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Обзор литературы / Review article

Exploring glutamate-gated chloride channels in cancer cells: A narrative review on a hypothetical mechanism underpinning the anticancer effects of antiparasitic drugs

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Abstract

Chloride channels play a fundamental role in cellular homeostasis, influencing ion balance, pH regulation, and apoptotic signaling. While glutamate-gated chloride channels (GluCl) are traditionally restricted to invertebrates, recent evidence suggests that functionally analogous chloride conductances may exist in cancer cells, contributing to tumor survival and metabolic adaptation. Notably, chloride intracellular channels (CLICs), particularly CLIC6, have emerged as strong candidates for chloride-mediated oncogenic signaling. CLIC6 is overexpressed in multiple malignancies, including breast, ovarian, lung, gastric, and pancreatic cancers, and is known to interact with dopamine D_2-like receptors. Patch-clamp studies have confirmed its chloride-selective conductance, localization to the plasma membrane, and regulation by pH and redox potential. The unexpected anticancer effects of antiparasitic drugs such as ivermectin, which targets GluCl channels in parasites, suggest a possible chloride-mediated mechanism of cytotoxicity in tumors. Ivermectin-induced chloride influx may disrupt ionic equilibrium, hyperpolarize the plasma membrane, and trigger mitochondrial dysfunction, leading to oxidative stress, cytochrome *c* release, and caspase activation. This ionic disruption may also interfere with key oncogenic pathways, including PI3K/AKT, Wnt/β-catenin, and NF-κB, impairing tumor proliferation and immune evasion. Given the structural and functional parallels between GluCl channels and CLIC6, ivermectin's efficacy may be partially mediated through chloride channel dysregulation. This review synthesizes molecular, electrophysiological, and pharmacological evidence supporting the existence of GluCl-like chloride conductance in cancer cells and its therapeutic implications. Further research is needed to characterize chloride ion dynamics in tumors, validate CLIC6 as a potential GluCl channel analog, and explore chloride channel-targeting strategies for cancer treatment, opening new frontiers in oncology.

Key words: glutamate-gated chloride channels, CLIC6, ionic dysregulation, antiparasitic drug repositioning, tumor metabolism**.**

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Изучение глутамат-регулируемых хлоридных каналов в раковых клетках: нарративный обзор гипотетического механизма, лежащего в основе противоопухолевого эффекта антипаразитарных препаратов

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Резюме

Хлоридные каналы играют фундаментальную роль в поддержании клеточного гомеостаза, влияя на ионный баланс, регуляцию pH и апоптотические сигнальные пути. Хотя глутамат-регулируемые хлоридные каналы (GluCl) традиционно ограничены беспозвоночными, последние данные свидетельствуют о том, что функционально-аналогичные проводимости хлоридов могут присутствовать в раковых клетках, способствуя выживанию опухоли и метаболической адаптации. Особенно выделяются внутриклеточные хлоридные каналы (CLIC), в частности CLIC6, как потенциальные участники онкогенной хлорид-зависимой сигнализации. CLIC6 сверхэкспрессируется при различных злокачественных новообразованиях, включая рак молочной железы, яичников, легких, желудка и поджелудочной железы, и взаимодействует с дофаминовыми рецепторами D_2-подтипа. Электрофизиологические исследования методом патч-кламп подтвердили хлорид-селективную проводимость CLIC6, его локализацию в плазматической мембране и регуляцию pH и редокс-потенциалом. Неожиданные противораковые эффекты антипаразитарных препаратов, таких как ивермектин, который воздействует на каналы GluCl у паразитов, предполагают возможный механизм цитотоксичности в опухолях, опосредованный нарушением хлоридного обмена. Индуцированный ивермектином приток хлоридов может нарушить ионное равновесие, гиперполяризовать плазматическую мембрану и вызвать митохондриальную дисфункцию, что ведет к окислительному стрессу, выходу цитохрома *c* и активации каспаз. Это нарушение ионного обмена также может вмешиваться в ключевые онкогенные пути, включая PI3K/AKT, Wnt/β-катенин и NF-κB, нарушая пролиферацию опухоли и избегание иммунного ответа. Учитывая структурные и функциональные параллели между каналами GluCl и CLIC6, эффективность ивермектина может быть частично обусловлена дисрегуляцией хлоридных каналов. Данный обзор объединяет молекулярные, электрофизиологические и фармакологические данные, подтверждающие существование проводимости хлоридов, аналогичной опосредуемой каналами GluCl, в раковых клетках и ее терапевтические перспективы. Необходимы дальнейшие исследования для характеристики динамики хлоридных ионов в опухолях, подтверждения роли CLIC6 как потенциального аналога каналов GluCl и разработки стратегий, направленных на хлоридные каналы для лечения рака, что открывает новые горизонты в онкологии.

Ключевые слова: глутамат-регулируемые хлоридные каналы, CLIC6, ионная дисрегуляция, репозиционирование антипаразитарных препаратов, метаболизм опухолей.

