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Mini Review

Nav channels in cancers: Non-classical roles

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Abstract

Voltage-gated sodium channels (Nav channels) are transmembrane proteins that allow the permeability of sodium ions across membranes. They are critical for the initiation of the action potential. Research has revealed that Nav channel α and β subunits expressed abnormally and play non-classical roles in some cancer types. However, the understanding of Nav channel proteins in cancers remains insufficient and the lack of specific Nav channel drugs impedes the study in this field. The purpose of this mini-review is to summarize and comment on the present understanding of the roles of Nav channels in cancers. The membrane potential in non-excitable cells is critical for cell activities. Cancer cells usually have a higher resting membrane potentials than non-cancer cells. Nav1.5 and Nav1.7 are the two most expressed Nav channels in human cancers, while Nav1.2 and Nav1.6 are also expressed in some cancer types. There are several mechanistic speculations for the role of Nav channels in cancer, which include sodium-other ions homeostasis, the β subunits, and humoral regulation. To be mentioned, the review includes some personal perspectives that are required for further validation. This review will be conducive to the field of Nav channels in cancers.

Classical roles of Nav channels

Voltage-gated sodium channels (Nav channels) are transmembrane proteins that allow the permeability of sodium ions across membranes. They have been known as critical proteins for the initiation of the action potential. The Nav channels are comprised of α subunits and β subunits. To date, a total of nine Nav channel α subunit isoforms (Nav1.1–1.9) and four types of β subunits (β1-4) have been identified in different tissues, which are encoded by "SCN_A/B" genes (Figure 1) [1,2]. As one of the major channels participate in action potential, Nav channels play a critical role in neurons and other electrically excitable tissues. In this mini-review, I will introduce Nav1.5 and Nav 1.7 as two examples and briefly summarize the function of β subunits.

Nav1.5 is responsible for the initiation of the cardiac action potential. Certain regulatory proteins and post-translational modifications can regulate membrane trafficking and the electric property of Nav1.5 [3]. Many inherited cardiac arrhythmias were caused by abnormal Nav1.5 [4]. For example, long QT syndrome type 3, Brugada syndrome, atrial fibrillation, and congenital sick sinus syndrome are thought to result from the genetic mutations in the Nav1.5 gene (SCN5A). The expression level of Nav1.5 is through to account for some acquired cardiac disorders like heart failure. So far, the molecular mechanisms underlying these disorders are not well understood.

α-subunit	Gene	β-subunit	
Nav1.1	SCN1A	β1	SCN1B
Nav1.2	SCN2A	β2	SCN2B
Nav1.3	SCN3A	β3	SCN3B
Nav1.4	SCN4A	β4	SCN4B
Nav1.5	SCN5A		
Nav1.6	SCN8A		
Nav1.7	SCN9A		
Nav1.8	SCN10A		
Nav1.9	SCN11A		
Nax	SCN7A		

Figure 1: Genes encoding Nav channel α and β subunits.

On the other hand, Nav1.7 plays a crucial role in pain syndromes. Mutations that inactivate Nav1.7 function result in the loss-of-pain syndromes in patients who act normally in other aspects [5]. Other mutations in Nav1.7 lead to hyper-active channels and such patients suffer excessive pain syndromes Generally, terminals of sensory neurons highly express Nav1.7 channels, which also supports their pain-sensitive function. The Nav1.7 channels have relatively faster activation and inactivation, but slower recovery, thus even when depolarizations are very small, they can be activated and amplify ramp stimuli to reach the action potential threshold of the neuron [6].

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The presence of β subunits facilitates the switch of activation, inactivation, and closed states [7], but the exact mechanism of the gating regulation of β subunits remains largely unexplored. One possible effect that has been proposed is that β subunit Ig domains might bind to the α subunit where they can influence the electric field of VSMs [8]. In addition, the β subunit also has functions independent of the α subunit, such as cell adhesion [9], gene regulation [10] and brain development [11].

The membrane potential in non-excitable cells

As the membrane potential is critical for the electrophysiological signaling in the body, most of the studies focus on its effect on the propagation of action potentials in excitable tissues, such as muscle and nerve. However, the membrane potential depends on the ion channels on the membrane and ion concentrations inside and outside of the cells, which are not unique for excitable cells. The membrane potential was thought to be involved in many biological processes in non-excitable cells [12]. A study showed that the resting membrane potential of cancer cells was about -5 to -52 mV, as a comparison, that of highly proliferating non-cancer cells was about -5 to -25 mV and that of other non-cancer cells was about -95 to -40 mV [13]. Thus, cancer cells have relatively higher resting membrane potentials and these potentials are too positive for Na channels to have a 'classical' excitable function.

It has long been found that higher membrane potentials facilitate the proliferation of cells, which is believed to be associated with the initiation of mitosis and DNA synthesis [14,15]. Cancer cells usually have higher membrane potentials compared to their normal counterparts [13], which might be a reason for their fast proliferation. Interestingly, some tumor tissues have a higher level of sodium ions compared to non-cancer tissues, whereas their potassium ions level was similar [16-18], which implies that the intracellular sodium ions level could be the determinant of the abnormal membrane potentials in cancer cells. Therefore, sodium permeable channels might play a critical role in cancers.

The expression of Nav channels in cancers

Several types of channels involving sodium ions transportation have been found different in cancer [19]. One of the most reported channel types is Nav channels. Some of the known expression of Nav channel α subunits in cancers were summarized in Table 1 [20]. Functional Nav channel expression has also been reported in some cancer types, for example, in gastric cancer cell line BGC-823, Nav channel currents were measured by patch-clamp experiments [21]. Nav1.5 and Nav1.7 are the two most expressed Nav channels in human cancers, while Nav1.2 and Nav1.6 are also expressed in some cancer types, such as Mesothelioma [20]. Notably, some cancers express Nav channels neonatal splice variants, which are shown to be more adaptable to the acidified cancer microenvironment [22].

