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Perspective of Ion Channels in Prostate Cancer

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Abstract

Ion channels are membrane proteins, which play a great role in regulating cellular excitability. Alteration of ion channel may contribute to prostate cancer. This could be linked to inherited mutations of ion channel genes which alter channel's biophysical properties, in a prostate cancer. It is an observed fact that genomic instability is the main cause as well as the major characteristics of prostate cancer. Prostate cancer cell genotypes are mainly characterized by uncontrolled metastasis, resistance to programmed cell death, sustained angiogenesis as well as tissue invasion and metastasis. It is known that genes encoding ion channels are affected in prostate cancer. The Membrane proteins which is involved in signaling in cell and among cells, for coupling of extracellular events with intracellular responses, and for maintaining intracellular ionic homeostasis ion channels which contribute to some extents to pathophysiological features of each prostate cancer.

Keywords: Ion channels; Prostate cancer; Perspective.

1. Introduction

Ion channels are ion-permeable pores in the lipid membranes of all cells. They open and close in response to stimuli, gating the flow of specific small ions. They are pore-forming proteins that permeate the flow of ions across membranes, either plasma membranes or the membranes of intracellular organelles. Some of these ion channels are gated by voltage while are relatively voltage-insensitive and are gated by second messengers. They are integral membrane proteins that consists of an aqueous pore in which, when it is open, some ions can move freely between these compartments [1]. It could be referred to as specialized proteins in the plasma membrane that enable a passageway via which charged ions can cross the plasma membrane down their electrochemical gradient. The resulting ionic current, generated by the movement of charged ions via membrane channels, can be measured. Ion channels are remarkable proteins, present in the lipid bilayer membrane of both animal and plant cells and their organelles [2]. Indeed, cell membranes have individual ion channels through which tiny currents can pass, which are big enough to generate communications between pre- and postsynaptic neurons by converting chemical or mechanical events into electrical signals [3].

Ion channel is protein expressed by mainly all living cells which acts as a pore in a cell membrane and allows the selective flow of ions such as potassium ions, sodium ions, and calcium ions, through which electrical current passes in and out of the cell. It can play important roles including chemical signalling, transcellular transport, regulation of pH, and regulation of cell volume. The dysfunction of ion channels can result to prostatic cancer in prostate tissues. There are various human diseases linked with defects in ion channels. These diseases are referred to as channelopathies [4]. The contraction of the heart, operation of cells in the nervous system, and of skeletal muscle, and secretion in the pancreas are good examples of physiological processes that require ion channels. Also, ion channels in the membranes of intracellular organelles are important for regulating cytoplasmic calcium concentration and acidification of specific subcellular compartments Ions flow passively through channels toward equilibrium. This movement may be driven by electrical or chemical gradients. It is necessary to note that events occur in the prostate cancer cells due to the mutations and overexpression of genes encoding the ion channels [5].

Furthermore, the genetic and autoimmune disorders of the ion channels cause ion channel disorders. If a mutant gene encodes an ion channel protein that is present on the cell membrane of prostate, it results in the development of diseases in prostate called prostate cancer [6]. It is very important to note the three functional domains of all ion channels which are:

i. Ion conducting pore: An aqueous pathway for ions with a narrow selectivity filter that distinguishes among the ions that do go through and the ions that do not
ii. Gates: a part of the channel that can open and close the conducting pore
iii. Sensors: detectors of stimuli that respond to electrical potential changes or chemical signals. The sensors couple to the channel gates to control the probability that they open or close [7].

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Most ion channels are gated. This implies that they open and close either spontaneously or in response to a specific stimulus, such as the binding of a small molecule to the channel protein known as ligand-gated ion channels or a change in voltage across the membrane that is sensed by charged segments of the channel protein known as voltage-gated ion channels. In fact, most ion channels are selective, permeating only certain ions to pass through. Some channels conduct only one type of ion (e.g., potassium), whereas other channels exhibit relative selectivity—for instance, permeating positively charged cations to pass through while excluding negatively charged anions [8]. Most cells in higher organisms may prompt more than 100 different types of ion channel, each with different selectivity and different gating properties [9].

These ion channels are classified into three superfamilies: voltage-gated, ligand-gated and mechano-sensitive ion channels

2. Voltage-Gated Ion Channels

These are in channels that respond to agitations in cell membrane potential, and are highly selective for a specific ion, i.e., Na+, K+, Ca2+, and Cl-. Voltage-Gated Ion Channels are subdivided into families based on the major permeant ion to (i) Voltage-gated Na+ channel - which are responsible for the generation of action potentials of long duration, and thus are targets of local anesthetics, such as lidocaine and benzocaine.(ii)Voltage-gated Ca2+ channels – which maintain intracellular Ca2+ concentrations, and hence are responsible for a wide range of biochemical processes within cells. One of the most important processes regulated by these channels is the release of neurotransmitters at synapses. Calcium channel blockers are important in treating a variety of conditions ranging from heart disease to anxiety disorders.(iii)Voltage-gated K+ channels – which comprises the largest and the most varied class of voltage-gated ion channels. They are imperative in generating the resting membrane potential. (iv) Voltage-gated Cl- channels – which are present in every type of neuron and are involved in regulating excitability and cell volume. They are also known to contribute to the resting membrane potential [9].

