Medical Hypotheses 117 (2018) 59–62

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Combined targeted ion channel therapy: Can it be an alternative choice for esophageal cancer patients?

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ARTICLE INFO

Keywords:
Esophageal cancer
Ion channel
Calcium (Ca^{2+}) channel
Potassium (K^{+}) channel
Voltage-gated sodium (Na^{+}) channel

ABSTRACT

Esophageal cancer is a relatively common malignancy with a poor prognosis and is conventionally treated by surgery, chemotherapy, and radiotherapy. However, due to the prevalence of cancer relapse with treatment resistance, novel molecular targets must be identified for the development of alternative therapies. Emerging evidence indicates that ion channels play important roles in cell proliferation, migration, apoptosis and differentiation and could therefore be considered as a potential oncological therapy. Therapies that target single oncogenic channel have shown promise. However, therapies that target more than one ion channel have not been developed. We propose that therapies targeting more than one type of ion channel might be an alternative treatment for esophageal cancer.

Introduction

Incidence rates of esophageal cancer (EC) have increased in recent decades. Worldwidely, EC is the eighth most common cancer and the sixth most common cause of cancer-related deaths in 2012 [1]. In China, EC ranks as the third most common and fourth most common cause of cancer-related deaths [2].

The current management strategies for localized EC depend on the tumor and nodal stages, that is, the extent of tumor invasion into the wall of the esophagus and adjacent tissues, and nodal involvement [3]. The main treatment options include surgery, chemotherapy, and radiotherapy. However, EC is associated with a poor prognosis, even after surgery. According to the National Cancer Institute, the current 5-year relative survival rates for localized, regional, and distant EC are 43%, 23%, and 5%, respectively [4,5]. Hence, there is an urgent need for therapies that improve survival and optimize palliative care for patients with EC. The prime research targets are chemotherapeutic agents to maximize antitumor activity and minimize toxicity.

Ion channels constitute pores in cellular membranes, comprised of transmembrane proteins that regulate the exchange of specific ions. The transport of ions through ion channels is rapid and does not require metabolic energy. Rather, ions pass down an electrochemical gradient, depending on ion concentration and membrane potential. Thus, ion channels function to maintain extracellular and intracellular ion homeostasis and transmit cell signals, and are crucial in regulating cellular volume, proliferation, apoptosis, migration, invasion, and adhesion [6–8]. Ion channels referred to as oncogenic channels have been implicated in multiple cancer processes in various cancers [9]. Oncogenic channels that are associated with EC may be treated as pharmaceutic targets.

Ion channels may be classified according to the opening and closing mechanism of the channel, or gating. For example, they may be controlled by the voltage of the membrane (voltage-gated), binding of extracellular ligands (or ligand-gated), or intracellular secondary messengers. The latter include types of potassium channels (inward-rectifier, calcium-activated, and leak channels), or are controlled by other factors such as cyclic nucleotides.

Besides the gating mechanism, ion channels may be alternatively classified by the ions for which they are selectively permeable. There are various types of calcium (Ca^{2+}), potassium (K^{+}), and sodium (Na^{+}) ion channels (Table 1).

Calcium (Ca^{2+}) channels

Calcium (Ca^{2+}) channels, Ca^{2+} transporters, and Ca^{2+}-ATPases (enzymes that catalyze adenosine triphosphate) are putatively altered in human cancer. Blockers, inhibitors, or regulators of Ca^{2+} channels/transporters or Ca^{2+}-ATPase pumps have been used as anti-cancer

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https://doi.org/10.1016/j.mehy.2018.06.010
Received 27 August 2017; Accepted 7 June 2018

Table 1
Ion channels and their encoding genes.

Ion channels	Subfamily	Encoding genes
Ca^{2+}	Canonical TRP* (TRPC) Vanilloid TRP* (TRPV) Melastatin TRP*	
K^+	Calcium-activated Voltage-gated Inward rectifying Background/tandem pore domain	Human ether-á-go-go-related gene (hERG)
Na^+	Voltage-gated sodium channel (Nav)	

* TRP: transient receptor potential.

drugs for novel therapies to improve the survival of cancer patients [10].

Calcium channels may be either voltage- or ligand-gated. Among the former are a family of highly conserved cation channels known as transient receptor potential (TRP) Ca^{2+} channels. There are 7 subfamilies of TRP Ca^{2+} channels, among which are the canonical, vanilloid receptor, and melastatin. Canonical TRPs (TRPC) regulate the cell cycle, specifically the G2/M phase transition, and are essential for glioma progression [11]. For example, TRPC6 channels are abundant in esophageal squamous cell carcinoma (ESCC) and are essential for cell proliferation. Inhibition of TRPC6 channels in human ESCC cells suppresses their proliferation and induces G2/M phase arrest [12,13].

The vanilloid receptor (TRPV) and melastatin channels have been associated with prostate and breast cancers, respectively [14]. TRPV6 is downregulated in ESCC and is predictive of survival of ESCC patients [15]. TRPV2 is involved in the maintenance of cancer stem cells, and the TRPV2 channel inhibitor tranilast has potential as a targeted therapeutic agent against ESCC [16].