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Introduction

Ion channels are fundamental components of cellular physiology, playing a crucial role in maintaining ionic homeostasis, regulating cell volume, mediating intracellular signaling, and orchestrating apoptotic processes [1]. Dysregulation of ion channel function has been increasingly implicated in tumorigenesis, where aberrant ion fluxes contribute to uncontrolled proliferation, evasion of apoptosis, and enhanced metastatic potential [2]. In particular, ion channels modulate key oncogenic pathways, including the PI3K/AKT/mTOR, MAPK/ERK, and Wnt/β-catenin signaling cascades, which are frequently hyperactivated in cancer cells, facilitating their survival and adaptation to hostile microenvironments [3]. Recent advances in cancer research have identified ion channels as potential therapeutic targets, with emerging evidence suggesting that pharmacological modulation of these channels may exert antitumor effects [4]. Notably, certain antiparasitic drugs, including ivermectin, have demonstrated promising anticancer activity, though the precise molecular mechanisms underlying their effects remain largely elusive. These drugs are known to disrupt ion homeostasis in parasitic organisms, raising the intriguing possibility that similar mechanisms may be at play in cancer cells [5].

One class of ion channels that has garnered attention in parasitology is glutamate-gated chloride channels (GluCl), which are primarily found in invertebrates and play a pivotal role in regulating neuronal excitability and chloride ion conductance [6]. These ligand-gated channels are crucial for maintaining neuromuscular function in parasitic nematodes, making them a key target for anthelmintic agents such as ivermectin [7]. While GluCl channels are absent in vertebrates, indirect evidence suggests the possible existence of functionally analogous channels in cancer cells. These putative GluCl-like channels may contribute to tumor cell survival by modulating chloride ion influx, thus counteracting metabolic stressors such as intracellular acidosis and

oxidative damage, which are characteristic of the Warburg effect and tumor microenvironment. This review aims to explore the potential role of GluCl-like channels in cancer biology, examining their hypothesized contribution to tumor progression, ionic regulation, and metabolic adaptation. We will also discuss the possibility that antiparasitic drugs exert their anticancer effects through modulation of these channels, providing a novel perspective on their therapeutic potential. Additionally, we will evaluate existing transcriptomic, proteomic, and electrophysiological studies for evidence supporting the presence of chloride channels with GluCl-like properties in human malignancies. By integrating insights from cancer metabolism, immunology, and ion channel physiology, this review seeks to provide a framework for future research into GluCl-like channels as a novel therapeutic target in oncology.

Material and methods

A comprehensive narrative review was conducted to explore the potential role of GluCl and chloride intracellular channels (CLICs), particularly CLIC6, in cancer cells and their implications for anticancer therapy. A systematic literature search was performed using PubMed, Scopus, and Web of Science, incorporating Medical Subject Headings (MeSH) terms and free-text keywords, including "glutamate-gated chloride channels," "CLIC6 in cancer," "ion channel dysregulation in tumors," "antiparasitic drug repositioning," "chloride homeostasis in cancer," and "ivermectin and tumor metabolism". Boolean operators (AND/OR) were applied to refine search sensitivity and specificity. The review included peer-reviewed studies published in English from 2000 to 2025, spanning clinical, preclinical, and mechanistic research on chloride channels, tumor ionic regulation, and targeted pharmacological interventions. Reference lists of key articles were manually screened to identify additional relevant publications.

Studies were selected based on their investigation of GluCl-like and CLIC-mediated chloride conductance in cancer cells, tumor microenvironmental adaptation, and the anticancer effects of antiparasitic drugs targeting ion channels. Exclusion criteria eliminated non-English studies, case reports with insufficient statistical power, articles without full-text availability, and studies lacking direct relevance to the hypothesis. The selection process followed a two-stage screening approach, initially retrieving 872 studies, with 189 duplicates removed. Title and abstract screening excluded 457 studies based on irrelevance, leaving 226 for full-text review. Among these, 64 studies were included for qualitative synthesis, focusing on chloride ion dynamics, tumor metabolism, and targeted therapeutic applications. Quality assessment was conducted using the SANRA (Scale for the Assessment of Narrative Review Articles) checklist, evaluating six domains: review justification, clarity of objectives, literature search methodology, inclusion of primary references, evidence-based reasoning, and data synthesis. Studies scoring ≥9/12 were considered methodologically rigorous. While this review does not present direct experimental data, it synthesizes preclinical and observational evidence to assess the hypothetical role of GluCl-like and CLIC6-mediated chloride conductance in tumor biology. The analysis integrates findings on chloride-dependent apoptotic regulation, metabolic adaptation, and the repositioning of ion channel-targeting antiparasitic drugs, establishing a foundation for future electrophysiological validation and clinical translation.

Ion channel dysregulation as a survival strategy in the tumor microenvironment: mechanisms of hypoxia, acidosis, and metabolic adaptation

The tumor microenvironment presents a dynamic and hostile landscape shaped by hypoxia, extracellular acidosis, and nutrient deprivation, all of which impose significant metabolic and survival challenges on malignant cells [8]. To withstand these stressors, cancer cells have evolved intricate adaptive mechanisms, leveraging ion channels and transporters to maintain intracellular homeostasis, sustain proliferative signaling, and evade apoptotic triggers [9]. These ion transport systems are instrumental in facilitating metabolic reprogramming, modifying cell-extracellular matrix interactions, and enabling resistance to both immune surveillance and therapeutic interventions [10].

