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REVIEW ARTICLE

Altered expression and functional role of ion channels in leukemia: bench to bedside

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Abstract

Leukemic cells' (LCs) survival, proliferation, activation, differentiation, and invasiveness/migration can be mediated through the function of cation and anion channels that are involved in volume regulation, polarization, cytoskeleton, and extracellular matrix reorganization. This study will review the expression of ion channels in LCs and their possible function in leukemia progression. We searched relevant literature by a PubMed (2002–2019) of English-language literature using the terms "ion channels", "leukemia", "proliferation", "differentiation", "apoptosis", and "migration". Altered expression and dysfunction of ion channels can have a strong impact on hematopoietic cell and LCs physiology and signaling, which contributes to the vital processes such as proliferation, differentiation, and apoptosis. Indeed, it can be stated that changing expression of ion channels can affect the onset and progression as well as clinical features and therapeutic responses of leukemia via inducing the maintenance of LCs. Since ion channels are membrane proteins, they can be easily accessible in LCs for understanding their influence on leukemia progression. On the other hand, ion channels can be new potential targets for chemotherapeutic agents, which may open a novel clinical and pharmaceutical field in leukemia therapy.

Article highlights

- Ion channels may be implicated in leukemia as the genes subjected to altered expression.
- Expression and function of ion channels can regulate proliferation, activation, differentiation, malignant progression, and invasiveness/migration of leukemic cells.
- Ion channels can be used as pharmacologic targets in leukemia therapy.

Keywords Ion channels · Leukemia · Proliferation · Differentiation · Apoptosis · Migration

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Introduction

Ion channels are membrane proteins that play an essential role in preserving the normal physiology of cells by participating in processes such as neurotransmission, heart rate, muscle contraction, insulin secretion, immunity, and cellular proliferation [1]. The most important feature of ion channels is their selective permeability that enables only certain types of ions with a given charge and size to pass through. In addition, the opening and closing of these channels are influenced by various stimuli such as voltage, elongation and pressure applied to the membrane, or by connecting to certain effectors [2]. The trafficking of ions by ion channels creates an electric potential difference on two sides of the membrane, which is necessary to produce various intracellular signals involved in processes such as mitosis and cell migration [2]. Evidence suggests that abnormal expression and function of almost all types of ion channels can contribute to the development of tumors, metastasis, and drug resistance of solid tumors and leukemia [3]. Volatility and mitotic control points that play a significant role in survival and proliferation of tumor cells are processes affected by the aberrant expression and stable properties of ion channels [4–6]. Leukemias are a group of hematological malignancies originating from hematopoietic stem cells (HSCs) of the bone marrow (BM) that are associated with an increase of immature precursors in peripheral blood (PB). These malignancies are clinically divided into acute and chronic leukemias and originate from myeloid and lymphoid lineages [7]. Although cytogenetic alterations such as mutations and translocations are a major cause of leukemia, changes in the function and expression of ion channels that are involved in the control of proliferation, apoptosis, and migration of leukemic cells (LCs) by ions passage can play a crucial role in the progression of leukemias [3]. Ion channels appear to trigger a cascade of intracellular signals affecting vital processes of LC growth through the passage of certain ions capable of producing macromolecular complexes with intracellular proteins [8, 9]. Cl^-, K^+, Ca^{2+}, and Na^+ are the most important ions associated with the regulation of physiological processes in cells. It has already been shown that changing expression and function of channels transmitting these ions are major causes of non-differentiation and increased migration of LCs as well as drug resistance in leukemia [10]. However, it has also been shown that targeting ion channels with anti-cancer compounds and modulation of their function can be associated with desirable therapeutic results [11], which highlight the vital role of ion channels in the development and progression of leukemia.

Over the past decade, studies have focused on the role of ion channels in excitatory cells (neurons, cardiac, secretive). A large number of investigations have focused on the role of these channels in the behavior of cancer cells in solid tumors, indicating that overexpression of some of these channels is related to poor prognosis [12–15]. Thus, ion channels can be considered as new biomarkers for the diagnosis and treatment of leukemia. Therefore, in this article, we try to discuss the effects of onset and progression of these malignancies by reviewing the most important changes in the expression and function of ion channels in leukemia.

