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Review Article

Role of transient receptor potential melastatin type 7 channel in gastric cancer

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ABSTRACT

Transient receptor potential (TRP) proteins are a family of ion channels, which are responsible for a wide array of cellular functions. In particular, TRP melastatin type (TRPM) 7 is expressed everywhere and permeable to divalent cations such as Mg^{2+} and Ca^{2+}. It contains a channel and a kinase domain. Recent studies indicate that activation of TRPM7 plays an important role in the growth and survival of gastric cancer cells. In this review, we describe and discuss the findings of recent studies that have provided novel insights of the relation between TRPM7 and gastric cancer.

1. Introduction

Gastric cancer is responsible for almost 1 million deaths worldwide per year, and thus is an important global healthcare issue. Although the age-adjusted mortality of gastric cancer has decreased over the past few decades, it remains the third leading cause of cancer-related mortality.[1] Cytosolic free Ca^{2+} concentration ($[Ca^{2+}]_i$) changes represent a ubiquitous signaling mechanism, which integrates with other signal-transduction cascades and controls a variety of cellular processes.[2] Alterations of calcium signaling and homeostasis have wide ranging consequences, and it is not surprising that some Ca^{2+}-mediated signaling pathways are implicated in tumorigenesis and tumor progression.[3–5] Accordingly, Ca^{2+} channels are crucial for a wide variety of biological processes, including tumor development and cancer growth.[6,7] Transient receptor potential (TRP) proteins are a family of ion channels

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and are responsible for many cellular functions. They were initially identified in *Drosophila*, in which spontaneously occurring mutations in the *trp* and *trpl* genes selectively abolish the delayed, light-sensitive, sustained depolarization caused by Na^+ and Ca^{2+} influx into photoreceptors.[8] As a consequence, TRP *Drosophila* mutants exhibit transient rather than sustained light sensitive depolarization and receptor potentials, which are used to designate TRP channels.[9] These channels have been shown to be gated by a variety of physical and chemical stimuli, such as stretch, temperature changes, and a large number of endogenous (e.g., diacylglycerol and Ca^{2+}) and exogenous ligands. Furthermore, some of these channels have been reported to be activated by intracellular Ca^{2+}-store depletion.[8–10]

Research over the years has added considerably to our knowledge of the expressions and functional aspects of TRP melastatin 7 (TRPM7) channels. TRPM7 currents have an outward-rectifying cation current with reversal potential of 0 mV. However, in the absence of external divalent cations, TRPM7 outward rectification is largely abolished.[11] Also, TRPM7 has a property of more permeability with trace metal ions. Monteilh-Zoller et al[11] published a permeation profile order for TRPM7, as follows: $Zn^{2+} \approx Ni^{2+} \gg Ba^{2+} > Co^{2+} > Mg^{2+}$.

TRPM7 currents are evoked with pipette solutions lacking magnesium or magnesium adenosine triphosphate and activated constitutively in whole-cell configuration patch clamp experiments.[12] TRPM7 has the same properties as TRPM6. First, they Exhibit 49% primary amino acid sequence identity. In addition, they are Mg^{2+} and Ca^{2+} permeable ion channels with a channel kinase (atypical α-kinases) and show Mg^{2+} and Ca^{2+} permeable ion channels.[13–15] Recent studies have demonstrated that the TRPM7 channels can be modulated by 2-aminoethoxydiphenyl borate (2-APB). 2-APB can be used to differentiate between TRPM7 and TRPM6. 2-APB inhibits TRPM7 currents but potentiates TRPM6 at micromolar concentrations.[15,16] TRPM7 is also inhibited by carvacrol,[17] 5-lipoxygenase (LOX) inhibitors (NDGA, AA861, and MK886),[18] nafamostat mesylate,[19] Ca^{2+}-activated small conductance K^+ channel blocker NS8593,[20] waixenicin A,[21] sphingosine, and FTY720.[22] TRPM7 channel activity is regulated by extracellular pH,[23] and although the effects of protons on TRPM7 currents remain controversial,[24–26] it is known that TRPM7 can be regulated by acidic conditions, which is associated with ischemic stroke.[27,28]