One of the central regulators of tumor adaptation is hypoxia-inducible factor-1α (HIF-1α), a master transcriptional regulator activated under low-oxygen conditions.[11] HIF-1α orchestrates a wide range of cellular responses, including the upregulation of Na^+/H^+ exchanger 1 (NHE1), a critical acid-base regulator that extrudes protons in exchange for sodium ions [11-12]. This activity results in extracellular acidification and intracellular alkalinization, a dual process that profoundly impacts tumor progression [13]. The acidic extracellular milieu promotes local tissue remodeling by activating matrix metalloproteinases, which degrade the extracellular matrix and facilitate cancer cell invasion [14]. Simultaneously, cytosolic alkalinization enhances metabolic efficiency and inhibits caspase-dependent apoptotic pathways, thereby promoting tumor cell survival under hypoxic stress [15].

Beyond NHE1, HIF-1α also drives the expression of carbonic anhydrases (CAIX, CAXII) and monocarboxylate transporters (MCT1, MCT4), which cooperate to regulate pH homeostasis by facilitating lactate and proton efflux [16]. The persistent acidification of the tumor microenvironment exerts a profound impact on immune evasion strategies, as T-cell activation and cytotoxicity are significantly impaired under acidic conditions [17]. Additionally, acidosis has been shown to alter the polarization of tumor-associated macrophages, promoting an M2-like immunosuppressive phenotype that supports tumor progression, angiogenesis, and resistance to immunotherapy [18].

The dysregulation of chloride channels further reinforces tumor adaptation to environmental stress [19]. Volume-regulated anion channels (VRACs) and CLICs modulate apoptotic volume decrease, a process that precedes caspase activation during programmed cell death [19-20]. By tightly regulating chloride efflux and osmotic balance, these channels enable cancer cells to resist apoptotic triggers and sustain survival in hypoxic and nutrient-deprived conditions [21]. Moreover, chloride transport plays a role in intracellular signaling, affecting pathways such as PI3K/AKT, MAPK/ERK, and NF-κB, all of which are essential for oncogenic progression and therapy resistance [19, 21, 22].

Calcium channels also contribute significantly to the adaptive responses of cancer cells within the tumor microenvironment [23]. Store-operated calcium entry and transient receptor potential channels regulate intracellular Ca^{2+} dynamics, influencing cell proliferation, migration, and survival [24]. Increased calcium influx activates calmodulin-dependent kinases and phosphatases that modulate transcription factors such as NFAT, which in turn enhance the expression of oncogenes and pro-survival factors [25]. Dysregulated Ca^{2+} homeostasis also intersects with mitochondrial signaling, influencing cytochrome *c* release and oxidative phosphorylation efficiency, thereby promoting metabolic plasticity in cancer cells [26].

The role of sodium (Na^+) channels in cancer progression is increasingly recognized, particularly in highly invasive tumors [27]. Voltage-gated sodium channels have been implicated in the promotion of epithelial-to-mesenchymal transition, a process critical for metastatic dissemination [28]. By modulating intracellular Na^+ levels, these channels influence Rho-GTPase signaling, cytoskeletal reorganization, and focal adhesion turnover, all of which contribute to increased cellular motility [29]. Additionally, sodium influx has been linked to the activation of Wnt/β-catenin signaling, a pathway that sustains cancer stemness and enhances resistance to chemotherapeutic agents [30].

Taken together, ion channels serve as key mediators of tumor cell adaptation, enabling malignant cells to thrive despite the adverse conditions imposed by hypoxia, acidosis, and nutrient deprivation. By regulating intracellular pH, apoptosis resistance, and invasive potential, these channels not only facilitate tumor progression but also represent promising targets for novel therapeutic interventions aimed at disrupting the ionic homeostasis that cancer cells depend upon for survival.

Glutamate-gated chloride channels (glucl) in parasites: molecular mechanism and functional significance

GluCl channels are specialized ligand-gated ion channels that are unique to invertebrates, playing a central role in neuromuscular regulation, synaptic inhibition, and osmoregulation in parasitic nematodes and arthropods. These Cys-loop receptors, structurally related to GABA; A and glycine receptors, function as chloride-selective ion channels that mediate inhibitory neurotransmission. Their activity is crucial for maintaining parasite locomotion, feeding, and host attachment, making them indispensable for survival and an attractive target for antiparasitic pharmacotherapy [6].

At the molecular level, GluCl channels function as pentameric transmembrane proteins, each subunit containing an extracellular ligand-binding domain, four transmembrane helices (TM1–TM4), and an intracellular domain critical for channel gating. The binding of L-glutamate to the ligand-binding domain induces a conformational shift in the transmembrane helices, leading to the opening of the ion-conducting pore. This allows an influx of chloride ions into the neuronal or muscular cytoplasm, resulting in membrane hyperpolarization and subsequent inhibition of action potential propagation [31].

Role of GluCl channels in neuromuscular and osmoregulatory homeostasis

GluCl-mediated chloride conductance serves as a key modulator of neuromuscular excitability in parasitic nematodes. The influx of Cl^- through these channels suppresses excitatory neurotransmission by counteracting the depolarizing effects of cationic influx through nicotinic acetylcholine receptors (nAChRs). This mechanism is essential for regulating motor coordination, rhythmic locomotion, and pharyngeal pumping, all of which are critical for parasite survival within the host environment. Beyond neuronal inhibition, GluCl channels are implicated in osmotic homeostasis, particularly in parasitic filariae. By controlling intracellular chloride

levels, these channels contribute to fluid balance, ionic equilibrium, and cellular turgor pressure, mechanisms that are vital for parasite adaptation to fluctuating host environments. Disrupting these processes through GluCl channel inhibition leads to cellular swelling, lysis, and metabolic collapse, further augmenting the lethality of pharmacological agents that target this pathway [32].

