Trends in Molecular Medicine

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Review

Could venom-derived therapeutics resolve treatment resistance in refractory EAC?

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The incidence of esophageal adenocarcinoma is rising in Western countries. Despite advances in chemotherapy and immunotherapy, the prognosis remains poor, with an overall 5-year survival rate below 15%. A major challenge is the cancer's poor and often unpredictable response to current treatments. Animal venoms represent a promising yet underexplored source of therapeutic agents, offering millions of structurally diverse and highly potent bioactive peptides that can modulate a wide array of molecular targets. However, only a small fraction of these peptides has been pharmacologically characterized. This review presents the therapeutic potential of venom-derived peptides in cancer treatment, summarizes the role of ion channels in esophageal adenocarcinoma (EAC), and discusses peptides targeting ion channels that may offer new opportunities for future EAC treatment.

Highlights

Esophageal adenocarcinoma remains highly refractory, highlighting the urgent need for target-driven strategies beyond conventional cytotoxic therapies.

Convergent transcriptomic evidence identifies ion channel remodeling as a mechanistic hallmark and potential vulnerability in esophageal adenocarcinoma.

Venom-derived peptides, already validated in other clinical indications, provide evolutionarily optimized and highly selective modulators of ion channels.

Target-aligned engineering and rational combination strategies may transform venomics into a precise therapeutic avenue for esophageal adenocarcinoma.

Harnessing venoms to tackle treatment resistance in esophageal adenocarcinoma

Esophageal cancer is associated with high mortality and poor prognosis, with a 5-year survival rate ranging from 5 to 15% [1], largely due to diagnosis at advanced clinical stages. Although esophageal squamous cell carcinoma (ESCC) remains the most prevalent subtype worldwide, its incidence has declined over the past 4 decades, whereas esophageal adenocarcinoma (EAC) has become predominant in developed countries [2]. EAC responds poorly to chemotherapy and radiotherapy, and clinical responses to **immunotherapy** (see Glossary), alone or in combination, remain heterogeneous. Even with multimodal treatment strategies, long-term survival remains limited, underscoring an urgent need for innovative therapeutic strategies capable of addressing treatment resistance and disease heterogeneity.

Animal venoms are complex mixtures of bioactive molecules that have evolved to interact with defined molecular targets, including ion channels and G protein-coupled receptors (Box 1). Despite an estimated 40 million distinct toxins across more than 220 000 venomous species [7], fewer than 5000 have been pharmacologically characterized. Recent advances in **omics** technologies and mass spectrometry have enabled systematic venom exploration, giving rise to venomics [8]. This review article examines venomics as a discovery platform for oncology, with a specific focus on EAC, highlighting ion channels as emerging molecular vulnerabilities and discussing venom-derived peptides that modulate these targets.

The key challenges in treating EAC

Barrett's esophagus (BE) is the only known premalignant precursor to EAC. Although the likelihood of progression from nondysplastic BE to invasive adenocarcinoma is relatively low, this risk rises significantly once dysplasia develops. Progression rates are estimated at approximately 1–13% for low-grade dysplasia and may reach up to 20% in cases of high-grade dysplasia [9]. Notably, approximately 95% of patients with EAC do not have a prior diagnosis of BE, and

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Box 1. Venom composition

Venomous animals are found across a wide range of taxa and habitats [3]. Venoms are composed of hundreds to thousands of biologically active molecules, depending on species. The active components of venoms are primarily peptides and proteins, although various enzymes such as L-amino oxidases, phospholipases A_2, proteinases, acetylcholinesterases, and hyaluronidases are also commonly present. In addition to proteins, venoms contain nonproteinaceous compounds, including salts, amino acids, and lipids. Venom composition is highly species-specific, and even within a species, geographic variations have been observed. As a result, the proportions of venom components can vary significantly.

In snake venoms, four primary and six secondary protein families have been identified [4]. The main families include phospholipases A_2, metalloproteinases, serine proteases, and three-finger toxins. Phospholipases A_2 are found in nearly all snake species, whereas other components, such as defensins, tend to be more species-specific.

Scorpion venom-derived peptides fall into two broad categories: those with disulfide bridges and those without [5]. The disulfide-rich peptides are further subclassified based on their molecular targets, such as sodium, potassium, or calcium ion channels. The nondisulfide peptides include short antimicrobial peptides and bradykinin-potentiating peptides.

Spider venoms, like those of scorpions, are rich in disulfide-containing peptides. These toxins primarily target ion channels, particularly VGSCs and VGCCs [6].

most cases are diagnosed at an advanced stage (T3–T4 based on the **cTNM** staging system), thereby limiting curative treatment options. Only a few candidates are eligible for endoscopic resection, while others require chemoradiotherapy and surgery. Patient responses to chemotherapy, chemoradiotherapy, and immunotherapy are highly variable. Neoadjuvant and perioperative treatments can increase postoperative complications and mortality. The effectiveness of immunotherapy is often limited to programmed death-ligand 1 (PD-L1)-positive tumors, with uncertain benefit in others. For locally advanced, nonoperable, or metastatic EAC, several **targeted therapies** have been approved, including trastuzumab, trastuzumab–deruxtecan, ramucirumab, zolbetuximab, nivolumab, and pembrolizumab [10]. Despite targeting multiple pathways [human epidermal growth factor receptor 2 (HER2), PD-L1, vascular endothelial growth factor receptor 2 (VEGFR2), and Claudin 18.2], resistance often develops, and many patients lack actionable mutations. There is a critical need for better biomarkers to guide therapy choices and predict treatment responses. Even with aggressive multimodal therapy, long-term survival remains low, with an overall 5-year survival rate of 10.6% [11], highlighting the urgent need for novel treatments.

Venoms as a tool for next-generation therapies

Although the number of compounds produced through synthetic chemistry has increased fivefold since the mid-1980s, the number of FDA-approved drugs has not risen proportionally. One contributing factor is the restricted chemical diversity of contemporary drug libraries, which are largely shaped by a limited set of reaction chemistries, leading to an overrepresentation of structurally similar molecules [12]. Venom-derived peptides offer an alternative source of structurally diverse, biologically validated molecules shaped by evolutionary pressure to achieve high potency and selectivity toward defined targets, including ion channels and G protein-coupled receptors [3]. To date, 11 venom-derived drugs have reached clinical use, primarily in pain, thrombosis, and metabolic disorders [13].

Venom-derived peptides in cancer therapy

Although no venom-derived anticancer drug is currently approved, several candidates have entered clinical or late preclinical development. Crotoxin (CTX), a neurotoxic complex isolated from the venom of the rattlesnake *Crotalus durissus terrificus*, has been investigated in a Phase 1 clinical trial in patients with refractory solid tumors, administered intravenously (NCT01481532[i]). The study was expected to be completed in December 2025, and the results have not yet been published.

Glossary

Animal venom: has been defined as 'a secretion, produced in a specialized gland in an animal, and delivered to a target animal through the infliction of a wound' [3].
Channelopathy: a group of diseases caused by ion channel dysfunction.
cTNM: clinical tumor–node–metastasis staging includes determination of the depth of local invasion by the primary tumor (T), the presence and number of regional lymph nodes involved (N), and the presence or absence of distant metastasis (M).
Ferroptosis: iron-dependent programmed cell death, characterized by the accumulation of lipid reactive oxygen species.
Genome-wide association study (GWAS): a research approach used in genetics to associate specific genetic variations with diseases.
Immunotherapy: a type of cancer treatment that uses the immune system to fight cancer.
Mucin: a high molecular weight glycoprotein secreted at the surface of epithelial cells to protect the epithelium from external aggressions.
Omics: several areas of biology research, such as genomics, transcriptomics, and proteomics, are defined by the investigation of the entire complement of a specific type of biomolecule or the totality of a molecular process within an organism.
Oncogene: a mutated gene that originates from a nonmutated gene called a proto-oncogene, which has the potential to cause cancer.
Phospholipase A2: an enzyme that catalyzes the hydrolysis of the ester bond in position 2 of glycerophospholipids.
Targeted therapy: a type of cancer treatment that uses substances that target cancer cells, in contrast to chemotherapy, which kills all dividing cells. Targeted therapies are either small-molecule drugs or monoclonal antibodies.