Expression and functional role of ion channels in HSCs and leukemic stem cells

$CD34^+$HSCs are cells capable of propagating and differentiating into various cell types residing in BM niches that can be linked to BM matrix through ion channels [16]. Fluctuations in volume and membrane potential are characteristics of HSCs, which can be associated with the passage of various stages of cell cycle including G1 transition to S phase [17]. Transient receptor potential (TRP) proteins are a family of Ca^{2+} transducer channels that can form a cascade of intracellular signals, including apoptosis-related signals in cells via increasing penetration of Ca^{2+} into HSCs [17, 18]. TRPM2 is a member of this family that is activated in response to oxidative stress and tumor necrosis factor alpha (TNF-α), inducing apoptosis by transferring Ca^{2+} into HSCs as well as increasing the levels of caspase-8, -9, -3, and -7 [18]. It can be inferred that decreasing expression of TRPM2 channels in normal HSCs can be a reason for resistance to apoptosis, uncontrolled proliferation, and transformation into leukemic stem cells (LSCs), which requires further studies to provide convincing evidence in this regard. LSCs are the first malignant cells in leukemia, which have a potent self-renewal and proliferation potential that plays an essential role in the onset and increase of LC populations. Li et al. showed that the human ether-a-go-related (herg) gene encodes a family of voltage-dependent K^+ channels called HERG K^+ channels at the surface of $CD34^+/CD38^-/CD123^{high}$ LCs, K562 cells [a chronic myeloid leukemia (CML) cell line], cellular and HL60 leukemia cell lines while normal $CD34^+/CD38^-$ HSCs lack these channels [19, 20]. Although the possible relationship between the expressions of HERG K^+ channels with occurrence of cytogenetic changes and clinical findings has not yet been determined, the use of the HERG K^+ channel inhibitors associated with the inhibition of G1/S transition phase of cell cycle has highlighted the role of these ion channels in inducing cell cycle and proliferation of LSCs [19, 20]. In addition, increased expression of HERG1 K^+ channels on the surface of primary acute myeloid leukemia (AML) blast cells and immature neoplastic B-chronic lymphoblastic leukemia (B-CLL) cells ($CD5^+$) shows that the aberrant expression of these ion channels can induce oncogenicity in LSCs

[10]. In this regard, increasing electrical potential of plasma membrane (V_m) by HERG K^+ channels has been introduced as a possible mechanism for inducing proliferation in tumor cells. Moreover, studies have shown that the progression of cell cycle and mitosis is strongly related to the number and function of HERG K^+ channels [21]. However, reducing the expression and blocking HERG1 K^+ channels in K562, CEM, and U937 by HERG channel blockers such as E-4031 and inducing apoptosis in them are indicative of the fact that these ion channels can be diagnostic biomarkers and potential targets for controlling the progression of leukemia and solid tumors [10, 19, 22, 23].

BM mesenchymal stem cell induction of ion channel expression and migration in LCs

Migration is the most important physiological process of LCs, which is related to the ability of these cells to leave BM and accumulate in PB [24]. BM mesenchymal stem cells (BM-MSCs) that are capable of differentiation to a variety of cells are among the most basic components of BM niches and umbilical cord blood [25–27]. Furthermore, BM-MSCs can be involved in the secretion of chemokines such as stromal cell-derived factor-1 (SDF-1) that play a vital role in migration or homing of LCs by binding to chemokine receptor CXC4 (CXCR4) at the surface of these cells [28]. It has been shown that SDF-1/CXCR4 interaction can induce HERG1 K^+ channels at the surface of B-ALL LCs, which enhance their anti-apoptotic property (Fig. 1) [29]. The molecular mechanism proposed for this feature is cascade activation of intracellular signals by HERG1 K^+ channels, which forms the β1 integrin subunit and CXCR4 complex in B acute lymphoblastic leukemia (B-ALL) while normal B lymphocytes lack this complex [29]. It has been indicated that these complexes are specific for LCs and that their formation activates the intracellular signals of Flt-1-dependent pathway in AML-LCs, leading to increase of their excretion from BM to PB and enhancement of resistance to chemotherapy (Fig. 1) [6, 29]. Similar to B-ALL LCs, the activation of MAP kinase and phosphoinositide 3-kinase (PI3 K)/Akt pathways is a molecular mechanism resulting from CXCR4/SDF-1 interaction and increased expression of HERG1 K^+ channels with anti-apoptotic effect and drug resistance in AML, CML and CLL [30, 31]. Interestingly, studies have shown that blocking HERG1 K^+ channels can induce SDF-1 as well as migration of leukemic blasts in HL-60 cell lines [32]. In fact, these findings indicate that overexpression of HERG1 K^+ channels could be associated with poor prognosis via the development of drug resistance and migration of LCs. Also, expression induction of HERG1 K^+ channels in LCs has been reported as one of the basic mechanisms for protecting LCs against cytotoxic effects of asparaginase as well as other chemotherapeutic agents such as cytarabine (Ara-C) and etoposide (VP-16) [33]. Therefore, blocking HERG1 K^+ channels and CXCR4/SDF-1 interaction, which has been reported in previous studies as an approach to overcome resistance to chemotherapy in AML and ALL [34], may be related to increased LC apoptosis, decreased migration, and drug resistance of these cells. In this regard, various HERG1 inhibitors are known to control the function of HERG1 K^+ channels (Table 1) [29, 35]. Nevertheless, due to the involvement of HERG1 K^+ channels in cardiac repolarization potential, there is evidence that the inhibition of these channels can slow down repolarization in the heart muscle and eventually lead to arrhythmia [10], which can account for the limited use of HERG1 K^+ channel blockers and the meticulousness in choosing different forms of these inhibitors.