3. Ligand-Gated Ion Channels (LGIC)

LGIC are targets for many drugs, such as anesthetics, antipsychotics, and antidepressants. They are named according to the ligand to which they respond and are classified into three families based upon molecular biology and protein structure criteria. They include (i) **Cys-Loop LGIC which** constitute the largest class of LGICs and include nicotinic acetylcholine receptors (nAChR), γ-aminobutyric acid (GABA) receptors, 5-hydroxytryptamine-3 (5HT3) receptors, and glycine receptors. The nAChR and 5-HT3R are excitatory receptors, while the GABA receptors and glycine receptors are inhibitory in nature.

The nAChRs are activated endogenously by the neurotransmitter acetylcholine. Acetylcholine plays an important role in various cognitive processes, such as learning, memory, and attention. It is also an important signaling chemical at the neuromuscular junction.

Activation of 5-HT3 receptors plays an important role in a variety of sympathetic, parasympathetic and sensory functions. In the central nervous system (CNS), 5-HT3 receptors are involved in emesis, cognition, and anxiety. It helps in the regulation of various cognitive, physiological, emotional and metabolic systems. It affects physiological processes, such as sleep patterns, circadian rhythms, appetite, aggression levels and body temperature [10].

The GABA receptor selectively conducts Cl^- through its pore, which causes hyperpolarization and a resultant increase in the threshold for generation of action potential. A reduction in the probability of action potential generation causes neuronal inhibition. GABA inhibits wake-promoting regions and hence is involved in supporting sleep. Impairment in GABA signaling is also a major reason for anxiety disorders. Benzodiazepines reduce unwanted brain excitability, by increasing GABA signaling in the brain, and hence can be used to treat anxiety disorders [11].

Glycine receptors mediate synaptic inhibition in the spinal cord, brainstem, and other regions of the central nervous system. They regulate the excitability of motor and afferent sensory neurons, including pain fibers, and are also involved in the processing of visual and auditory signals. Hence, they represent a promising target for the development of therapeutically useful compounds.

(ii)Ionotropic Glutamate Receptors which are activated by the neurotransmitter glutamate and mediate most fast excitatory transmission in the CNS. They are subclassified into α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors, kainate receptors and N-methyl-D-aspartate (NMDA) receptors.

AMPA receptors mediate fast excitatory synaptic transmission at the majority of central synapses. Kainate receptors regulate neuronal excitability, whereas NMDA receptors play a major function in synaptic plasticity.

P2X Receptors: They are the most recently discovered membrane ion channels. They are preferably permeable to Na+, K+ and Ca2+ and are activated by ATP. P2X receptors are widely expressed in many tissues and are shown to play important function in various physiological processes, such as nerve transmission, pain sensation, and various inflammatory responses [11].

4. Mechano-Sensitive Ion Channels

These are phenomenon in which ion channels respond to changes in mechanical forces on the cell membrane These channels are involved in detection and transduction of external mechanical forces into electrical and/or chemical intracellular signals [12].

They are involved in regulation of blood pressure and cell volume, stimulation of muscle and bone development, and the senses of hearing and touch. Studies have shown these channels to be involved in various

conditions like cardiac arrhythmias, muscular dystrophy, neuronal degeneration, polycystic kidney disease, and tumor metastasis [13].

As ion channels are responsible for the regulation of major physiological functions, an understanding of their mechanisms at a molecular level. Recently, there is an increased understanding of how ion channels function. Reports have indicated that discovery of a variety of mutations in ion-channel genes, results to various channelopathies [14].

4.1. Ion Channels Serve Three Main Physiological Roles

Firstly, ion channels set up the resting membrane potentials of the cells. The flow of ions moves charge and consists an electric current, channel opening and closing underlie all electrical signaling of electrically excitable cells such as nerve and muscle. Hence, when open, potassium ion-selective channels and anion channels hyperpolarize cells, whereas sodium- or calcium-selective channels and non-selective cation channels depolarize cells [15].

Secondly, the flux of ions through ion channels gives to the electrolyte movements required for volume regulation of single cells and for the net polarized transport of salt across epithelia like gut, kidney, or the choroid plexus.

