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Review

Understanding autoimmunity: The ion channel perspective

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ABSTRACT

Ion channels are integral membrane proteins that orchestrate the passage of ions across the cell membrane and thus regulate various key physiological processes of the living system. The stringently regulated expression and function of these channels hold a pivotal role in the development and execution of various cellular functions. Malfunction of these channels results in debilitating diseases collectively termed channelopathies. In this review, we highlight the role of these proteins in the immune system with special emphasis on the development of autoimmunity. The role of ion channels in various autoimmune diseases is also listed out. This comprehensive review summarizes the ion channels that could be used as molecular targets in the development of new therapeutics against autoimmune disorders.

Contents

Abbreviations: ASIC, Acid Sensing Ion Channel; CLIC, Chloride Intracellular Channel; CRAC, Calcium Release Activated Channel; hERG, Human Ether A Go-go Related Gene; LTCC, L-Type Calcium Channel; MuSK, Muscle Specific Kinase Receptor; STIM, Stromal Interaction Molecule; VGSC, Voltage Gated Sodium Channel; VGKC, Voltage Gated Potassium Channel; VGCC, Voltage Gated Calcium Channel.

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1. Introduction

Transport of ions and solutes across the plasma membrane is critical in driving various cellular processes. This crucial process is stringently orchestrated by transmembrane proteins called ion channels that permit the selective passage of ions across the cell membrane. These proteins are implicated in most physiological processes including the electrical excitability of cardiac and neuronal cells, cell growth and proliferation and the secretion of hormones. Deficiencies in the normal functioning of these channels manifest themselves as debilitating disorders collectively called channelopathies. Some channelopathies include the Long QT Syndrome, Cerebral Ataxia, Cystic Fibrosis, and the Romano Ward Syndrome. Ion channels facilitate a high throughput passage of ions (close to a rate of 10^6 ions per second) across the cell membrane, while at the same time maintaining a high degree of selectivity. These channels gate (i.e. open and close) in response to a number of stimuli like transmembrane potential difference, ligands, pH, temperature, mechanical stimuli etc. The importance of these proteins in human physiology has been well acknowledged by the scientific community with 4 Nobel prizes been awarded to stalwarts in ion channel biology research including Neher, Sakmann, R. Mackinnon and P. Agre.

1.1. Role of ion channels in physiological processes of the body

Ion channels orchestrate action potential generation and propagation in electrically excitable cells like the neurons, cardiomyocytes and skeletal muscle cells. Both voltage-gated and ligand-gated channels are involved in the synaptic transmission of the nerve impulses. Ion channels are classified into various types, as summarized in Table 1. In addition to ion channels, receptors linked to ion channels like the NMDA (N-methyl D-aspartate) are reported to be implicated in the process of learning and memory (short-term and long-term memory), and in the maintenance of Long Term Potentiation (LTP) by regulating the passage of calcium, sodium and potassium ions across the cell membrane. nAChR (nicotinic Acetylcholine Receptor) is mainly involved in the learning process mediated by a regulation of calcium signaling in the post-synaptic terminals [1]. In the cardiac conduction system, ion channels like Hyperpolarization activated Cyclic Nucleotide (HCN), Human Ether-a-go-go Related (hERG) potassium channel, and Voltage Gated Sodium Channel (VGSC) have been demonstrated to be pivotal to the generation and conduction of the cardiac action potential and a unique signatory pattern of ion channels in the different types of cardiomyocytes are responsible for the difference in the action potentials recorded from atrial, ventricular and pacemaker cells.

Ion channels are reported to play a role in the function of non-excitable cells, some of which include fluid transport, cell volume regulation, cell proliferation and differentiation, and also in mediating ion transport across intracellular membranes in organelles. Ion channels are also implicated in cell proliferation, commitment of stem cells into a particular lineage and their differentiation into specialized terminally differentiated cells. For instance, proliferation and differentiation of neuronal cells have also been shown to involve the calcium activated potassium channel and nAChR [2,3].

2. Role of ion channels in immune response

The immune cells including the subsets of the T and B lymphocytes like Treg (Tregulatory) cells, T helper (Th) cells, NK (Natural Killer) cells, and neutrophils and other antigen presenting cells like the macrophages and dendritic cells function round the clock to maintain the humoral- and cell-mediated responses of the immune system. Ion channels have been implicated in the functioning of the immune cells