Potential effect of K+ channel expression and leukemia progression

The fact that K^+ channels as key factors in controlling membrane potential play a central role in the growth of cells in both physiological and pathological conditions has been proved in numerous studies [35]. Voltage-dependent channels are divided into K_V1–K_V12 types. Human voltage-gated potassium ion channel ether-à-go-go 1 (hEag1 or $K_v10.1$) is one of the most well-known voltage-dependent K^+ channels whose expression has been shown to increase in many solid tumors and has been introduced as a poor prognostic factor in these malignancies due to its oncogenicity [36–39]. Furthermore, Agarwal et al. showed that hEag1 expression significantly increases in primary myeloid leukemia, CML, and myelodysplastic syndrome (MDS) [40]. Interestingly, the increase in hEag1 expression in these malignancies is directly related to the age of patients and is accompanied by adverse clinical outcomes such as increased relapse rate and shorter overall survival [40]. Although targeting hEag1 with different types of inhibitors is suggested as a therapeutic approach in cancers (Table 1) [35, 40], it seems that therapeutic intervention to control the molecular mechanisms involved in expression regulation of this gene is an alternative strategy to reduce the adverse effects of hEag1 expression. In this regard, Lin et al. showed that P53/Mir34/E2f is a molecular pathway that regulates the expression of hEag1 in cells. Defective expression and function of the components of this molecular pathway, including P53 and Mir34, are associated with the overexpression of hEag1 as well as tumor cell proliferation (Fig. 1) [41]. Since methylation has been reported to be responsible for decreased P53 expression and increased LC proliferation [42], demethylation drugs may be useful as a therapeutic strategy to reduce the expression of hEag1 and its adverse effects in leukemia.