GluCl channels as targets for anthelmintic therapy: pharmacological implications

GluCl channels represent the primary molecular targets for avermectin-based anthelmintics, including ivermectin, selamectin, and moxidectin, which function as positive allosteric modulators of these receptors. These macrocyclic lactones bind to distinct hydrophobic pockets within the transmembrane helices (TM3–TM4 interface), stabilizing the open-state conformation of the channel. This results in sustained chloride influx, prolonged membrane hyperpolarization, and irreversible neuromuscular paralysis, ultimately leading to parasite death [33]. The pharmacodynamic effects of GluCl channel modulators extend beyond neuromuscular inhibition to modulation of immune evasion mechanisms. In filarial parasites, the suppression of motor function impairs their ability to evade innate immune effectors, such as macrophages and eosinophils, facilitating immune-mediated clearance [34]. Additionally, disruption of chloride homeostasis compromises parasite antioxidant defenses, rendering them more susceptible to reactive oxygen species (ROS) and nitric oxide-mediated cytotoxicity from host immune cells [35].

The specificity of GluCl channels to invertebrates confers a high therapeutic index, minimizing neurotoxicity in mammalian hosts due to the absence of homologous receptors in vertebrate nervous systems. This selective toxicity has been a cornerstone of anthelmintic drug development, allowing for broad-spectrum efficacy against a range of parasitic infections [6].

Broader implications: could GluCl-like channels exist in mammalian pathophysiology?

While GluCl channels are classically considered absent in vertebrates, the existence of functionally analogous chloride channels in mammalian cells remains an open question. Certain chloride transport mechanisms, such as VRACs and CLICs, share functional and pharmacological similarities with GluCl channels, raising intriguing hypotheses regarding their potential role in regulating ionic balance in pathological conditions such as cancer [19]. Given the reliance of cancer cells on pH homeostasis, ionic adaptation, and metabolic reprogramming [36], it is plausible that GluCl-like channels if present could contribute to tumor cell survival under metabolic stress. Understanding the structural and functional properties of GluCl channels has not only advanced the field of parasitology but has also paved the way for potential cross-disciplinary insights into ion channel dysregulation in human diseases. The exploration of GluCl-like mechanisms in mammalian pathophysiology, particularly in tumor microenvironments, could open new avenues for targeted ion channel therapeutics in oncology.

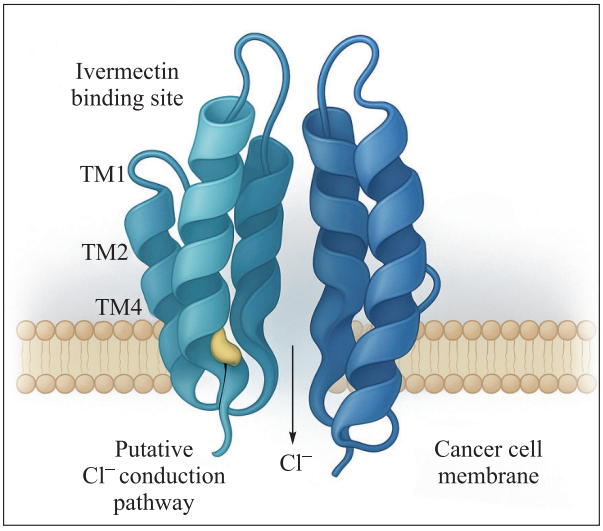
Hypothesis: do cancer cells possess GluCl-like channels?

Although GluCl channels have not been identified in vertebrates, growing evidence suggests the potential existence of functionally analogous chloride channels in cancer cells that may contribute to tumor progression and microenvironmental adaptation. One compelling piece of evidence supporting this hypothesis is the elevated extracellular glutamate levels observed in numerous malignancies [37], particularly in glioblastoma multiforme [38], triple-negative breast cancer, and pancreatic adenocarcinoma [39]. The abnormal accumulation of glutamate in the tumor microenvironment results from the dysregulated activity of system X_c^- (SLC7A11/SLC3A2), a cystine/glutamate antiporter that extrudes glutamate in exchange for cystine, promoting oxidative stress resistance and fueling tumorigenic pathways [40]. Excess extracellular glutamate in these tumors activates multiple oncogenic signaling cascades, including PI3K/AKT/mTOR, Wnt/β-catenin, and ERK/MAPK, all of which drive proliferation, migration, and resistance to apoptosis [41]. Given that GluCl channels in invertebrates function as glutamate-gated inhibitory chloride conductors, the persistent presence of high glutamate concentrations in cancer raises the possibility that cancer cells may express chloride channels that respond to glutamate similarly to GluCl channels, potentially regulating ionic homeostasis, intracellular signaling, and tumor cell excitability under metabolic and hypoxic stress [6-19].