TRPM7 channel is ubiquitously expressed in almost all tissues,[29,30] and several research groups[31–34] have suggested that it is closely associated with cellular growth and development under physiological conditions. Furthermore, the overexpression of TRPM7 in HEK-293 cells has been reported to lead to cell rounding and reduced adhesion and m-calpain activation,[35,36] which suggest that TRPM7 also plays a role in cell adhesion. In sympathetic neurons, synaptic vesicles have TRPM7 proteins, and in synaptic vesicles, synaptic vesicular synapsin 1, synaptotagmin 1, and snapin form complexes with TRPM7.[37] In addition, TRPM7 channel has a characteristic to alter acetylcholine release in neurons.[37] TRPM7 also has an important role in cardiac pathophysiology. TRPM7 is critical for myocardial proliferation during early cardiogenesis,[38] and impaired automaticity in *Trpm7*-deleted sinoatrial node cells induces abnormal diastolic depolarization, associated with a slowed diastolic Ca^{2+} rise and reduced pacemaker current I_f (encoded by *Hcn4* expression).[39] In the gastrointestinal tract, TRPM7 protein is essentially required for the pacemaking activities of interstitial cells of Cajal.[28,40]

Recently, many research studies have been conducted about the relationship between TRPM7 channel and cancer, such as the regulation of tumor proliferation, differentiation, apoptosis, angiogenesis, migration, and invasion.[30,31] Moreover, TRPM7 overexpression has been found in head and neck carcinoma,[41] retinoblastoma,[33] breast cancer,[42] and in gastric cancer.[43] Thus, TRPM7 channel is an important diagnostic and/or prognostic marker, and is a recognized target for pharmaceutical intervention. Nevertheless, further investigations are required to improve our understanding of the role of TRPM7 channel in cancer.[28,41] In this review, we discuss the findings of recent studies and provide novel insights of relations between TRPM7 and gastric cancer.

2. Gastric cancer

Gastric cancer is responsible for considerable morbidity and mortality, and is the third leading cause of cancer-related death in men and women.[1] Clinically, the symptoms of gastric cancer tend to emerge late during disease development, and thus treatment options are often limited. However, the search to find an optimal treatment continues amid improvements in our understanding of key aspects of its pathogenesis, which undoubtedly improve the likelihood of our identifying potential therapeutic targets. The majority of gastric cancers are adenocarcinomas, and traditionally gastric cancer is classified as intestinal or diffuse, as described by Lauren.[44] In general, gastric cancer arises from a gastric change, such as atrophic gastritis, which then develops into intestinal metaplasia and dysplasia. Moreover, *Helicobacter pylori* infection often induced gastric cancer through a chronic inflammation.[45] By contrast, diffuse gastric cancer is associated with pathological characteristics, such as loss of cell cohesion and signet ring cells, and (usually) negative *H. pylori* conditions.[45] In the past several years, many advances in science and technology have provided greater opportunity for molecular treatments of gastric cancer.[46]

3. TRPM7 channels and gastric cancer

The TRPM7 cation channel supports multiple cellular and physiological functions, including cell death. Jiang et al[25] suggested that TRPM7 channel inhibits the growth and proliferation of FaDu and SCC25 cells, two common human head and neck squamous carcinoma cell lines. Furthermore, suppression of TRPM7 channels by Gd^{3+}, 2-APB, or small interfering RNA (siRNA) about TRPM7 inhibited the growth and proliferation of these cells.[25] TRPM7 is required for pancreatic adenocarcinoma cell proliferation and metastasis via the mitogen-activated protein kinase (MAPK) pathway.[47,48] In the BxPC-3 cell line, dialyzing cytoplasm during patch clamp whole-cell recordings with a Mg^{2+} free pipette solution activated a non-selective cation current with strong outward rectification,