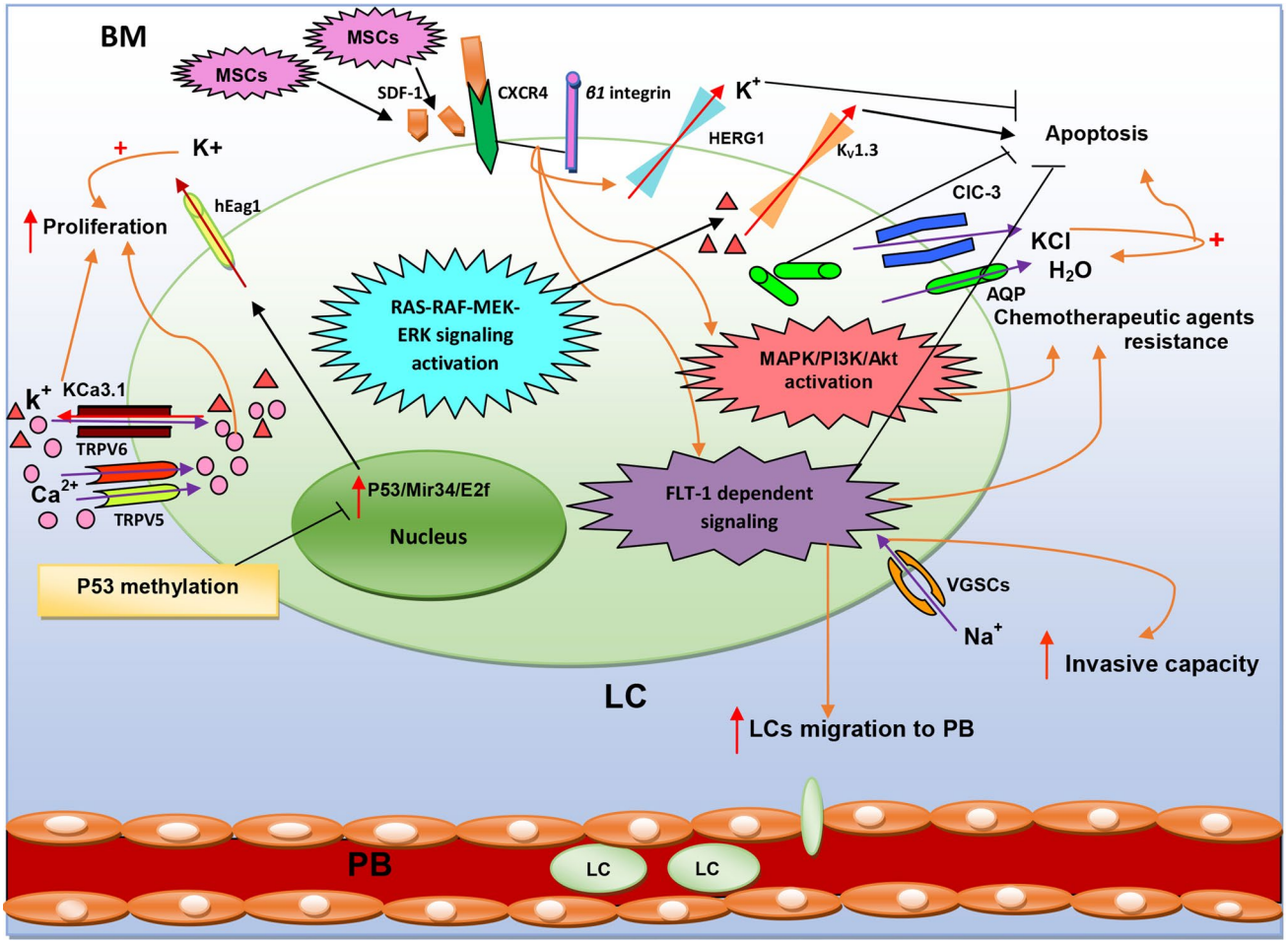

Fig. 1 Ion channels in the plasma membrane of LCs and their participation in leukemia progression. In BM, production of SDF-1 by MSCs can cause SDF-1/CXCR4 interaction as well as CXCR4/1-integrin complex formation that lead to decreased intracellular K^+ and LCs apoptosis. On the other hand, activation of CXCR4/1-integrin complex can be associated with resistance to chemotherapeutic agents and LC migration from BM toward PB via stimulating MAPK/PI3 K/Akt and Flt-1-dependent signaling pathways. Activation of RAS–RAF–MEK–ERK signaling pathway can promote $K_V1.3$ expression as well as apoptosis that lead to K^+ excretion and induction of cellular contraction. Also, excretion of K^+ via ClC-3 channels induces plasma membrane expression of AQPs and loss of LC H_2O and apoptosis. While accumulation of AQPs in intracellular space is associated with inhibition of apoptosis, localization of KCa3.1, TRPV5, and TRPV6 can be associated with accumulation of Ca^{2+} in intracellular environment that can promote LC proliferation. Also, proliferation of LCs can be mediated by activation of P53/Mir34/E2f signaling in nucleus that leads to overexpression of hEag1 channel. However, increased proliferation of LCs can inhibit it by P53 methylation. *BM* bone marrow, *MSCs* mesenchymal stem cells, *SDF-1* stromal cell-derived factor 1, *CXCR4* C–X–C chemokine receptor type 4, *HERG1* human ether-a-go-go 1, *hEag1* human voltage-gated potassium ion channel ether-à-go-go 1, *ClC-3* chloride channel 3, *TRPV* transient receptor potential vanilloid, *PB* peripheral blood, *AQP* aquaporin, *LCs* leukemic cells, *VGSCs* voltage-gated sodium channels