More targeted venom-derived peptides are also progressing in clinical development. SOR-C13 is a truncated peptide derived from soricidin, found in the saliva of the northern short-tailed shrew (*Blarina brevicauda*). SOR-C13 inhibits the calcium channel Transient Receptor Potential Vanilloid 6 (TRPV6) and has completed Phase 1 clinical trials in solid tumors (NCT01578564[ii] and NCT03784677[iii]) [14]. TRPV6, when overexpressed, is linked to tumor aggressiveness, metastatic potential, and poor prognosis in multiple cancer types [15]. Although TRPV6 is expressed in the superficial layers of the esophageal epithelium, it is downregulated in ESCC, and its expression status in EAC remains unclear.

Beyond clinically advanced candidates, a broad array of venom-derived peptides from diverse animal sources has demonstrated anticancer activity in preclinical models [3]. For example, scorpion venom peptides, such as chlorotoxin and potassium channel blockers, have demonstrated inhibition of tumor cell proliferation, migration, and invasion in glioma and other solid tumor models by targeting chloride and potassium channels involved in cell volume regulation and motility [16,17]. In parallel, snake venom peptides display multifaceted anticancer effects, including membrane disruption, apoptosis induction, and metastasis inhibition, indicating that venoms can influence tumor biology through diverse mechanisms [18].

Collectively, these studies establish venoms as a reservoir of anticancer lead compounds, while also revealing a critical limitation: most candidates have been evaluated outside disease-specific molecular contexts. Aligning venom peptide targets with EAC-relevant vulnerabilities is, therefore, essential and forms the focus of the following sections.

Venom-derived peptides in esophageal cancer treatment

Several studies have evaluated venom-derived peptides in esophageal cancer, predominantly focusing on ESCC, with limited investigation in EAC (Table 1). Early studies examined CTX, which inhibited Eca-109 cell proliferation, increased apoptotic and G1-phase populations, and reduced tumor growth and angiogenesis in xenograft models [19]. Subsequent work confirmed variable cytotoxic sensitivity across ESCC cell lines (KYSE30 and KYSE270), with CTX exhibiting lower cytotoxicity than gemcitabine, a standard chemotherapeutic agent [20]. Crotoxin's mechanism relies on its **phospholipase A2** subunit, with limited tumor specificity.

Additional compounds, including toad venom bufadienolides, induce apoptosis via Na^+/K^+-ATPase inhibition in ESCC cells while sparing normal cells in some experimental settings [22]. Melittin, the major peptide of *Apis mellifera* venom, radiosensitizes ESCC cells. Melittin modulates Wnt signaling, which is implicated in the progression from BE to adenocarcinoma, but requires encapsulation to mitigate hemolytic toxicity [24–26]. Overall, these studies highlight biological activity in ESCC but have limited relevance to EAC-specific vulnerabilities.

Beyond modulating ion channels, venom-derived peptides activate a wide range of anticancer mechanisms, including membrane disruption, enzymatic hydrolysis of phospholipids, inhibition of ion pumps such as Na^+/K^+-ATPase, modulation of oncogenic signaling pathways, and induction of regulated cell death programs [16,18]. Although these mechanisms can produce potent cytotoxic effects *in vitro*, they often lack disease-specific selectivity and are associated with narrow therapeutic windows, particularly in epithelial tissues such as the esophagus. In the context of EAC, where chronic inflammation and barrier fragility already limit treatment tolerance, this nonspecific cytotoxicity represents a major obstacle to translation. In contrast, ion channel dysregulation in EAC offers a mechanistic opportunity to exploit tumor-specific dependencies, allowing venom peptides to act as precision modulators rather than broad-spectrum cytotoxic agents.

Table 1. Venom-derived molecules tested on esophageal cancer cells

Toxin used	Composition	Target	Organism	Genus, species, and subspecies	ESCC cell line	Effects	Refs
CTX	Heterodimer composed of a nontoxic and nonenzymatic component and a toxic phospholipase A2	β-neurotoxin	Snake	*C. d. terrificus*	Eca-109	- Inhibition of cell growth - Induction of apoptosis - Induction of cell cycle arrest in G1 phase - Reduction in tumor size *in vivo*	[19]
CTX			Snake	*C. d. terrificus*	KYSE30 and KYSE270	- Inhibition of cell growth	[20]
Arenobufagin	Steroid	Na^+/K^+-ATPase	Toad	*Bufo gargarizans*	Eca-109, EC9706, TE5, Hec2, and TE11	- Inhibition of cell growth - Induction of apoptosis - Reduction in tumor size *in vivo*	[21]
Bufotalin	Steroid	Na^+/K^+-ATPase	Toad	*B. gargarizans*	Eca-109, EC9706, TE5, Hec2, and TE11	- Inhibition of cell growth - Induction of apoptosis - Reduction in tumor size *in vivo*	[22]
Melittin	Peptide	Cytotoxin The positively charged amino acids enable it to pierce holes directly through cell membranes	Bee	*A. mellifera*	Eca-109 and TE13	- Increase radiosensitivity *in vitro* and *in vivo* - Radiation + melittin = increased apoptosis - Inhibition of Bax	[23]
Modified melittin: pc-telomerase reverse transcriptase (TERT)-melittin	Peptide		Bee	*A. mellifera*	TE1	- Inhibition of cell growth - Induction of apoptosis - Increase in ROS production - Inhibition of cell migration and invasion - Induction of cell cycle arrest	[24]

Venom-derived peptides targeting ion channels to advance the treatment of EAC

Ion channels are transmembrane proteins that contain an aqueous pore and regulate the exchange of specific ions. This transport requires no energy. Ion channels are classified according to the type of ion they transport (Ca^{2+} K^+, etc.) and their opening/closing mechanism (voltage, ligands, etc.) (Box 2). They are involved in ion homeostasis across membranes, which is crucial for many cellular processes, from electrical stimulation to proliferation. Some ion channels are involved in cancer processes [34,35]. Indeed, dysfunction or abnormal expression of certain ion channels can dysregulate cellular processes, leading to the transformation of a normal cell into a malignant cell [36]. For this reason, cancer has been described as a form of **channelopathy**.

Several ion channels are differentially expressed in EAC compared with normal tissue (Figure 1).

Box 2. Ion channels

Potassium (K^+) channels constitute the largest and most diverse family of ion channels and are divided into four classes: calcium-activated (K_{Ca}), voltage-gated (K_V), inwardly rectifying (K_{ir}), and tandem-pore domain (K2P) channels. Voltage-gated potassium channels are essential for membrane repolarization during action potentials and play a role in controlling membrane potential, ion homeostasis, and secretory processes [27]. Beyond excitability, K^+ channels regulate cellular processes such as proliferation, differentiation, migration, cell cycle progression, and apoptosis, contributing to oncogenic phenotypes when dysregulated [28].

Chloride (Cl^-) channels and transporters not only contribute to membrane excitability but also participate in nonexcitable cell functions, including regulation of intracellular pH, cell volume, metabolism, inflammation, apoptosis, and immune responses. Altered chloride flux can influence cytoskeletal dynamics and cell motility, and dysregulation of Cl^- channels has been linked to malignant transformation and tumor progression in epithelial cancers [29].

Calcium (Ca^{2+}) channels, classified as voltage- or ligand-gated, regulate intracellular signaling. Acting as a second messenger, Ca^{2+} controls gene transcription, cell motility, proliferation, and programmed cell death. Tight spatial and temporal regulation of Ca^{2+} signaling is essential for cellular homeostasis, and aberrant calcium influx or intracellular Ca^{2+} release can promote tumor growth, invasion, and therapy resistance [30].