Thirdly,a few ions, notably Ca^{2+}, make regulatory signals inside cells. Cytoplasmic calcium signals are generated by the opening of Ca^{2+}-permeable ion channels that let Ca^{2+} ions flow into the cytoplasm. The Ca^{2+} may come from the extracellular medium or from intracellular organelles. Entry from the outside is the primary mechanism for translation of electrical signals into chemical signals. It is how electrical signals in electrically excitable cells couple to hormone secretion, neurotransmitter release, muscle contraction, and changes in gene expression [16].

The ability of ion channels to accomplish these three physiological functions also requires the housekeeping operation of another class of membrane proteins, the transporters and pumps, to set up standing ion concentration gradients across cell membranes. Ion concentration gradients and electrical forces drive the flow of ions through channel pores [17, 18].

5. Conclusion

The redistribution of ions in cellular compartments due to channels' opening can affect many cellular processes and functions ranging from electrical excitation to locomotion. These processes are necessary for maintaining normal tissue homeostasis, such as cell proliferation, migration, and apoptosis. Hence, dysfunction of ion channels can negatively affect these processes driving the transformation of normal cells into malignant associated ones that exhibit uncontrolled multiplication and spreading, which are characteristics of prostate cancer

References

[1] Arcangeli, A., 2011. "Ion channels and transporters in cancer. 3. Ion channels in the tumor cell-microenvironment cross talk." *Am. J. Physiol. Cell Physiol.*, vol. 301, pp. C762–C771.

[2] Becchetti, A. and Arcangeli, A., 2010. "Integrins and ion channels in cell migration: implications for neuronal development, wound healing and metastatic spread." *Adv. Exp. Med. Biol.*, vol. 674, pp. 107-123.

[3] Camerino, D. C., Tricarico, D., and Desaphy, J. F., 2007. "Ion channel pharmacology." *Neurotherapeutics*, vol. 4, pp. 184-98.

[4] Verkman, A. S. and Galietta, L. J., 2009. "Chloride channels as drug targets." *Nature Reviews. Drug Discovery*, vol. 8, pp. 153-71.

[5] Hansen, S. B., 2015. "Lipid agonism: The PIP2 paradigm of ligand-gated ion channels." *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids.*, vol. 1851, pp. 620-8.

[6] Smith, R. S. and Walsh, C. A., 2020. "Ion channel functions in early brain development." *Trends in Neurosciences*, vol. 43, pp. 103-114.

[7] Molenaar, R. J., 2011. *Ion channels in glioblastoma*. ISRN Neurology.

[8] Becchetti, A., 2011. "Ion channels and transporters in cancer. 1. Ion channels and cell proliferation in cancer." *Am. J. Physiol. Cell Physiol.*, vol. 301, pp. C255-C265.

[9] Gouaux, E. and Mackinnon, R., 2005. "Principles of selective ion transport in channels and pumps." *Science*, vol. 310, pp. 1461-1465.

[10] Camerino, D. C., Desaphy, J. F., Tricarico, D., Pierno, S., and Liantonio, A., 2008. "Therapeutic approaches to ion channel diseases." *Advances in Genetics*, vol. 64, pp. 81-145.

[11] Gabashvili, I. S., Sokolowski, B. H., Morton, C. C., and Giersch, A. B., 2007. "Ion channel gene expression in the inner ear." *Journal of the Association for Research in Otolaryngology*, vol. 8, pp. 305-28.

[12] Arcangeli, A., Crociani, O., Lastraioli, E., Masi, A., Pillozzi, S., and Becchetti, A., 2009. "Targeting ion channels in cancer: a novel frontier in antineoplastic therapy." *Curr. Med. Chem.*, vol. 16, pp. 66-93.

[13] Okada, Y., 2006. "Cell-volume sensitive chloride channels: phenotypic properties and molecular identity." *Contrib Nephrol*, vol. 152, pp. 9-24.

[14] Okada, Y., Sato, K., and Numata, T., 2009. "Pathophysiology and puzzles of the volume-sensitive outwardly rectifying anion channel." *J. Physiol.*, vol. 587, pp. 2141-1459.

[15] Suzuki, M. and Mizuno, A., 2004. "A novel human Cl- channel family related to Drosophila flightless locus." *J. Biol. Chem.*, vol. 279, pp. 22461-22468.

[16] Verkman, A. S. and Galietta, L. J., 2009. "Chloride channels as drug targets." *Nat. Rev. Drug. Discov.*, vol. 8, pp. 153-171.

[17] Wang, Z., 2004. "Roles of K+ channels in regulating tumour cell proliferation and apoptosis." *Pflugers Arch.*, vol. 448, pp. 274-286.

[18] Lang, P. A., Kaiser, S., Myssina, S., Wieder, T., Lang, F., and Huber, S. M., 2003. "Role of Ca2+-activated K+ channels in human erythrocyte apoptosis." *Am. J. Physiol. Cell Physiol.*, vol. 285, pp. 1553-1560.