$K_v1.3$ is another voltage-dependent member of K^+ channel families that is expressed in the internal membrane of mitochondria with a crucial role in the formulation of apoptotic processes. It has been shown that the inhibition of $K_v1.3$ by Bax and Bak can lead to hyperpolarization of the internal mitochondria membrane and the release of reactive oxygen species (ROS) causing death of cells [43]. In addition, the inhibition of mitochondrial $K_v1.3$ channels in animal models and human cell lines by three distinct membrane-permeant inhibitors of $K_v1.3$, namely Psora-4, PAP-1, and clofazimine, reveals the crucial function and expression of these ion channels in cell death even in the absence of Bax and Bak [44]. Another mechanism regarding the association of $K_v1.3$ channels with apoptotic process is the stimulation of the function of these channels in cellular membrane by Fas receptors. This mechanism results in K^+ excretion of cells and induction of cellular contraction, which is one of the first cell responses to the onset of pro-apoptotic processes [45]. Meanwhile, other K^+ channels such as $K_v3.4$ can cause resistance of AML-LCs to radiotherapy and reduce the apoptosis of these cells [46]. Interestingly, the expression and activity of $K_v1.3$ channels

Table 1 Altered ion channel expression and pharmacological treatment in leukemias

Ion channels	Gene name	Cro.	Leukemia	Expression	Function	Inhibitor drug	References
K^+ channels							
k11.1 (hERG)	KCNH2	7q36.1	PAML, B-CLL, B-ALL, CML	UP	Inducing cell cycle and proliferation, migration, anti-apoptotic effect and drug resistance	Erythromycin, sertindole, WAY 123, dofetilide, astemizole, roscovitine, E4031	[10, 19, 40]
K10.1 hEag1	KCNH1	1q32.1	PAML, CML, MDS	UP	Inducing cell proliferation and adverse clinical outcomes such as increases relapse rate and shorter overall survival	Astemizole, imipramine, mAb56	[40, 41]
$K_v1.3$	KCNA3	1p13.3	B-CLL, AML, ALL	UP	Initiation of apoptotic process	Correolide, Psora-4, clofazimine, benzamides, piperidines, tetraphenyl-porphyrins, dihydrophenanthridines, memantine	[44, 47–49, 86]
$K_v3.4$	KCNC4	1p13.3	AML	UP	Reduced apoptosis and radioresistance	BDS-I	[46]
$K_{2p}18.1$	KCNK18	10q25.3	T-ALL	UP	Inducing proliferation and migration of LCs	Bisindolylmaleimide, Ro-32-0432, and chelerythrine	[58, 87]
$Ca2^+$ channels							
kCa3.1	KCNN4	19q13.31	B lymphoma	UP	Associated with increased migration of LCs	TRAM-34	[51]
TRPV2	TRPV2		AML, CML, ALL, CLL	UP	Increased LC proliferation		[66]
TRPV5	TRPV5	7q34	K562 and Jurkat T cell lines	UP	Increased LC proliferation and resistance to apoptosis	Fentamate, capsazepine	[60, 64, 65]
TRPV6	TRPV6	7q34					
P2X7	P2X7	12q24.31	AML, B-CLL, ALL, MDS, CML	UP	Leukemogenesis, proliferation, resistance to apoptosis	KN62, A-438079	[67, 88]
Na^+ channels							
Na1.3	SCN3A	2q24.3	Jurcat leukemic T cell line	UP	Motility and invasiveness of LCs	TTX, flecainide, mexiletine	[70, 74]
Na1.5	SCN5A	3p22.2					
Na1.6	SCN8A	12q13.13					
Na1.7	SCN9A	2q24.3					
Na1.9	SCN11A	3p22.2					
Cl^- channels							
CLC3	CLCN3	4q33	CML	UP	Can be associated with apoptosis and proliferation of LCs	Tamoxifen, 5-nitro-2-(3-phenylpro-pylamino benzoic acid	[81, 85]

Cro chromosome, *UP* up-regulation, *hERG* human ether-a-go-go-related, *KCNH* potassium voltage-gated channel subfamily H, *hEag1* human voltage-gated potassium ion channel ether-à-go-go 1; *KCNA* potassium voltage-gated channel subfamily A, *KCNC* potassium voltage-gated channel subfamily C, *KCNC* potassium voltage-gated channel subfamily K, *PAML* primary acute myeloid leukemia, *CML* chronic myeloid leukemia, *ALL* acute lymphoblastic leukemia, *CLL* chronic lymphoblastic leukemia, *MDS* myelodysplastic syndrome, *LCs* leukemic cells, *TTX* tetrodotoxin, *BDS-I* blood depressing substance-I, *KCNN4* potassium–calcium-activated channel subfamily N member 4, *TRPV* transient receptor potential vanilloid, *SCNA* sodium voltage-gated channel alpha, *CLC3* chloride channel 3, *CLCN3* chloride voltage-gated channel 3