VGSCs, classically associated with excitable tissues, are increasingly recognized as functional regulators in nonexcitable cancer cells. Persistent sodium currents at depolarized resting membrane potentials can influence intracellular Na^+ and Ca^{2+} homeostasis, extracellular acidification, and cytoskeletal remodeling. Aberrant expression of Na_V channel isoforms has been associated with enhanced migration, invasion, and metastatic potential in solid tumors [31].

ASICs are proton-gated, voltage-independent cation channels belonging to the epithelial sodium channel (ENaC) family. Functional ASICs assemble as homo- or heterotrimers. While predominantly studied in neuronal tissues, ASICs are increasingly implicated in cancer, where extracellular acidosis is a feature of the tumor microenvironment. In particular, ASIC1a has been linked to cancer cell proliferation, migration, and invasion through Ca^{2+}-dependent signaling pathways [32].

TRP channels represent a superfamily of nonselective cation channels, subdivided into several families including TRPA (Ankyrin), TRPC (Canonical), TRPM (Melastatin), and TRPV. TRP channels function as cellular sensors of chemical, mechanical, and thermal stimuli and regulate Ca^{2+} and Na^+ entry. In cancer, altered TRP channel expression or activity has been associated with changes in cell survival, stemness, migration, and responses to environmental stressors, underscoring their role as modulators of tumor behavior [33].

Potassium channels

In EAC, increasing evidence indicates that potassium channels are not merely passive markers of malignant transformation but actively participate in tumor biology, although their functional characterization remains less advanced than in other epithelial malignancies [37].

Among potassium channel subfamilies, members of the KCNQ (K_V7) family have recently emerged as particularly relevant in EAC. The $K_V7.1$ channels, encoded by *KCNQ1*, requires association with KCNE auxiliary subunits for full functionality. $K_V7.1$ plays a well-established role in gastric luminal pH regulation in the gastrointestinal tract when associated with KCNE2, whereas association with KCNE3 results in a constitutively active channel. In the context of EAC, *KCNQ1* is downregulated in tumor tissues, supporting a potential **tumor-suppressive** function. In contrast, *KCNQ3* is frequently overexpressed and hypermutated in EAC and displays multiple hallmarks of an **oncogene** [38]. Functional studies indicate that *KCNQ3* overexpression promotes cell proliferation and is often accompanied by coamplification of the *MYC* locus, positioning it as an indirect therapeutic target in a disease where *MYC* itself remains largely undruggable. Moreover, *KCNQ3* has been implicated in Wnt signaling regulation, a pathway central to EAC pathogenesis [39]. Interestingly, specific genomic alterations in KCNQ3 may preferentially enhance noncanonical Wnt signaling, potentially reducing metastatic dissemination, highlighting the context-dependent complexity of its functional impact [38]. Collectively, these findings support KCNQ3 as a more plausible potassium channel target in EAC than KCNQ1. However, its systemic inhibition raises substantial cardiac safety concerns, limiting its therapeutic attractiveness.

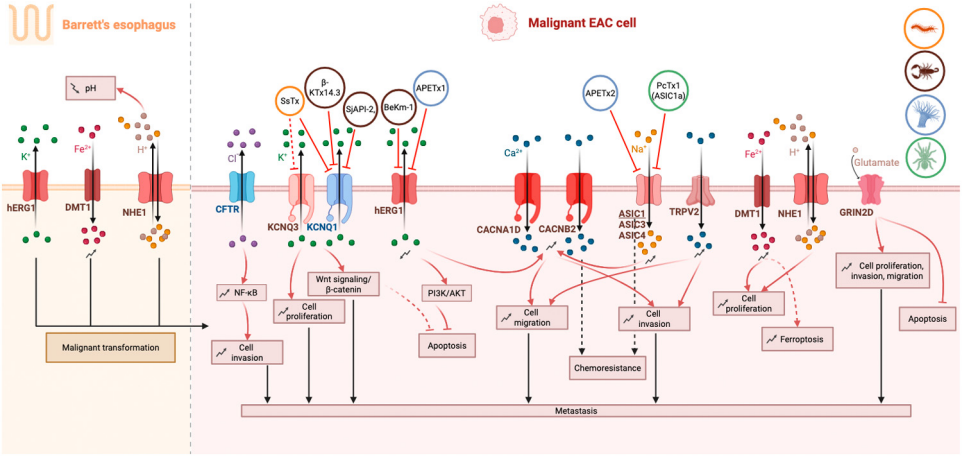

Figure 1. Ion channel remodeling and venom-derived peptides in Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC). Schematic representation of ion channel dysregulation during progression from BE to malignant EAC. Remodeling of K^+, Ca^{2+}, Na^+, Cl^-, and metal transport pathways integrates bioelectric signaling, Ca^{2+} dynamics, pH control, and iron metabolism to drive proliferation, invasion, chemoresistance, and metastasis. Venom-derived peptides selectively inhibit several of these channels, exposing actionable vulnerabilities in EAC. Channels shown in shades of red are upregulated; channels in shades of blue are downregulated. Solid lines indicate experimentally supported mechanisms, whereas dotted lines represent proposed links. This figure was drawn using BioRender (www.biorender.com). ASIC1/3/4: acid-sensing ion channel 1/3/4; CFTR: cystic fibrosis transmembrane conductance regulator.

Other potassium channels, notably those of the K_V1 and the human Ether-à-go-go-Related Gene (hERG, KCNH2) families, are also thought to be overexpressed in cancers of the esophagus and upper digestive tract, where they have been associated with increased proliferation and survival, although their direct functional validation in EAC remains limited. $K_V11.1$ (hERG1) is well known for its implication in long QT syndrome when deficient [38]. Indeed, this channel mediates the hyperpolarizing K^+ current underlying the cardiac action potential repolarization, making it essential for normal cardiac physiology. Consequently, pharmacological modulation of hERG channels can lead to QT interval prolongation and potentially severe arrhythmias, which represent a major constraint when considering this channel in therapeutic strategies [40]. Beyond its physiological role in the heart, hERG1 has been reported to be under- or overexpressed in many types of human cancers [41]. Interestingly, hERG1 is overexpressed in BE and EAC and is associated with malignant progression to EAC. This suggests that hERG1 may be a biomarker to identify patients whose BE lesions will progress to EAC [42]. Although functional studies directly linking hERG activity to oncogenic processes in EAC are still limited, data from other epithelial cancers support a role in regulating proliferation, survival, and cellular signaling, supporting further investigation in EAC-specific models [40,41].

Mechanistically, potassium channels in EAC are likely to contribute to tumor progression through both conductance-dependent effects, by shaping membrane polarization and calcium influx, and nonconductive roles involving interactions with oncogenic signaling pathways such as phosphatidylinositol 3'-kinase(PI3K)-Akt, MAPK (Mitogen-activated protein kinases), and Wnt. Nevertheless, important limitations remain. Most available data rely on bulk transcriptomic analyses, with relatively limited validation at the protein and electrophysiological levels in patient-derived samples. In addition, functional studies employ pharmacological inhibitors with suboptimal subtype selectivity, complicating the attribution of observed phenotypes to individual channels.

Several peptides have been identified as inhibitors of potassium channels relevant to EAC. The Ssm Spooky Toxin (SsTx), isolated from the venom of the golden-headed centipede *Scolopendra*

subspinipes mutilans, inhibits KCNQ channels, with a particular affinity for KCNQ1 [43]. More recently, the β-KTx14.3 toxin from the scorpion *Lychas mucronatus* inhibits approximately 50% of the KCNQ1 current at micromolar concentrations (22 μM) [44]. SjAPI-2, from *Scorpiops jendeki*, represents the first Ascaris-type fold peptide reported to inhibit KCNQ1, further expanding the diversity of venom-derived KCNQ modulators [45]. In parallel, BeKm-1, from *Buthus eupeus*, and APETx1, from the sea anemone *Anthopleura elegantissima*, exhibit high specificity toward hERG1 without affecting other potassium channels [46]. Additional peptides from sea anemone, sea snail, and scorpion venoms have since been reported to modulate hERG channel activity [46–49].