Structural and functional similarities between GluCl and cancer-associated chloride channels

While no direct genetic or proteomic evidence has confirmed the presence of GluCl channels in mammalian cells, functionally similar chloride-conducting pathways have been identified in tumors, further supporting the hypothesis of a GluCl-like channel subclass. Among these, VRACs and CLICs share key physiological roles with GluCl channels, particularly in osmotic balance, apoptotic volume decrease, and intracellular pH regulation

[19]. VRACs, primarily composed of LRRC8A-E subunits, mediate chloride and organic osmolyte flux in response to cell swelling, a process critical for maintaining volume homeostasis in both physiological and pathological conditions [42]. In cancer, VRAC activity is frequently dysregulated to counteract apoptotic triggers, allowing tumor cells to evade programmed cell death and sustain survival under mechanical and metabolic stress [43]. Similarly, CLIC family proteins, including CLIC1, CLIC4, and CLIC5, exhibit both cytosolic and membrane-localized chloride channel activity, modulating NF-κB, STAT3, and HIF-1α signaling pathways, all of which are implicated in tumorigenesis, inflammation, and resistance to oxidative stress [44]. Another cancer-associated chloride channel with functional parallels to GluCl channels is anoctamin 1 (ANO1/TMEM16A), a calcium-activated chloride channel that is overexpressed in multiple cancers and has been linked to EGFR-dependent proliferation, epithelial-to-mesenchymal transition, and chemoresistance mechanisms [45]. Given their roles in ion transport, tumor adaptation, and interaction with oncogenic pathways, these channels may serve as functional analogs of GluCl channels, suggesting the presence of an as-yet-uncharacterized chloride conductance mechanism that supports cancer cell survival and progression (Fig. 1).



Tumor acidosis and the need for chloride ion regulation

The tumor microenvironment is characterized by persistent extracellular acidosis, primarily driven by the metabolic shift towards aerobic glycolysis (Warburg effect) and the hyperactivation of monocarboxylate transporters (MCT1, MCT4), which mediate lactate and proton efflux [46]. This metabolic adaptation results in a pronounced extracellular pH gradient, with the tumor microenvironment becoming acidic (pH 6.2–6.8) while intracellular pH remains neutral-to-alkaline (pH 7.2–7.4), thereby supporting tumor cell viability and therapy resistance [47]. To counteract acidosis and maintain intracellular pH homeostasis, cancer cells depend on multiple ion transport mechanisms, including NHE1, CAIX, and chloride channels, which facilitate charge compensation and acid-base equilibrium [48]. NHE1 extrudes protons in exchange for sodium, contributing to extracellular acidification while preserving cytosolic alkalinization, a process that enhances metastatic potential through the activation of pH-sensitive proteases such as matrix metalloproteinases [49]. Similarly, CAIX catalyzes the reversible hydration of carbon dioxide to bicarbonate and H^+, further supporting intracellular alkalinization and buffering tumor cells against acidosis-induced apoptosis [50]. Given the essential role of chloride flux in charge balance and cellular pH regulation, the presence of a GluCl-like chloride conductance in cancer cells could provide a crucial

Fig. 1. *Conceptual model of a GluCl-like chloride channel in the cancer cell membrane as a potential ivermectin-binding site*

This schematic illustrates a hypothetical chloride channel inspired by the structural principles of invertebrate GluCl channels and mammalian CLIC6 proteins, proposed to mediate chloride influx in tumor cells. The model depicts the channel embedded within the lipid bilayer and the flow of chloride ions (arrow) across it, representing a novel, unconfirmed but biophysically plausible mechanism of ionic dysregulation with potential therapeutic relevance in oncology.

Рис. 1. *Концептуальная модель GluCl-подобного хлоридного канала в мембране опухолевой клетки как потенциального сайта связывания ивермектина*

Данная схема иллюстрирует гипотетический хлоридный канал, созданный на основе структурных принципов каналов GluCl беспозвоночных и белков CLIC6 млекопитающих; предполагается, что он опосредует поступление ионов хлора в опухолевые клетки. Модель изображает канал, встроенный в липидный бислой, и поток через него хлорид-ионов (стрелка), представляя собой новый, неподтвержденный, но биофизически обоснованный механизм ионной дисрегуляции, имеющий потенциальную терапевтическую перспективность в онкологии.

adaptive mechanism, allowing tumor cells to fine-tune intracellular pH, mitigate oxidative stress, and maintain ionic equilibrium under hypoxic and metabolically stressed conditions.

Potential experimental evidence

Although no direct transcriptomic or proteomic confirmation of GluCl-like channels in cancer cells currently exists, multiple indirect lines of evidence support their potential presence. Electrophysiological studies have identified aberrant chloride currents in tumor cells that do not correspond to known chloride channel families, suggesting the existence of uncharacterized chloride conductances that may function analogously to GluCl channels. Among these, CLICs represent a compelling candidate family, as they can exist in both soluble and transmembrane forms, allowing for dynamic regulation of chloride homeostasis. Recent studies on CLIC6, the latest identified member of this family, have implicated its involvement in multiple malignancies, including breast, ovarian, lung, gastric, and pancreatic cancers. Notably, CLIC6 has been shown to interact with dopamine D(2)-like receptors, hinting at a broader role in cellular signaling beyond ion transport. While its soluble structure has been resolved, its exact physiological function, membrane conformation, and biophysical properties remain largely uncharacterized. Electrophysiological analysis using a patch-clamp approach has demonstrated that ectopically expressed CLIC6 localizes to the plasma membrane of HEK-293 cells, where it preferentially conducts chloride (Cl^-) over other anions such as bromide, fluoride, and potassium.