in malignant B-CLL cells are higher in membrane resting potential than in normal cells [47]. The induction of $K_v1.3$ expression by oncogenic B-RAF signaling, which is a major component of RAS–RAF–MEK–ERK signal transduction crucial for obtaining survival signals by B-cell receptor (BCR) in malignant B cells, is a molecular mechanism reported to increase the expression and activity of these ionic channels in B-CLL LCs [48]. It is inferred that the induction of expression and function of $K_v1.3$ channels in cytoplasmic membrane and its inhibition in mitochondrial membrane could change membrane potential and concentration of intracellular potassium to pave the way for the initiation of apoptosis processes. In addition to apoptosis, the expression of $K_v1.3$ channels is known as a proliferation marker in CLL [49]. KCa3.1 channels or Ca^{2+}-activated K^+ is another potassium channel with low expression levels in normal B lymphocytes and resting CLL cells in contrast to its increased expression in activated CLL cells, suggesting the fact that these channels may be involved in the induction of proliferation in CLL cells [50]. The noteworthy point about $K_v1.3$ and KCa3.1 is their complexity in the regulation of potassium flow. For example, it has been shown that human Daudi cell line, a B-lymphoma cell line, expresses both $K_v1.3$ and KCa3.1 channels that interfere with their growth. While selective blocking of KCa3.1 inhibits cell cycle, simultaneous expression of both channels can induce cell cycle and proliferation in this cell line [51]. Therefore, the use of K^+ channels as therapeutic targets for the induction of apoptosis and reduction of proliferation seems to require the use of compounds that can selectively target these channels in plasma or mitochondria membrane.

Two-pore domain K^+ (K_{2P}) channels are a family of potassium channels that play a role in maintaining the resting potential and depolarization of the membrane. Unlike $K_v1.3$ channels, the performance of these channels is independent of voltage and is only sensitive to changing physiological parameters such as pH, temperature, membrane stretch, and some intracellular signaling pathways, as well as in response to vital cell processes such as proliferation, differentiation, and apoptosis [52, 53]. It has been shown that four members of this family, including $k_{2p}2.1$ (TREK-1), $K_{2P}3.1$ (TASK-1), $K_{2P}18.1$ (TRESK), and $K_{2P}5.1$ (TASK2), are increased in a variety of cancers such as leukemia and are considered as therapeutic targets in many cancers (Table 1) [54, 55]. It has been shown that the expression of these channels at the surface of T lymphocytes plays a significant role in maintaining their osmotic volume [56, 57]. Although little information is available on the expression of K_{2P} channels in humans LCs, it has recently been shown that increased expression of $K_{2P}18.1$ in plasma membranes of several T-lymphocytic cell lines (Jurkat, JCaM, H9) and T-ALL cells is associated with the proliferation of these cells. This is despite the fact that the expression rate of this potassium channel in resting T lymphocytes is negligible or is not generally expressed, which may indicate their oncogenicity characteristic [58]. Interestingly, the dependence of TRESK channels on Ca^{2+} is different from that of KCa^{2+} channels. While KCa^{2+} channels are rapidly activated by increased concentration of Ca^{2+} and deactivated in its absence, TRESK channels maintain their activity in the absence of Ca^{2+} for a long time as a result of phosphorylation by compounds such as calcineurin, affecting the survival and function of the cells. Studies have also shown that TRESK can be involved in the expression of different genes and immune dysfunction in T-ALL LCs. This finding suggests that TRESK is a potential therapeutic target for immunomodulation in this malignancy [59].