In addition, plasma membrane channels known as calcium release-activated channels function to maintain calcium in the endoplasmic reticulum. Patients with ESCC putatively have elevated levels of calcium release-activated calcium channel protein 1 (ORAI1), which correlates with poor overall and recurrence-free survival [17].

Potassium (K^+) channels

There are 4 main classes of K^+ channels (calcium-activated; voltage-gated; inward rectifying; and background/tandem pore domain, or K2P), and examples of each have been associated with tumor development [18,19]. For example, TREK-1 (also known as potassium channel subfamily K member 2 or KCNK2) is a K2P channel that is overexpressed in prostate cancer and associated with G1/S cell cycle arrest [20]. Intermediate-conductance calcium-activated potassium channel (SK4) is overexpressed in triple-negative breast cancer [21]. The voltage-gated (KV) silent subunit KV9.3 is associated with regulation of the cell cycle in colon carcinoma and lung adenocarcinoma cells [22]. In addition, increasing cellular levels of the inward rectifier K^+ channel hERG1 (human ether-à-go-go-related gene 1) was linked to the progression from normal esophageal tissue to Barrett's esophagus to adenocarcinoma [23].

Sodium (Na^+) channels

Voltage-gated sodium (Na^+) channels are responsible for membrane depolarization and the regulation of cellular invasion and migration. Their use as therapeutic targets has also been explored [24]. In particular, levels of the voltage-gated Na^+ channel Nav1.5 subunit are elevated in human colon cancer specimens, and Nav1.5 was reported as a high regulator of colon cancer invasion [25]. The alpha subunit of the Na^+ channel Nav1.7 was found to be crucial to the invasion of non-small cell lung cancer cells [26]. In addition, elevated levels of Nav1.6 in cervical cancer and associated invasiveness led authors to conclude that Nav1.6 may be a potential marker of metastatic behavior [27].

Much evidence has supported the downstream pathways of ion channel signaling. As the targets of a number of intracellular signaling pathways, ion channels function as signal transducers. Studies have also revealed crosstalk between ion channels and cellular molecules; ion channels form signaling complexes with cell adhesion proteins, growth factors, and other signaling molecules [28]. Several enzymes, including the tyrosine kinase Src, focal adhesion kinase, and GTPases such as Ras, initiate downstream phosphorylation events. These events modulate a variety of cellular processes such as cell cycle control, migration, adhesion, apoptosis [29].

Although hints for the implication of ion channels in the pathogenesis and evolution of cancer have been available for at least 20 years [30], only recently a significant number of channels have been directly linked to cancer, including Na^+, Ca^+, and K^+ channels [31–34]. Studies have shown that some voltage-gated Na^+ channels (VGSC) blockers can inhibit cell behaviors associated with metastasis. For example, the anticonvulsant phenytoin suppressed migration of prostate cancer cells [35], and also inhibited migration and invasion in metastatic breast cancer cells [36]. Riluzole, which is both a VGSC blocker and metabotropic glutamate receptor inhibitor, reduced beast cancer tumor volume in mice, and suppressed metabolic activity of tumors in patients with stage III and IV melanoma in a phase 0 trail [37]. Recently, K^+ channels EAG1 (EAG1, voltage gated eag related subfamily H, member 1) and human ether-á-go-go-related gene (hERG) were identified as most critical ion-channel encoding genes as a target for cancer therapy [34,38]. Furthermore, some studies have also found that specific inhibitors of the Na^+/K^+ pump (Na^+/K^+-ATPase) can activate multiple intracellular signaling pathways, including the MAPK (mitogen-activated protein kinase), PLC-γ (phospholipase C-gamma), and PI3K (phosphatidylinositol-4,5-bisphosphate 3-kinase)-PDK (phosphoinositide-dependent kinase)-Akt pathways [39].

Although all the above ion channels have been associated with tumor development, therapies that target more than one ion channel have not been developed.

Hypothesis

In an increasing number of studies investigators have observed that instead of a single type of K+ channel being present in cancer cells from prostate, colon, lung, breast and other tissues, a variety of K+ channels are found in these tissues, basically members of all known subfamilies of K+-selective ion channels. The different subfamilies consist of Ca2+-activated K+ channels, Shaker-type voltage-gated K+ channels, the ether a‘ go-go (EAG) family of voltage-gated K+ channels, as well as 2P-domain K+ channels [31,40–42]. We therefore propose that therapies with combined ion channel targets may be an alternative choice in EC. Every channel contributes to tumor development, and the mechanisms of ion channels interact. For example, hyperpolarization caused by the efflux of K+ ions through potassium (K+) channels may be compensated by the influx of Na+ ions via voltage-gated sodium (Na+) channels. To maximize the killing of tumors, normal ion homeostasis requires the coordinated manipulation of all channels (Fig. 1).

Ion channels simultaneously influence tumorigenesis and development. Focusing on a single channel type cannot achieve the maximum effect. Furthermore, the roles of different ion channels differ according to the stage of the cancer, whether it is a precancerous lesion, or during tumor growth, invasion, or metastasis. Thus, the combined application of different ion channel inhibitors is needed to inhibit tumor progression to the maximum.