Additionally, CLIC6 activity is modulated by pH and redox potential, with specific histidine (H648) and cysteine (C487) residues playing key roles in its conformational regulation. Importantly, qRT-PCR data reveal that CLIC6 is highly expressed in the lung and brain, and chloride currents attributed to CLIC6 have been recorded in lung epithelial cells. Given its expression in multiple cancers and its confirmed chloride channel activity, CLIC6 represents a strong candidate for further investigation into GluCl-like chloride conductance in tumors, potentially providing a new avenue for targeted ion channel modulation in oncology [51]. High-throughput RNA sequencing and mass spectrometry analyses of various tumor types have revealed an upregulation of chloride channel-related genes, particularly those encoding VRACs, CLICs, and calcium-activated chloride channels, many of which exhibit functional convergence with ligand-gated chloride channels [51]. Drug sensitivity assays have demonstrated that ivermectin and other GluCl-targeting anthelmintics exert potent anticancer effects in multiple tumor models, raising the possibility that their mechanism of action may involve chloride channel modulation (Table) [52].

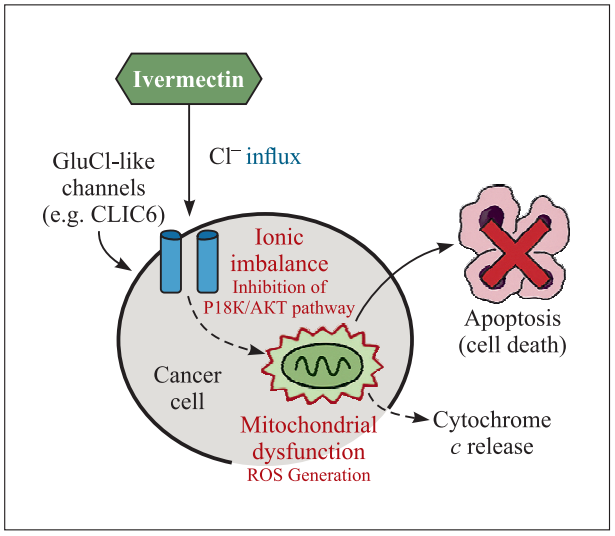
A comparative summary of GluCl channel characteristics in parasites and GluCl-like channels in cancer cells, such as CLIC6

Сравнительное обобщение характеристик глутамат-регулируемых хлоридных каналов (GluCl) у паразитов и GluCl-подобных каналов в опухолевых клетках, таких как CLIC6

Feature	GluCl channels in parasites	GluCl-like channels in cancer cells (e.g., CLIC6)
Molecular identity	Well-characterized GluCl subunits (e.g., in C. elegans, H. contortus)	Putative identity; CLIC family proteins (particularly CLIC6)
Ligand activation	Activated by extracellular L-glutamate	Not confirmed; hypothesized sensitivity to glutamate-rich tumor microenvironment
Ion selectivity	Highly selective for Cl^-	Selective for Cl^-; CLIC6 shows chloride over bromide, fluoride, and potassium
Localization	Expressed in neuronal and muscular membranes	CLIC6 localized to plasma membrane and cytosol in cancer cells
Physiological function	Inhibition of neuromuscular excitation, osmoregulation	Regulation of cell volume, redox balance, and apoptotic signaling
Pharmacological target	Primary target of ivermectin and other macrocyclic lactones	Potential target of ivermectin; mechanism remains under investigation
Electrophysiological profile	Well-defined chloride current upon glutamate stimulation	Patch-clamp studies confirm chloride conductance and modulation by pH/redox in CLIC6
Expression in human tissues	Absent	CLIC6 overexpressed in various malignancies (breast, lung, ovarian, gastric, pancreatic)
Relevance to cancer biology	Not applicable	Implicated in tumor cell survival, mitochondrial function, immune evasion, and drug resistance

Antiparasitic drugs as potential cancer therapeutics

The repositioning of antiparasitic agents has shown promise in oncology, owing to their ability to disrupt tumor homeostasis via ion channel modulation, metabolic interference, and apoptosis induction. Originally developed to target parasite-specific channels like GluCl, drugs such as ivermectin, moxidectin, mebendazole, and albendazole have demonstrated cytotoxicity in cancer cells, suggesting a shared vulnerability in chloride ion regulation [53]. Ivermectin enhances GluCl channel activation in nematodes, causing chloride influx and paralysis [54]. In cancer, it increases chloride conductance, disrupts ionic balance, and impairs survival by inhibiting PI3K/AKT and Wnt/β-catenin pathwayskey regulators of proliferation, metastasis, and resistance [55, 56]. Additionally, ivermectin induces mitochondrial dysfunction and ROS generation, promoting apoptosis [57]. Structurally related to ivermectin, moxidectin disrupts tumor ion homeostasis and induces oxidative stress through chloride influx, leading to mitochondrial depolarization, cytochrome *c* release, and apoptosis (Fig. 2) [58–60]. Its ROS-mediated DNA damage is particularly effective against tumors with TP53 mutations or NRF2 overactivity, triggering p53-independent apoptosis and ferroptosis [61]. These benzimidazole anthelmintics target chloride transport and mitochondria, impairing apoptotic volume decrease, enhancing caspase activation, and causing cell cycle arrest [62–63]. By inhibiting succinate dehydrogenase, they deplete ATP and disrupt AMPK signaling, sensitizing cancer cells to metabolic collapse and improving response to therapy [64].