Calcium activated ion channels in leukemia

Sustained Ca^{2+} flow is an essential mechanism for regulating vital processes, including cytokine production, proliferation, and differentiation in blood cells [60]. The passage of Ca^{2+} through the membrane of blood cells is mediated by two types of Ca^{2+} channels, including Ca^{2+} release-activated Ca^{2+} (CRAC) channels and transient receptor potential (TRP) family proteins [61]. Two members of TRP channels, namely TRP vanilloid type 5 (TRPV5) and TRPV6, are voltage-dependent Ca^{2+} channels that regulate cell proliferation. Also, it has been shown that increasing expression of TRPV5 and TRPV6 channels in K562 cell line results in the activation of Ca^{2+}/calmodulin-dependent kinase II (CaMKII) that can lead to increase of intracellular Ca^{2+} and thus induce proliferation, differentiation, and resistance to apoptosis in these cells [62–64]. Moreover, it has been shown that the expression of TRPV5 and TRPV6, as well as entry of Ca^{2+}, is directly related to the activity and proliferation of lymphocytes (Fig. 1). In fact, the direct relationship between the expression of TRPV5 and TRPV6 with leukemia Jurkat T-cell proliferation may indicate the pathological role of these ion channels in leukemias, especially lymphoid leukemias [65]. There is also widespread evidence indicating that TRPV2 expression is higher in myeloid and lymphoid LCs than in normal cells, which is associated with the growth of these malignant cells [66]. However, the presence of some polymorphisms in TRPM5 gene (another member of the TRP channels) in children with AML and ALL is linked with a reduction in disease progression [66]. These finding suggests that the genetic background of patients can have a significant relevance to ion channels' expression and function. Purinoreceptors (P2X) are a group of specific ATP-dependent Ca^{2+} channels in T lymphocytes with a significant role in mitosis and proliferation of these cells. Studies have shown that this group of Ca^{2+} channels has seven members, three of which (P2X1, P2X4, and P2X7) have been detected at the surface of hematopoietic progenitor cells and different hematopoietic cell lines [67]. Evidence suggests that there is a direct

relationship between the expression of P2X7 in BM of AML and CLL patients with leukemogenesis in these malignancies [68]. Although there is a relatively high level of P2X7 expression in patients with ALL, there is no evidence of the origin of LCs (B-ALL or T-ALL cells) [68]. Nonetheless, the results of these studies have shown that P2X7 channels can trigger a network of signaling pathways with a key role in tendency of normal cells toward leukemic form via facilitating the entry of Ca^{2+} into cells. In fact, the expression of P2X7 channels is known as a poor prognostic factor of leukemogenesis characteristic that causes the progresses of leukemia [68].

Sodium channel expression in leukemia

Voltage-gated sodium channels (VGSCs) are membrane proteins that cause Na^+ to enter the cells in the direction of concentration gradient. Research has shown that increasing expression of VGSCs in breast and prostate cancer cells is associated with an increase in their invasiveness, while inhibiting the expression and function of these ion channels with tetrodotoxin (TTX) in vitro is accompanied with a dramatic reduction in cancer cell metastasis and invasiveness [69, 70]. Studies on Jurkat T lymphocytes have shown that various types of VGSCs, including Na1.3, Na1.5, Na1.6, Na1.7, and Na1.9 channels, are expressed in this cell line and are related to Jurkat cell invasiveness; however, VGSC blockers are able to reduce the expression of these channels as well as Jurkat cell invasiveness by approximately 93% [70]. However, amilorides as blockers of another group of Na^+ channels called non-voltage-gated sodium (NVGS) channels are not capable of inhibiting their expression and function in K562, U937, and AML-M5 cell lines [71, 72]. Since the expression of VGSCs and NVGS may be associated with invasive cellular behaviors such as secretion, adhesion, and motility in solid tumor cells [73], their expression in normal physiological conditions may be a mechanism for invasive T lymphocytes towards infectious tissues. In contrast, the expression of VGSCs and NVGS in T LCs is a factor in stimulating invasion into the lymph nodes and involvement of these organs. Despite extensive studies on inhibiting Na^+ channels in solid tumors and the use of various inhibitors for inhibiting these channels (Table 1) [74–76], limited studies have been conducted on the use of such inhibitors in leukemia. Therefore, further studies are needed to confirm the use of Na^+ blockers in patients with leukemia.