However, structural similarity does not necessarily translate into functional equivalence. APETx2, despite sharing 76% sequence homology and a similar three-dimensional structure with APETx1, selectively targets acid-sensing ion channel 3 (ASIC3) rather than potassium channels [50]. At higher concentrations, APETx2 can also inhibit several voltage-gated sodium channels (VGSCs)—Nav1.2, Nav1.6, and Nav1.8—highlighting potential issues of selectivity and off-target effects [51]. More broadly, many venom-derived peptides, including Hcr1b toxins from *Heteractis crispa*, PcTx1 from *Psalmopoeus cambridgei*, Hi1a from *Hadronyche infensa*, and mambalgins from *Dendroaspis* species, primarily target ASIC channels rather than potassium channels [48,50,52–56]. While these toxins exhibit anticancer activity in several solid tumor models, their relevance to EAC remains indirect at present [57,58].

Taken together, venom-derived potassium channel inhibitors provide valuable molecular probes and promising lead structures to explore ion channel dependencies in EAC. However, a major gap remains between channel inhibition and demonstrated therapeutic relevance. Future studies will need to establish whether targeting KCNQ3, hERG1, or other potassium channels translates into meaningful anticancer effects in EAC-specific models, while carefully addressing selectivity, cardiac safety, and delivery constraints.

Calcium channels

In epithelial tissues, calcium signaling is orchestrated by a complex toolkit comprising voltage-gated calcium channels (VGCCs), ligand-gated channels, intracellular Ca^{2+} release channels, and associated regulatory proteins. In EAC, systematic analyses of this calcium toolkit have begun to reveal specific alterations with potential functional relevance.

Large-scale transcriptomic profiling of 275 Ca^{2+} toolkit-encoding genes in EAC, based on The Cancer Genome Atlas and OCCAMS datasets, revealed widespread alterations in calcium signaling components [59]. Across both datasets, 68 genes were consistently upregulated in EAC compared with normal esophageal tissue. Among these, the VGCC pore-forming subunit α1D (*CACNA1D*) and the auxiliary α2δ4 subunit (*CACNA2D4*) ranked among the top genes based on weighted significance and association with patient survival. *CACNA1D* expression correlated with advanced tumor grade and metastatic disease, whereas *CACNA2D4* upregulation was restricted to metastatic stages. Although both subunits have been implicated in other malignancies, their precise functional contribution to EAC biology remains undefined.

Additional complexity is illustrated by the auxiliary VGCC subunit *CACNB2*. While *CACNB2* is predominantly expressed in cardiac tissue and associated with Brugada syndrome, epigenetic alterations suggest a possible tumor-suppressive role in the esophageal epithelium [60]. *CACNB2* is hypermethylated in BE but transcriptionally upregulated in EAC tumors [61], pointing to context-dependent functions, epigenetic heterogeneity, or compensatory mechanisms during

tumor progression. Notably, *CACNB2* has been implicated in chemotherapy resistance in ESCC [62]. However, direct functional validation in EAC models is currently lacking.

Venom-derived peptides provide highly selective molecular probes of calcium signaling, particularly through modulation of intracellular Ca^{2+} release channels. Scorpion venoms are rich in calcium-active toxins, including calcins, a family of small cell-penetrating peptides (CPPs) targeting ryanodine receptors (RyRs) with nanomolar affinity [63]. Imperacalcin and maurocalcin, isolated from *Pandinus imperator* and *Scorpio maurus palmatus*, respectively, potently activate RyR1 and RyR2 [64,65]. In addition, CPP-Ts, from *Tityus serrulatus* venom, activates inositol 1,4,5-trisphosphate receptors (InsP3Rs) and displays preferential internalization into cancer cells, positioning it as a potential intracellular delivery vector rather than a direct cytotoxic agent [66]. Ongoing venom research continues to expand the repertoire of calcium-modulating peptides, as illustrated by κ-LhTx-1, an inhibitor of L-type calcium channels from *Pandercetes* sp. spider venom [67].

Despite their mechanistic precision, venom peptides targeting calcium channels currently lack a clear translational link to EAC. The channels most frequently targeted by venom-derived peptides, particularly RyRs, are not known to be functionally dysregulated in EAC. However, this apparent disconnect may partly reflect historical research biases in toxinology, where certain ion channel families have been extensively studied while others remain largely unexplored. This contrast highlights a recurring gap between venom pharmacology and disease-specific channel remodeling, emphasizing that target relevance, rather than peptide potency, should guide candidate prioritization in EAC. Consequently, systematic venom screening approaches directed toward ion channels implicated in EAC may help uncover peptides with previously unrecognized therapeutic or diagnostic potential.

Chloride channel

Chloride channels play a central role in epithelial physiology by regulating ion and fluid transport, epithelial barrier function, and luminal pH. Among them, the cystic fibrosis transmembrane conductance regulator (CFTR) is the best-characterized chloride channel in the gastrointestinal tract. CFTR is expressed at the apical surface of luminal epithelial cells, where it mediates chloride and bicarbonate transport along their electrochemical gradients. CFTR contributes to mucus hydration and epithelial secretions. Loss-of-function mutations in CFTR cause cystic fibrosis, a multisystem disease characterized by highly viscous secretions and profound respiratory and gastrointestinal dysfunction [68].

Beyond inherited disease, CFTR has emerged as a molecule of interest in cancer biology, particularly in epithelial malignancies of the gastrointestinal tract [69,70]. Epidemiological data indicate that patients with cystic fibrosis exhibit an increased susceptibility to several cancers, including BE and EAC. Supporting a direct link between CFTR and esophageal tumorigenesis, **genome-wide association studies** (GWASs) identified a risk locus for BE and EAC (rs17451754) located within intron 21 of the *CFTR* gene. This finding suggests that genetic variation affecting *CFTR* expression or regulation may contribute to disease susceptibility, potentially through shared pathophysiological mechanisms linking gastroesophageal reflux disease and BE [71]. Consistent with this hypothesis, CFTR expression is significantly downregulated in EAC compared with normal esophageal epithelial cells [69]. Functional analyses further revealed that *CFTR* silencing promotes invasive behavior, at least in part through deregulation of the nuclear factor kappa-light chain enhancer of activated B cell (NF-κB) signaling, positioning CFTR as a negative regulator of proinflammatory and proinvasive signaling. Collectively, these findings support a tumor-suppressive role for CFTR in EAC. However, they also indicate that CFTR itself is

unlikely to represent a viable therapeutic target, as its inhibition would be expected to exacerbate rather than restrain malignant progression. Instead, altered *CFTR* expression appears to provide insight into disease mechanisms and progression rather than offering a direct avenue for pharmacological intervention.

In contrast to CFTR, other chloride channels and chloride channel-associated complexes have been explored as potential therapeutic targets in cancer using venom-derived peptides. The most extensively studied example is chlorotoxin, derived from the venom of the scorpion *Leiurus quinquestriatus.* Chlorotoxin was initially characterized as a chloride channel inhibitor but was subsequently shown to interact with a broader molecular complex that includes matrix metalloproteinase-2 (MMP-2), annexin A2, estrogen receptor α, and neuropilin-1. These proteins are critically involved in cell migration, invasion, and extracellular matrix remodeling. Chlorotoxin has, therefore, been widely investigated in glioblastoma and neuroblastoma, where it exhibits tumor-targeting properties and has been exploited for both imaging and therapeutic applications [72].

Despite these advances, the relevance of chloride channel-targeting toxins, such as chlorotoxin, for EAC remains uncertain. While *CFTR* dysregulation clearly contributes to EAC pathophysiology, its tumor-suppressive role argues against therapeutic inhibition. Moreover, the chloride channel complexes targeted by chlorotoxin have not been functionally validated in EAC, and their expression patterns in esophageal tumors remain poorly defined. This highlights a broader limitation in the field. Although chloride channels and associated proteins are increasingly recognized as modulators of cancer cell behavior, their functional contribution to EAC has not been explored with the same depth as potassium or calcium channels. Future studies will, therefore, be required to determine whether chloride channels other than CFTR represent actionable vulnerabilities in EAC and whether venom-derived peptides can be repurposed as selective probes to interrogate their role in tumor invasion and progression.