Future directions: GluCl-like channels as a novel therapeutic target in cancer

Given the emerging evidence suggesting the existence of GluCl-like chloride conductance in cancer cells, we propose the designation of these putative ion channels as “GluCl-like channels”, acknowledging their potential role in tumor biology and ionic regulation. The characterization of these channels could pave the way for innovative targeted therapies aimed at disrupting chloride homeostasis, modulating tumor metabolism, and sensitizing cancer cells to apoptotic signals. To validate their existence and therapeutic relevance, future research should focus on genetic, functional, and clinical investigations that comprehensively explore their molecular identity, physiological function, and pharmacological modulation.

Fig. 2. *Proposed antitumor mechanism of ivermectin via GluCl-like chloride channels (e.g., CLIC6) in cancer cells.*

This schematic illustration outlines a hypothetical pathway by which ivermectin exerts cytotoxic effects on malignant cells. The process begins with ivermectin binding to GluCl-like channels, facilitating chloride ion influx, which disrupts ionic homeostasis and induces intracellular ionic imbalance. This imbalance is proposed to inhibit the PI3K/AKT signaling cascade and promote mitochondrial dysfunction, evidenced by increased ROS generation and cytochrome c release. The cumulative effect leads to the activation of intrinsic apoptotic pathways and subsequent cancer cell death. The diagram emphasizes the potential of targeting chloride channels as a novel strategy in oncologic pharmacotherapy

Рис. 2. *Предполагаемый противоопухолевый механизм действия ивермектина через хлоридные каналы типа GluCl (например, CLIC6) в опухолевых клетках.*

На данной схеме представлена гипотетическая последовательность событий, посредством которой ивермектин проявляет цитотоксическое действие на злокачественные клетки. Начальный этап включает связывание ивермектина с GluCl-подобными каналами, что способствует поступлению ионов хлора в клетку и нарушению ионного гомеостаза, которое предположительно приводит к ингибированию сигнального каскада PI3K/AKT и дисфункции митохондрий, сопровождающейся повышенной генерацией активных форм кислорода и выходом цитохрома с. Совокупность этих нарушений активирует внутренний путь апоптоза и приводит к гибели опухолевых клеток. Диаграмма подчеркивает перспективность таргетной модуляции хлоридных каналов как инновационной стратегии в противоопухолевой фармакотерапии

Genetic and proteomic profiling of GluCl-like channels in cancer

Unraveling the molecular identity of GluCl-like channels requires high-throughput genomic and transcriptomic analyses to identify chloride channel subunits with homology to known GluCl proteins. Advanced RNA sequencing, single-cell transcriptomics, and CRISPR-based genetic screening should be employed to pinpoint candidate genes encoding ligand-gated chloride channels in various tumor types. Comparative proteomic and interactome analyses can further elucidate their structural composition, post-translational modifications, and potential interactions with oncogenic signaling pathways such as PI3K/AKT, Wnt/β-catenin, and NF-κB. Additionally, bioinformatics approaches integrating The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) databases may reveal correlations between chloride channel expression and cancer progression, prognosis, and therapy resistance.

Functional characterization and pharmacological targeting of GluCl-like channels

To establish the role of GluCl-like channels in tumor biology, electrophysiological studies using patch-clamp recordings and fluorescence-based ion imaging should be conducted to measure chloride conductance in cancer cells under different metabolic and microenvironmental conditions. The use of genetically encoded chloride sensors (clomeleon, Cl-sensor) in live-cell imaging could provide real-time insights into their physiological activity. Functional assays assessing the effects of selective chloride channel inhibitors, such as DIDS (4,4′-diisothiocyanostilbene-2,2′-disulfonic acid) and IAA-94 (indanyloxyacetic acid-94), may help delineate their contribution to tumor cell proliferation, apoptosis evasion, and chemoresistance. Furthermore, CRISPR-Cas9 knockout and siRNA knockdown studies targeting putative GluCl-like genes can validate their essentiality in tumor survival and metastatic potential.

Clinical translation: investigating antiparasitic drugs in oncology

The potential role of GluCl-like channels in mediating the anticancer effects of antiparasitic drugs warrants rigorous clinical evaluation. Phase I/II clinical trials should investigate the efficacy of ivermectin, moxidectin, and benzimidazole derivatives in various malignancies, particularly in tumors with high extracellular glutamate levels and chloride channel dysregulation. Biomarker-driven clinical studies should explore whether GluCl-like expression correlates with treatment response, enabling the stratification of patient populations most likely to benefit from chloride channel-targeting therapies. Moreover, combination strategies integrating GluCl channel modulators with immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1) or metabolic inhibitors (e.g., dichloroacetate, metformin) could enhance therapeutic efficacy by exploiting tumor ionic vulnerabilities and immune evasion mechanisms.