Effect of chloride channels in leukemia progression

Chloride (Cl^-) channels are a group of membrane channels that play a role in a wide range of biological functions in cells, including regulating cell volume, stimulating the cells, and acidifying their environment [77]. Despite the fact that the precise performance of Cl^- channels in blood cells such as lymphocytes and neutrophils showing a high expression of these ion channels than other cells is not specified, investigations have shown that some of the volume-activated Cl^- channels are activated under isotonic conditions in ALL Molt4 cell line and play a critical role in maintaining the cellular volume via creating a stable Cl^- stream [78]. In addition, Jiang et al. indicated that the use of Cl^- channel blockers inhibits LC proliferation and cell cycle arrest in G0/G1 phase, which may indicate the role of these ion channels in leukemia progression [79]. ClC-3 channel is a Cl^- channel that has recently been the focus of much attention in leukemia. According to Kasinathan et al.'s study, ClC-3 channels are accumulated in intracellular resting state, while the expression of these ion channels in plasma membrane increases with oxidation, which could indicate the role of ClC-3 channels in stimulating the oxidation of current anions over the membrane [80]. Additionally, under these conditions, cell membrane permeability to anions such as KCl is increased. Excretion of these anions and H_2O from cells could lead to cellular contractions as well as apoptosis [81]. Indeed, as demonstrated in solid tumors that ClC-3 channels play an important role in apoptosis and proliferation [82, 83], it is inferred that the expression of ClC-3 channel in cytoplasmic membrane of LCs may indicate their tendency to apoptosis while the cytoplasmic expression of this channel leads to LC proliferation. Another mechanism by which Cl^- channels are involved in apoptosis and proliferation of LCs is the regulation of volume-regulated chloride currents (VRCCs) by intracellular sigma receptors. Renaudo et al. showed that sigma receptors could modify the expression of VRCC and LC volume by altering the pattern of apoptosis and proliferation [81]. A noteworthy point about VRCCs is the control of their function by aquaporins (AQPs), which has been shown to contribute to the development of chemotherapy resistance in epithelial cancers [84]. Chae et al. showed that increasing the expression of AQP5 due to its effect on cell volume can stimulate proliferation, inhibit apoptosis, and generally improve the CML LCs [85]. Also, it has been shown that higher expression of AQP5 in patients with CML in the accelerated and blastic phases relative to patients in the chronic phase is directly related to imatinib mesylate resistance [85]. Although the exact mechanism of AQPs' function in regulating the expression of VRCCs is unknown, the increase in the expression of AQPs, especially AQP5, may play an essential role in reducing the absorption and sensitivity of LCs to chemotherapeutic agents by H_2O transport as well as disturbance of osmotic balance and intracellular ion concentration.

Discussion

In the past decades, studies on the role of ion channels in leukemias have focused on their level of expression, function, and introduction of these channels as diagnostic and prognostic markers. For example, the first studies on the role of K^+ channels in leukemia showed that channel $K_v11.1$ is associated with aggressive AML phenotype and adverse clinical findings, including increasing relapses and shorter overall survival [6]. Subsequently, other studies have indicated that in addition to AML, the expression of other K^+ channels such as hEag1 ($K_v10.1$) is strongly associated with increasing risk of recurrence and short-term survival in patients with CML and MDS [40]. $K_v11.1$ and $K_v10.1$ are K^+ channels whose expression is associated with cell cycle progression and proliferation of LCs. Although ion channels are expressed in both normal and neoplastic cells, it seems that in the course of rapid transformations of neoplastic cells, the tendency to change the expression of ion channels increases, but they do not return to normal state due to rapid proliferation. For example, the stable expression of $K_v1.3$ and $K_v10.1$ on the surface of LCs has a significant impact on vital LC processes including proliferation, differentiation, migration, and apoptosis by regulating cell volume fluctuations and affecting intracellular signals [41, 50, 89]. These findings suggest that blocking of K^+ channels can have a significant effect on controlling the progression of leukemias. Intracellular Ca^{2+} signals are an essential mechanism for the survival of normal and cancerous cells, and the extensive expression of Ca^{2+} channels has been shown to increase Ca^{2+} and cell hyperpolarization, which is possibly associated with movement and proliferation of LCs [65, 68]. In addition to direct contribution of ion channels to transportation of ions, K^+, Na^+, and Cl^- channels can indirectly affect the susceptibility of LCs to chemotherapeutic agents through affecting resting potential and ion gradient change. However, investigations have shown that various drugs such as E4031, a potential blocker for hERG1 channels, alone or in combination with chemotherapy drugs can inhibit the expression and function of these channels in different aspects of LCs physiology in vivo and in vitro to induce its anti-leukemic effects [10, 19, 22]. In fact, these findings suggest that ion channels can be considered as new candidates for overcoming drug resistance in leukemias.

Conclusion

Changing expression and function of ion channels in LCs can affect different aspects of pathophysiology of leukemias by influencing intracellular signaling pathways. Since ion channels are easily accessible membrane proteins, targeting them with effective drug compounds that can selectively articulate their expression and function is an effective way to control patients' clinical conditions and improve their response to treatment. However, we believe that the effectiveness of ion channels as therapeutic goals in leukemias requires extensive clinical studies to understand the exact mechanism of changes in their expression and function in LC survival and maintenance.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

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