could be promising targets in cancer therapy in regards to sensitizing tumour cells to die.

9. Chloride channels as targets for apoptotic cell death in cancer cells

Chloride channels are known to have an important role in a wide variety of cellular functions including cell proliferation, membrane potential, fluid secretions and cell volume regulation [112]. Additionally, chloride channels are known to play a significant role during apoptosis [50–52], however, they have received considerably less attention than their potassium counterpart. Chloride channel activity has been observed in large variety of cell types undergoing apoptosis either via the extrinsic or intrinsic pathway [113]. Similar to other ion channels, inhibition of chloride channels to prevent apoptosis has been cell type and/or stimulus specific [51]. Early studies reported the importance of chloride channels during apoptosis where the death receptor pathway activated a tyrosine kinase-dependent chloride channel whose inhibition resulted in decreasing cell death [114]. Interestingly, impaired chloride efflux induced by a variety of cell death stimuli was shown to prevent internucleosomal DNA fragmentation, but not other classical characteristics of programmed cell death [115]. Calcium-activated chloride channels (CaCCs) have been reported to be pro-apoptotic and suppress tumour formation in epithelial cells [116]. However, other family members of the CaCCs along with the recently characterized 8-transmembrane receptor-activated CaCC (TMEM16A) can promote cellular proliferation and tumorigenesis [117,118]. These studies suggest a variable role of chloride and/or anionic current during apoptosis and cancer progression.

Recently, VSOR chloride channels, known to activate upon cell swelling, are active during AVD [119]. Inhibition of these channels was reported to prevent AVD and subsequent downstream apoptotic events [52]. Chloride channels, as is the case with potassium channels, can also be expressed on intracellular membranes [112]. A decrease in expression of these chloride channels using antisense constructs resulted in apoptosis upon TNF-alpha treatment [120]. A variety of anionic currents are known to be present in many cancers, and chloride channel activity occurs during cell death. However targeting chloride channels in tumour cells to restore apoptosis sensitivity is limited owing to the unknown molecular identity of many of these proteins. The difficulty in determining the identity of chloride channels is likely related to the recent data suggesting that many of these proteins are anti-porters and not just channels [112].

10. Conclusion

In retrospect, it is clear that cells spend a great deal of time and energy maintaining their ionic environment. All cells have the ability to die; however, resistance to cell death, specifically apoptosis is not monogenic. The physical intracellular environment of normal cells is not conducive to apoptosis. Thus, a change in intracellular ions is required for the full activation and activity of apoptosis. This change in intracellular ion may permit depolarization of the plasma membrane thus altering signal transduction pathways. Additionally, a change in the cellular environment may alter protein–protein interactions. While intracellular ions can control the volume of the cell, it is not a change in cell size that regulates apoptosis, but a change in the intracellular ionic environment that holds the key as to whether a cell lives or dies.

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