Sodium channels

VGSCs are increasingly recognized as being aberrantly expressed and functionally repurposed in several cancers [31]. In EAC, transcriptomic analyses reveal the deregulation of sodium channel-related pathways, although functional data remain limited. Notably, ASICs, a subfamily of sodium-permeable channels activated by extracellular acidosis, appear particularly relevant. ASIC4 expression is associated with patient survival and is upregulated across multiple EAC grades [59], while ASIC1 and ASIC3 are also overexpressed compared with normal tissue. Despite these observations, the precise contribution of ASICs to EAC progression, invasion, or therapy resistance remains largely unexplored.

Data specifically linking VGSC subtypes to EAC remain scarce. However, in other gastrointestinal cancers, including gastric and colorectal cancer, VGSCs such as $Na_V1.1$, $Na_V1.5$, and $Na_V1.7$ are strongly implicated, with their overexpression correlating with increased invasiveness and poor prognosis [73,74]. Mechanistically, persistent sodium currents at permissive membrane potentials elevate intracellular Na^+ levels, indirectly enhancing Ca^{2+} signaling through Na^+/Ca^{2+} exchanger reversal or activation of VGCCs, thereby promoting migratory and invasive phenotypes [75]. However, direct experimental validation of these coupled mechanisms remains limited, highlighting a general gap between correlative expression data and functional causality.

Venom-derived peptides provide some of the most selective pharmacological tools to interrogate sodium channel function. Spider venoms are rich in Na_V-targeting peptides with defined subtype selectivity. Peptides such as ProTx-III, HwTx-IV, CyrTx-1a, PhlTx1, and GrTx-1 preferentially

Clinician's corner

Esophageal cancer is the seventh most common cancer worldwide, with 604 100 new cases diagnosed in 2020, representing a significant global health burden.

Esophageal adenocarcinoma remains a major clinical challenge, with a 5-year survival rate of approximately 10%, despite the development of novel therapeutic options such as immunotherapies, anti-human epidermal growth factor receptor 2 agents, and anti-claudin therapies. Chemoresistance and tumor heterogeneity continue to limit treatment efficacy.

Despite the implementation of novel biomarkers and clinical tests designed to predict the progression of Barrett's esophagus to esophageal adenocarcinoma and enhance patient screening, the disease is frequently diagnosed in advanced stages, complicating the management of affected individuals.

Given that cancer is being described as a form of channelopathy, it would be beneficial to investigate the expression of ion channels in esophageal adenocarcinoma stages to gain a deeper understanding of the disease's pathogenesis. If we could identify genes that are responsible for chemoresistance, it would be worthwhile to consider incorporating ion channel inhibitors into standard chemotherapy regimens. It could also be interesting to predict which patients would be most at risk of not responding to treatment.

Venoms are a rich source of novel compounds that are structurally distinct from molecules currently implemented in clinical practice. The selectivity and efficacy of venom-derived peptides have already been demonstrated in the context of other therapeutic applications, including the management of diabetes and pain.

The success of venom-derived peptides in the treatment of esophageal adenocarcinoma is contingent upon the identification of an appropriate target and the mitigation of limitations associated with safety, pharmacokinetics, and delivery.

inhibit neuronal Na_V subtypes ($Na_V1.1$–1.3, $Na_V1.6$, and $Na_V1.7$) while sparing $Na_V1.5$ and other channel families [76]. However, the sodium channel subtypes most extensively targeted by venom peptides do not yet clearly overlap with those implicated in EAC, limiting immediate translational relevance.

An exception lies in ASIC-targeting toxins. PcTx1, a highly selective ASIC1a inhibitor from *P. cambridgei* venom, suppresses cation currents and invasive behavior in glioblastoma models, providing proof of concept that proton-sensitive sodium channels can be pharmacologically exploited in acidic tumor microenvironments [77]. APETx2, from *A. elegantissima* venom, is a specific inhibitor of ASIC3 [50]. Given the upregulation of ASIC1, ASIC3, and ASIC4 in EAC, ASIC-directed venom peptides may represent a more disease-relevant entry point than classical VGSC inhibitors.

Sodium channels emerge as biologically plausible but underexplored targets in EAC. While expression data support their involvement, the lack of functional validation in EAC-specific models remains a major limitation. Venom-derived peptides should, therefore, be viewed primarily as high-precision tools to dissect sodium channel dependencies in EAC, with ASIC-targeting peptides representing the most promising candidates for future therapeutic exploration.

To achieve this, research is primarily focused not only on modifying amino acids and incorporating additional molecules but also on inventive delivery methods. Furthermore, venom-derived peptides could be employed as carriers for other therapeutic agents. A deeper understanding of the molecular mechanisms involved in tumor progression could lead to significant advances in clinical practice, with the potential for a paradigm shift in the way that cancer is treated.

Nonselective cation channels

Several nonselective cation channels of the transient receptor potential (TRP) family have been implicated in EAC, although functional data remain limited. High TRPM5 expression has been associated with improved overall survival in EAC patients [59]. A proposed protective mechanism is that TRPM5-mediated Na^+ influx promotes **mucin** secretion, potentially reinforcing the esophageal barrier; however, this remains largely speculative and requires experimental validation.

Transcriptomic analyses further identified TRPC4 and TRPM2 among the highest-ranked ion channels in EAC [59], while TRPV2 was consistently upregulated across both TCGA and OCCAMS datasets. In other malignancies, TRPV2 has been linked to cancer stem cell populations, and pharmacological inhibition with Tranilast selectively increased cancer stem cell sensitivity and reduced tumor growth *in vivo* [78]. Whether TRPV2 plays a similar role in EAC remains unexplored.

From a translational perspective, venom-derived peptides targeting TRP channels remain scarce in the context of EAC. SOR-C13, a peptide inhibitor of TRPV6, has shown activity in ESCC [79], but the expression and functional relevance of TRPV6 in EAC are currently unknown. This highlights a recurrent limitation: while TRP channels emerge from transcriptomic studies as candidates of interest, their mechanistic roles and suitability as therapeutic targets in EAC remain largely unexplored.

Other ion channels

Other ion channels and transporters are involved in the pathogenesis of EAC. *SLC11A2* encodes the Divalent Metal Transporter DMT1, a key mediator of dietary iron uptake in enterocytes. Components of the iron import machinery, including DMT1, are overexpressed during the progression from BE to EAC, leading to increased intracellular iron levels and enhanced proliferative capacity [80]. However, the functional consequences of this dysregulation remain ambiguous. While inhibition of DMT1 induces **ferroptosis** in head and neck cancer models [81], increased DMT1 expression has been associated with ferroptotic sensitivity in other cancer types [82,83], suggesting context-dependent effects that have not yet been explored in EAC.

Altered intracellular pH regulation also represents a key feature of EAC. NHE1 (Sodium hydrogen exchanger isoform 1) (*SLC9A1*) activity is increased in BE, leading to transient intracellular alkalinization and enhanced cell proliferation [84]. Inhibition of NHE1 reduces proliferation in acid- and bile acid-exposed BE models [85] and induces apoptosis in EAC cells, where NHE1 expression is elevated. NHE2 (isoform 2) (*SLC9A2*) is also expressed in BE cells [86], though its functional role remains unclear. Together, these findings support a role for dysregulated proton transport in both early adaptation and tumor cell survival.

GRIN2D encodes a subunit of the NMDA glutamate receptor involved in Ca^{2+} signaling and is upregulated in EAC samples [59]. It has, therefore, been proposed as a potential diagnostic marker [87].

Compared with potassium, calcium, or sodium channels, direct links between these transporters and venom-derived peptides are limited. Scorpion antimicrobial peptides, such as Smp43 and Smp24 from *S. m. palmatus*, display anticancer activity in several tumor models via apoptosis, pyroptosis, and mitochondrial dysfunction [88,89], but these effects are largely nonspecific and not directly linked to defined ion channel targets relevant to EAC.