Potential mechanism of Nav channels in cancers

The activation of Nav channels is thought to be involved in some cancer metastatic cascades, including directional motility, pH balance, extracellular proteolysis, and invasion [23]. However, the mechanisms of Nav channels in cancer remain largely unexplored. So far, there are several mechanistic speculations for the role of Nav channels in cancer, which requires further validation and study.

Table 1: Expression and roles of Nav channel subtype in human cancer [20].

Cancer type	Nav channel	Role
Breast	Nav1.5 and 1.7	contribution to invasiveness/metastasis
Colon	Nav1.5	expressed early in invasiveness and contribution to invasiveness
Prostate	Nav1.7 and 1.6	contribution to invasiveness
Non-small cell lung carcinoma	Nav1.7	potentiation of invasiveness
Mesothelioma	Nav1.2, 1.6, and 1.7	promote migration
Cervical	Nav1.6	over-expression and potentiated invasiveness
Stomach	Nav1.7	Contribute to tumor growth
Ovary	Nav1.5	Contribute to tumor growth and invasiveness
Melanoma	Nav1.5	Expression induced membrane potential depolarization and inhibited Ca^{2+} uptake
Oral squamous cell carcinoma	Nav1.5	increase potentiation of proliferation and invasiveness
Astrocytoma	Nav1.5	Increase the potentiation of proliferation and invasiveness
Neuroblastoma	Nav1.5	not investigated
Endometrium	Nav1.7	contribution to invasiveness; increase positively with tumor size and local lymph node metastasis, and decrease survival (5–10 years)

Sodium and other ions homeostasis

Nav channels the sodium–hydrogen antiporter 1 (NHE1, a hydrogen ion channel co-expressed with Nav channels) increase intracellular alkalization and extracellular acidity. The acidic microenvironment of cancer cells promotes the degradation of the extracellular matrix by cysteine cathepsins [24], thereby facilitating cancer cells to leave the primary site [25-27]. On the other hand, sodium ions influx can activate calcium channels in cancer cells [28], which raises the intracellular concentration of calcium ions. This results in more uptake of calcium ions by mitochondria and further leads to a release of calcium ions into the cytosol [29], thereby promoting the formation of the invadopodia, the "feet of cancer cells", which can elongate the cancer cell to a morphology that facilitates cell movement. This hypothesis is largely based on the observation of Nav channels in macrophage and microglial podosomes [30]. In addition, the formation of invadopodia was also thought to result from Src kinase and cortactin phosphorylation involving cytoskeletal changes [31].

The β subunits

As Ig family cell adhesion molecules, β subunits are proposed to regulate cell adhesion, but studies have shown that β subunit subtypes regulated cancer migration and invasion in different ways. In breast cancer cells, β1 expression was negatively associated with cancer metastasis [32], while in prostate

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cancer, overexpression of β2 caused an increase in cancer migration and invasion [33]. The expression of β4 was reported to be downregulated in breast cancer cells compared to the non-cancer epithelial cells. Reduced β4 can promote migration and invasion while overexpressed β4 did the opposite [34]. Moreover, a recent study revealed that β3 can bind to tumor suppressor p53 and facilitate the degradation of p53 protein in liver cancer [35]. Although the effects of the β subunit on cancers have been observed, the mechanisms underlying the effects remain largely unknown.

Humoral regulation

Nav channels were through to be involved in the growth factors regulation in cancers. Epidermal growth factor (EGF) was reported to promote the migration and invasion of prostate and non-small cell lung cancer cells by increasing Nav 1.7 expression [36-38]. The regulatory role of nerve growth factor (NGF) in prostate cancer was also found to be associated with the up-regulation of Nav 1.7 [39,40]. Furthermore, the growth factors affecting Nav channels in non-cancer cells might play the same role in cancer cells. For instance, vascular endothelial growth factor (VEGF), a key regulator for cancer angiogenesis [41], has been found to increase Nav channels expression in the DRG neurons [42], while in cardiac myocytes and fibroblasts, the inhibition of Nav1.5 can up-regulate transforming growth factor-beta 1 (TGF-β1), a critical regulator in cancer [43]. Besides, studies have shown that Nav channels are closely associated with the secretion of hormones. In cardiomyocytes, insulin response elements in the SCN5A promoter region can affect the expression of Nav1.5 [44]. In adrenal chromaffin cells and breast cancer cells, insulin was also reported to regulate Nav channels expression [45,46]. Interestingly, the expression of functional Nav channels was found to be potentially associated with the expression of estrogen receptor (ER) in breast cancer cells [47] and basal expression of androgen receptor (AR) in prostate cancer cells [48].

Summary

Voltage-gated sodium channels (Nav channels) are transmembrane proteins that allow the passing of sodium ions through the cell membranes. Nav channels are a critical component of the system that initiates the action potential. Nav channel α and β subunits expression has been found abnormal in cancers. Some studies also indicated the non-classical roles of Nav channels in some cancer types. However, the roles of Nav channel proteins in cancers are still unclear. Cancer cells generally have a relatively higher resting membrane potentials than non-cancer cells. The two most expressed Nav channels in human cancers are Nav1.5 and Nav1.7, while some cancer types also expressed a lower level of Nav1.2 and Nav1.6. There are several mechanistic speculations for the role of Nav channels in cancer, which include sodium-other ions homeostasis, the β subunits, and humoral regulation. To be mentioned, the review includes some personal perspectives that are required for further validation. This review will contribute to the understanding of Nav channels in cancers.

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