Future perspective and proposed nomenclature

Should future experimental studies validate the existence of these GluCl-like channels in cancer cells, it would constitute a landmark discovery in the field of ion channel oncology. Such a discovery would redefine our understanding of chloride conductance mechanisms in tumor biology and open avenues for novel targeted therapies. In recognition of the original hypothesis presented in this review, the authors humbly propose that this novel chloride-conducting entity be designated as the "Akl channel", acknowledging the conceptual framework that laid the foundation for its theoretical identification.

Discussion

The hypothesis that cancer cells may harbor GluCl-like chloride channels introduces a novel perspective on tumor ion homeostasis, metabolic plasticity, and pharmacological vulnerabilities. While classical GluCl channels are exclusive to invertebrates, emerging evidence suggests that CLICs, particularly CLIC6, may serve as functionally analogous chloride conductances in human malignancies. CLIC6 has been identified in multiple cancers, including breast, ovarian, lung, gastric, and pancreatic malignancies, and has been shown to localize to the plasma membrane, where it exhibits chloride selectivity. Its regulation by pH and redox potential, along with its interaction with dopamine D_2-like receptors, suggests a broader role in oncogenic signaling. The presence of such chloride-conducting mechanisms raises the question of whether they contribute to tumor survival, proliferation, and immune evasion. Given the documented anticancer activity of GluCl-targeting antiparasitic agents, such as ivermectin, their cytotoxicity may extend beyond their established role in parasitic neuromuscular inhibition to tumor-specific ionic dysregulation. At the molecular level, ivermectin functions as a positive allosteric modulator of GluCl channels, promoting sustained chloride influx and hyperpolarization in parasitic cells, leading to neuromuscular paralysis. In cancer cells, a similar chloride-dependent mechanism could disrupt ionic equilibrium, impair volume regulation, and trigger apoptosis.

If CLIC6 or another unidentified GluCl-like channel mediates chloride influx, this could destabilize intracellular electrochemical gradients, suppress mitogenic signaling pathways, and induce metabolic collapse. This chloride-mediated perturbation has direct implications for oncogenic pathways such as PI3K/AKT, Wnt/β-catenin, and NF-κB, all of which are sensitive to changes in ionic balance and redox homeostasis.

One of the critical downstream effects of ivermectin-induced chloride dysregulation is mitochondrial dysfunction. Excessive chloride influx could promote mitochondrial depolarization, leading to permeability transition pore opening, cytochrome *c* release, and caspase activation, ultimately inducing apoptotic cell death. Furthermore, mitochondrial hyperpolarization has been linked to increased ROS generation, amplifying oxidative stress and further sensitizing tumor cells to apoptosis. This oxidative imbalance is particularly detrimental in cancer cells with already compromised antioxidant defenses, such as those with TP53 mutations or Nrf2 hyperactivation.

Additionally, ivermectin has been shown to disrupt tumor metabolism by interfering with glucose and lipid homeostasis. It has been demonstrated to inhibit the glucose transporter GLUT1, reducing glycolytic flux and ATP production, which is particularly relevant for highly glycolytic tumors relying on the Warburg effect. The convergence of ionic stress, metabolic disruption, and oxidative damage creates a multifaceted cytotoxic environment that compromises tumor adaptability. Beyond direct cytotoxicity, ivermectin's chloride-mediated effects may also modulate the tumor microenvironment. Acidic extracellular pH, a hallmark of aggressive tumors, is maintained through ion transporters such as NHE1, MCT1, and CAIX, all of which contribute to immune evasion and metastatic potential. If ivermectin disrupts chloride flux through a GluCl-like channel, such as CLIC6, it could interfere with pH regulation, impairing tumor cell survival in acidic niches and enhancing immune recognition by restoring T-cell cytotoxicity. Collectively, these mechanisms suggest that the anticancer effects of ivermectin may be fundamentally linked to chloride channel dysregulation, providing a mechanistic framework for its repositioning in oncology. Further research should focus on the electrophysiological characterization of CLIC6 and other chloride conductances in cancer, transcriptomic analyses to confirm their role, and clinical validation of ivermectin's efficacy in tumors exhibiting chloride ion dependence. Unraveling these ionic vulnerabilities could pave the way for targeted chloride channel modulation as a novel therapeutic strategy in cancer treatment.

Conclusions

The concept of GluCl-like chloride conductance in cancer cells represents a paradigm shift in our understanding of tumor ion homeostasis and its role in disease progression and therapy resistance. If validated, these channels could serve as a novel ionic checkpoint, enabling tumors to regulate pH, evade apoptosis, and sustain metabolic adaptation under hypoxic and acidic conditions. The unexpected anticancer effects of GluCl-targeting antiparasitic drugs suggest a potential pharmacological strategy to disrupt chloride-dependent tumor survival mechanisms. While current evidence remains largely indirect, the structural and functional parallels between GluCl and cancer-associated chloride channels warrant further genomic, proteomic, and electrophysiological investigations. Exploring these channels as therapeutic targets could transform oncology drug development, offering new avenues for precision medicine. Future research should prioritize the clinical translation of antiparasitic agents, evaluate their synergistic potential with immune checkpoint inhibitors and metabolic disruptors, and establish biomarker-driven patient selection criteria. By integrating cancer ion channel research with parasitology and neuropharmacology, this emerging hypothesis could redefine targeted cancer therapies, unveiling new opportunities to disrupt tumor ionic homeostasis and enhance therapeutic efficacy.

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