Overall, these transporters highlight important metabolic and homeostatic adaptations in EAC. However, their therapeutic exploitability remains uncertain, and future studies should clarify whether they represent actionable vulnerabilities or adaptive bystanders in EAC progression.

Concluding remarks

Despite the growing number of venom-derived peptides reported to display anticancer activity, their translation toward clinical applications, particularly in solid tumors such as EAC, remains limited. Traditional discovery pipelines have largely prioritized *in vitro* target engagement or cytotoxicity, often overlooking critical *in vivo* constraints, including rapid proteolysis, short systemic half-life, and limited bioavailability [90]. Consequently, many peptides with compelling pharmacological profiles fail to progress beyond early validation. Bridging this gap will require a shift toward developability-driven prioritization, in which biological activity is evaluated alongside stability, selectivity, and translational feasibility from the earliest stages of discovery [91].

Artificial intelligence and bioinformatics now provide powerful tools to support this transition [92]. Omics-scale venom resources can be leveraged to improve toxin annotation, identify conserved scaffolds, and rank candidates by integrating predicted potency with sequence features associated with stability and toxicity. Importantly, interpretable computational models can highlight key residues and structural motifs governing target selectivity, enabling rational peptide redesign rather than empirical optimization [93]. When combined with structural biology and functional assays, these approaches offer a coherent framework to transform venom peptides from natural products into engineered therapeutic leads [94].

Beyond discovery challenges, major biological barriers must be addressed in the context of EAC. A central limitation is balancing pharmacological potency with acceptable safety profiles, particularly regarding nonspecific cytotoxicity [18]. Many venom peptides are evolutionarily optimized for rapid immobilization or tissue damage and may induce off-target effects through membrane disruption or excessive ion flux [95]. This is especially relevant in EAC, where the esophageal epithelium is intrinsically fragile and chronically exposed to inflammation and acid reflux. However, emerging evidence suggests that tumor-specific remodeling of ion channel expression may confer selective vulnerability to certain venom-derived peptides, providing a rationale for functional selectivity [34].

Outstanding questions

Which ion channels constitute true functional dependencies in esophageal adenocarcinoma, rather than correlative expression changes, and how do they mechanistically drive carcinogenesis and chemoresistance in patients?

To what extent does ion channel remodeling predict treatment response, and can channel activity serve as a stratification biomarker in esophageal adenocarcinoma?

Which venom-derived peptides could be discovered through targeted screening of ion channels functionally dysregulated in esophageal adenocarcinoma?

How can venom-derived peptides selectively target tumor-specific channel states while minimizing systemic on-target toxicity in normal tissues?

What delivery and engineering strategies (e.g., stabilization, tumor-targeted transport, and half-life extension) are required to translate venom peptides into clinically viable agents for solid tumors?

Could venom-derived peptides be integrated into rational combination regimens with chemotherapy, targeted therapy, or immunotherapy, or even serve as selective carriers for cytotoxic payloads?

Beyond ion channels, are there additional venom peptide targets that converge on key esophageal adenocarcinoma hallmarks such as invasion, metastasis, immune escape, or microenvironmental adaptation?

Addressing these limitations will require systematic integration of chemical and structural optimization strategies [96]. Sequence minimization, structure-guided residue substitution, incorporation of noncanonical amino acids, cyclization, and disulfide bond surrogates can attenuate nonspecific cytotoxicity while improving stability and pharmacokinetic profiles [97]. In parallel, delivery technologies such as nanocarriers and peptide-mediated targeting can enhance biodistribution and intracellular access [98,99].

Importantly, venom-derived peptides should not be considered as standalone alternatives to existing treatments. Given the intrinsic limitations of chemotherapy, radiotherapy, targeted therapy, and immunotherapy as monotherapies, venom peptides are best envisioned as complementary agents within combination strategies, capable of enhancing therapeutic efficacy or reducing dose-limiting toxicity [100]. By embracing venom peptides as evolutionarily optimized starting points rather than fixed end products, the field can move toward clinically meaningful innovation for EAC. The conceptual and translational priorities that will shape this evolution are summarized (see Outstanding questions).

Declaration of interests

The authors declare no competing interests.

Resources

[i]https://clinicaltrials.gov/study/NCT01481532

[ii]https://clinicaltrials.gov/study/NCT01578564

[iii]https://clinicaltrials.gov/study/NCT03784677

References

1. Sung, H. *et al.* (2021) Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 71, 209–249
2. Uhlenhopp, D.J. *et al.* (2020) Epidemiology of esophageal cancer: update in global trends, etiology and risk factors. *Clin. J. Gastroenterol.* 13, 1010–1021
3. Freuville, L. *et al.* (2024) Venom-derived peptides for breaking through the glass ceiling of drug development. *Front. Chem.* 12, 1465459
4. Tasoulis, T. and Isbister, G.K. (2023) A current perspective on snake venom composition and constituent protein families. *Arch. Toxicol.* 97, 133–153
5. Xia, Z. *et al.* (2023) Scorpion venom peptides: molecular diversity, structural characteristics, and therapeutic use from channelopathies to viral infections and cancers. *Pharmacol. Res.* 197, 106978
6. Langenegger, N. *et al.* (2019) Spider venom: components, modes of action, and novel strategies in transcriptomic and proteomic analyses. *Toxins* 11, 611
7. Herzig, V. *et al.* (2020) Animal toxins—nature's evolutionary-refined toolkit for basic research and drug discovery. *Biochem. Pharmacol.* 181, 114096
8. Abd El-Aziz, T.M. *et al.* (2020) Advances in venomics: modern separation techniques and mass spectrometry. *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* 1160, 122352
9. Honing, J. *et al.* (2025) Surveillance of Barrett's esophagus patients in an expert center is associated with low disease-specific mortality. *United Eur. Gastroenterol. J.* 13, 220–228
10. Fatehi Hassanabad, A. *et al.* (2020) Esophageal carcinoma: towards targeted therapies. *Cell. Oncol.* 43, 195–209
11. Shah, M.A. *et al.* (2024) First-line pembrolizumab (pembro) plus chemotherapy (chemo) for advanced esophageal cancer: 5-year outcomes from the phase 3 KEYNOTE-590 study. *J. Clin. Oncol.* 42, 250
12. Brown, D.G. and Boström, J. (2016) Analysis of past and present synthetic methodologies on medicinal chemistry: where have all the new reactions gone? Miniperspective. *J. Med. Chem.* 59, 4443–4458
13. Bordon, K.D.C.F. *et al.* (2020) From animal poisons and venoms to medicines: achievements, challenges and perspectives in drug discovery. *Front. Pharmacol.* 11, 1132
14. Fu, S. *et al.* (2017) First-in-human phase I study of SOR-C13, a TRPV6 calcium channel inhibitor, in patients with advanced solid tumors. *Investig. New Drugs* 35, 324–333
15. Khattar, V. *et al.* (2022) Calcium selective channel TRPV6: structure, function, and implications in health and disease. *Gene* 817, 146192
16. El-Qassas, J. *et al.* (2024) Harnessing the potency of scorpion venom-derived proteins: applications in cancer therapy. *Bioresour. Bioprocess.* 11, 93
17. Mabunda, I.G. *et al.* (2025) Scorpion venoms from the Buthidae family: a dual study of proteomic composition and anticancer potentials. *Toxicon* 266, 108542
18. Almeida, J.R. *et al.* (2025) Snake venom-derived peptides as anticancer candidates: pioneering next-generation therapies. *Biochim. Biophys. Acta BBA Rev. Cancer* 1880, 189479
19. He, J. *et al.* (2013) Growth inhibitory effects and molecular mechanisms of crotoxin treatment in esophageal Eca-109 cells and transplanted tumors in nude mice. *Acta Pharmacol. Sin.* 34, 295–300
20. Muller, S.P. *et al.* (2018) Crotoxin from *Crotalus durissus terrificus* venom: *in vitro* cytotoxic activity of a heterodimeric phospholipase A2 on human cancer-derived cell lines. *Toxicon* 156, 13–22
21. Lv, J. *et al.* (2017) Arenobufagin activates p53 to trigger esophageal squamous cell carcinoma cell apoptosis *in vitro* and *in vivo*. *Oncol. Targets Ther.* 10, 1261–1267
22. Lin, S. *et al.* (2017) Bufadienolides induce p53-mediated apoptosis in esophageal squamous cell carcinoma cells *in vitro* and *in vivo*. *Oncol. Lett.* 15, 1566–1572
23. Zhu, H. *et al.* (2014) Melittin radiosensitizes esophageal squamous cell carcinoma with induction of apoptosis in vitro and in vivo. *Tumour Biol.* 35, 8699–8705

24. Zhou, C. *et al.* (2020) TERT promoter regulating melittin expression induces apoptosis and G_0/G_1 cell cycle arrest in esophageal carcinoma cells. *Oncol. Lett.* 21, 16
25. Huang, J.-Y. *et al.* (2021) Melittin suppresses epithelial–mesenchymal transition and metastasis in human gastric cancer AGS cells via regulating Wnt/BMP associated pathway. *Biosci. Biotechnol. Biochem.* 85, 2250–2262
26. Shi, P. *et al.* (2022) Pharmacological effects and mechanisms of bee venom and its main components: recent progress and perspective. *Front. Pharmacol.* 13, 1001553
27. Taura, J. *et al.* (2021) Comparison of K^+ channel families. In *Pharmacology of Potassium Channels* (Vol. 267) (Gamper, N. and Wang, K., eds), pp. 1–49, Springer International Publishing
28. Zúñiga, L. *et al.* (2022) Potassium channels as a target for cancer therapy: current perspectives. *Oncol. Targets Ther.* 15, 783–797
29. Kim, H.J. *et al.* (2022) Chloride channels and transporters: roles beyond classical cellular homeostatic pH or ion balance in cancers. *Cancers* 14, 856
30. Tajada, S. and Villalobos, C. (2020) Calcium permeable channels in cancer hallmarks. *Front. Pharmacol.* 11, 968
31. Liu, H. *et al.* (2024) Voltage-gated sodium channels in cancers. *Biomark. Res.* 12, 70
32. Gründer, S. *et al.* (2024) Acid-sensing ion channels and downstream signalling in cancer cells: is there a mechanistic link? *Pflüg. Arch. Eur. J. Physiol.* 476, 659–672
33. Marini, M. *et al.* (2023) TRP channels in cancer: signaling mechanisms and translational approaches. *Biomolecules* 13, 1557
34. Bell, D.C. *et al.* (2023) News and views on ion channels in cancer: is cancer a channelopathy? *Front. Pharmacol.* 14, 1258933
35. Zhang, G. *et al.* (2018) Combined targeted ion channel therapy: can it be an alternative choice for esophageal cancer patients? *Med. Hypotheses* 117, 59–62
36. Zhou, S. *et al.* (2025) Targeting ion channels for cancer therapy: from pathophysiological mechanisms to clinical translation. *Pharmaceuticals* 18, 1521
37. Arcangeli, A. *et al.* (2023) The role of potassium channels in tumours of the gastrointestinal tract: a focus on the human ether-à-go-go related gene 1 channels. *J. Physiol.* 601, 1597–1610
38. Shorthouse, D. *et al.* (2023) KCNQ potassium channels modulate Wnt activity in gastro-oesophageal adenocarcinomas. *Life Sci. Alliance* 6, e202302124
39. Foley, K. *et al.* (2024) SMAD4 and KCNQ3 alterations are associated with lymph node metastases in oesophageal adenocarcinoma. *Biochim. Biophys. Acta BBA Mol. Basis Dis.* 1870, 166867
40. He, S. *et al.* (2020) HERG channel and cancer: a mechanistic review of carcinogenic processes and therapeutic potential. *Biochim. Biophys. Acta BBA Rev. Cancer* 1873, 188355
41. Iorio, J. *et al.* (2022) Prognostic role of hERG1 potassium channels in neuroendocrine tumours of the ileum and pancreas. *Int. J. Mol. Sci.* 23, 10623
42. Lastraioli, E. *et al.* (2016) hERG1 behaves as biomarker of progression to adenocarcinoma in Barrett's esophagus and can be exploited for a novel endoscopic surveillance. *Oncotarget* 7, 59535–59547
43. Luo, L. *et al.* (2018) Centipedes subdue giant prey by blocking KCNQ channels. *Proc. Natl. Acad. Sci. U. S. A.* 115, 1646–1651
44. Titaux-Delgado, G. *et al.* (2023) Beta-KTx14.3, a scorpion toxin, blocks the human potassium channel KCNQ1. *Biochim. Biophys. Acta BBA Proteins Proteomics* 1871, 140906
45. Chen, J. *et al.* (2015) SjAPI-2 is the first member of a new neurotoxin family with Ascaris-type fold and KCNQ1 inhibitory activity. *Int. J. Biol. Macromol.* 79, 504–510
46. Matsumura, K. *et al.* (2021) Mechanism of hERG inhibition by gating-modifier toxin, APETx1, deduced by functional characterization. *BMC Mol. Cell Biol.* 22, 3
47. Beltrán-Vidal, J. *et al.* (2021) Colombian scorpion *Centruroides margaritatus*: purification and characterization of a gamma potassium toxin with full-block activity on the hERG1 channel. *Toxins* 13, 407
48. Pinheiro-Junior, E.L. *et al.* (2022) A tale of toxin promiscuity: the versatile pharmacological effects of Hcr 1b-2 sea anemone peptide on voltage-gated ion channels. *Mar. Drugs* 20, 147
49. Martínez-Hernández, L. *et al.* (2023) κO-SrVIA conopeptide, a novel inhibitor peptide for two members of the human EAG potassium channel family. *Int. J. Mol. Sci.* 24, 11513
50. Verkest, C. *et al.* (2022) Mechanisms of action of the peptide toxins targeting human and rodent acid-sensing ion channels and relevance to their *in vivo* analgesic effects. *Toxins* 14, 709
51. Peigneur, S. *et al.* (2012) A natural point mutation changes both target selectivity and mechanism of action of sea anemone toxins. *FASEB J.* 26, 5141–5151
52. Bychkov, M. *et al.* (2020) Mambalgin-2 induces cell cycle arrest and apoptosis in glioma cells via interaction with ASIC1a. *Cancers* 12, 1837
53. Cristofori-Armstrong, B. *et al.* (2019) The modulation of acid-sensing ion channel 1 by PcTx1 is pH-, subtype- and species-dependent: importance of interactions at the channel subunit interface and potential for engineering selective analogues. *Biochem. Pharmacol.* 163, 381–390
54. Duggan, N.M. *et al.* (2021) Total synthesis of the spider-venom peptide Hi1a. *Org. Lett.* 23, 8375–8379
55. Salinas, M. *et al.* (2021) Mambalgin-1 pain-relieving peptide locks the hinge between α4 and α5 helices to inhibit rat acid-sensing ion channel 1a. *Neuropharmacology* 185, 108453
56. Redd, M.A. *et al.* (2021) Therapeutic inhibition of acid-sensing ion channel 1a recovers heart function after ischemia–reperfusion injury. *Circulation* 144, 947–960
57. Bychkov, M.L. *et al.* (2021) Mambalgin-2 inhibits growth, migration, and invasion of metastatic melanoma cells by targeting the channels containing an ASIC1a subunit whose up-regulation correlates with poor survival prognosis. *Biomedicines* 9, 1324
58. Sudarikova, A.V. *et al.* (2022) Mambalgin-2 inhibits lung adenocarcinoma growth and migration by selective interaction with ASIC1/α-ENaC/γ-ENaC heterotrimer. *Front. Oncol.* 12, 904742
59. Cutliffe, A.L. *et al.* (2021) Alterations in the Ca^{2+} toolkit in oesophageal adenocarcinoma. *Explor. Target. Antitumor Ther.* 2, 543–575
60. Zhang, Q. *et al.* (2018) Mutations in voltage-gated L-type calcium channel: implications in cardiac arrhythmia. *Channels* 12, 201–218
61. Xu, E. *et al.* (2013) Genome-wide methylation analysis shows similar patterns in Barrett's esophagus and esophageal adenocarcinoma. *Carcinogenesis* 34, 2750–2756
62. Xie, F. *et al.* (2022) Analysis of cancer-promoting genes related to chemotherapy resistance in esophageal squamous cell carcinoma. *Ann. Transl. Med.* 10, 92
63. Huang, Y. *et al.* (2026) Scorpion venom neurotoxins: molecular diversity, mechanisms, and drug scaffolds. *Toxins* 18, 25
64. de Waard, S. *et al.* (2020) Maurocalcin and its analog MCa_{E12A} facilitate Ca^{2+} mobilization in cardiomyocytes. *Biochem. J.* 477, 3985–3999
65. Haji-Ghassemi, O. *et al.* (2023) Cryo-EM analysis of scorpion toxin binding to Ryanodine Receptors reveals subconductance that is abolished by PKA phosphorylation. *Sci. Adv.* 9, eadf4936
66. Oliveira-Mendes, B.B.R.D. *et al.* (2018) CPP-Ts: a new intracellular calcium channel modulator and a promising tool for drug delivery in cancer cells. *Sci. Rep.* 8, 14739
67. Tang, D. *et al.* (2026) Molecular diversity of peptides from Pandercetes sp. spider venom and antagonistic activity on voltage-gated calcium channels of the κ-LhTx-1 toxin. *Int. J. Biol. Macromol.* 337, 149490
68. Hanssens, L.S. *et al.* (2021) CFTR protein: not just a chloride channel? *Cells* 10, 2844
69. Bhattacharya, R. *et al.* (2022) CFTR and gastrointestinal cancers: an update. *J. Pers. Med.* 12, 868
70. Parisi, G.F. *et al.* (2023) Cystic fibrosis and cancer: unraveling the complex role of CFTR gene in cancer susceptibility. *Cancers* 15, 4244
71. Gharahkhani, P. *et al.* (2016) Genome-wide association studies in oesophageal adenocarcinoma and Barrett's oesophagus: a large-scale meta-analysis. *Lancet Oncol.* 17, 1363–1373
72. Boltman, T. *et al.* (2023) Diagnostic and therapeutic approaches for glioblastoma and neuroblastoma cancers using chlorotoxin nanoparticles. *Cancers* 15, 3388
73. Lopez-Charcas, O. *et al.* (2022) Voltage-gated sodium channel $Na_V1.5$ controls NHE-1-dependent invasive properties in colon cancer cells. *Cancers* 15, 46

74. Sui, Q. *et al.* (2021) Voltage-gated sodium channel Nav1.5 promotes tumor progression and enhances chemosensitivity to 5-fluorouracil in colorectal cancer. *Cancer Lett.* 500, 119–131
75. Horne, J. *et al.* (2021) Sodium ion channels as potential therapeutic targets for cancer metastasis. *Drug Discov. Today* 26, 1136–1147
76. Cardoso, F.C. (2020) Multi-targeting sodium and calcium channels using venom peptides for the treatment of complex ion channels-related diseases. *Biochem. Pharmacol.* 181, 114107
77. Wu, T. *et al.* (2019) Spider venom peptides as potential drug candidates due to their anticancer and antinociceptive activities. *J. Venom. Anim. Toxins Trop. Dis.* 25, e146318
78. Shiozaki, A. *et al.* (2023) Cancer stem cells of esophageal adenocarcinoma are suppressed by inhibitors of TRPV2 and SLC12A2. *Ann. Surg. Oncol.* 30, 8743–8754
79. Becskeházi, E. *et al.* (2020) Oesophageal ion transport mechanisms and significance under pathological conditions. *Front. Physiol.* 11, 855
80. Boult, J. *et al.* (2008) Overexpression of cellular iron import proteins is associated with malignant progression of esophageal adenocarcinoma. *Clin. Cancer Res.* 14, 379–387
81. Lee, J. and Roh, J.-L. (2023) Promotion of ferroptosis in head and neck cancer with divalent metal transporter 1 inhibition or salinomycin. *Hum. Cell* 36, 1090–1098
82. Kaftan, G. *et al.* (2024) Heteronemin promotes iron-dependent cell death in pancreatic cancer. *Naunyn Schmiedeberg's Arch. Pharmacol.* 397, 1865–1874
83. Song, Q. *et al.* (2021) Temozolomide drives ferroptosis via a DMT1-dependent pathway in glioblastoma cells. *Yonsei Med. J.* 62, 843
84. Fitzgerald, R.C. *et al.* (1998) Altered sodium-hydrogen exchange activity is a mechanism for acid-induced hyperproliferation in Barrett's esophagus. *Am. J. Physiol. Gastrointest. Liver Physiol.* 275, G47–G55
85. Park, S.Y. *et al.* (2015) Intrinsic resistance triggered under acid loading within normal esophageal epithelial cells: NHE1- and ROS-mediated survival. *J. Cell. Physiol.* 230, 1503–1514
86. Korsós, M.M. *et al.* (2021) Mouse organoid culture is a suitable model to study esophageal ion transport mechanisms. *Am. J. Physiol. Cell Physiol.* 321, C798–C811
87. Wang, L.-L. *et al.* (2023) The promoting effects of Grin2d expression in tumorigenesis and the aggressiveness of esophageal cancer. *Histol. Histopathol.* 39, 659–670
88. Chai, J. *et al.* (2021) Antitumor effects of scorpion peptide Smp43 through mitochondrial dysfunction and membrane disruption on hepatocellular carcinoma. *J. Nat. Prod.* 84, 3147–3160
89. Elrayess, R.A. *et al.* (2022) Scorpion venom antimicrobial peptides induce caspase-1 dependant pyroptotic cell death. *Front. Pharmacol.* 12, 788874
90. Muttenthaler, M. *et al.* (2021) Trends in peptide drug discovery. *Nat. Rev. Drug Discov.* 20, 309–325
91. Zheng, B. *et al.* (2025) Therapeutic peptides: recent advances in discovery, synthesis, and clinical translation. *Int. J. Mol. Sci.* 26, 5131
92. Carracedo-Reboredo, P. *et al.* (2021) A review on machine learning approaches and trends in drug discovery. *Comput. Struct. Biotechnol. J.* 19, 4538–4558
93. Goles, M. *et al.* (2024) Peptide-based drug discovery through artificial intelligence: towards an autonomous design of therapeutic peptides. *Brief. Bioinform.* 25, bbae275
94. Bian, H. *et al.* (2024) In silico discovery of stapled peptide inhibitor targeting the Nur77-PPARγ interaction and its anti-breast-cancer efficacy. *Adv. Sci. (Weinh.)* 11, 2308435
95. Kim, E.-J. *et al.* (2025) Anticancer activity of snake venom against breast cancer: a scoping review. *Toxins* 17, 477
96. Bezerra, P. and Motti, E.F. (2024) 3-NAntC: a potent crotoxin B-derived peptide against the triple-negative MDA-MB-231 breast cancer cell line. *Molecules* 29, 1646
97. Stepensky, D. (2018) Pharmacokinetics of toxin-derived peptide drugs. *Toxins* 10, 483
98. Li, Q. *et al.* (2025) Therapeutic peptides: chemical strategies fortify peptides for enhanced disease treatment efficacy. *Amino Acids* 57, 25
99. Wang, Y. *et al.* (2024) Peptide-mediated nanocarriers for targeted drug delivery: developments and strategies. *Pharmaceutics* 16, 240
100. Mahadevappa, R. *et al.* (2017) Venom peptides: improving specificity in cancer therapy. *Trends Cancer* 3, 611–614