Ions and Ion Channels

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Life depends upon the ability of cells to evaluate and adapt to a constantly changing environment and to maintain internal stability to allow essential biochemical reactions to occur. Ions and ion channels play a crucial role in this process and are essential for survival. Alterations in the expression of the transmembrane proteins responsible for maintaining ion balance that occur as a result of mutations in the genetic code or in response to iatrogenically induced changes in the extracellular environment is a characteristic feature of oncogenesis and identifies cancer as one of a constellation of diseases known as channelopathies.

cancer channelopathy targeted osmotic lysis ion channels

1. Introduction

For decades, the oncology community has regarded cancer from several viewpoints. Originally thought of only as a disease of uncontrolled growth, it is additionally viewed as a failure of cell death, genetic mutation, or a failure of the immune system. Moreover, metastasis can be thought of as an increase of motility and invasiveness, and recurrence can be viewed as cancer cells exiting an extended G0 phase of the cell cycle or hibernation and a return to the features of stem cells. The viewpoint from which the disease is viewed determines the approaches to treatment that are likely to be conceived.

Louis Ptáček and his colleagues [1][2][3], upon discovering that a mutation in the gene that codes for the expression of the sodium channel in muscle responsible for contraction was the cause of hyperkalemic periodic paralysis, introduced the term, channelopathy, to highlight the importance of altered ion channel functioning in the phenotypic presentation of the disease [4]. Since then, it has been recognized that many other diseases [5][6][7][8][9][10][11], similarly share altered ion channel expression and the resulting determinants of abnormal gain or loss of function associated with mutations in the genetic code or in response to changes in the extracellular environment [12], as major contributors to establishing the pathogenic state. Indeed, over the past 30 years or so, a small community of investigators has focused on the role of ion channels in cancer proliferation, metastasis and recurrence [13]. Voltage-gated Ca^{2+} and K^{+} channels, up-regulated in many forms of carcinoma and sarcoma, induce the suspension of apoptosis [13][14][15][16]. Treatments designed to inhibit Ca^{2+} channels can re-instate apoptosis [17][18]. Likewise, inhibition of voltage-gated K^{+} channels can restore apoptosis in many carcinomas [19]. Additionally, some ligand-gated ion channels, over-expressed in certain cancers, lead to enhanced cellular proliferation [20]. Importantly, an increase in voltage-gated sodium channel (VGSC) expression has been linked to increased motility, invasiveness, growth rate, and metastasis in most aggressive carcinomas [21][22][23][24][25][26][27][28][29][30][31][32]. Because of these findings, Prevarskaya et al. [33] proposed that cancer should viewed as an “oncochannelopathy”

which has led to the proposal of an array of novel treatments that in deference to approaches that eliminate the affected cells to deliver a cure, are designed to additionally modulate or mitigate the effects of altered channel expression in order to restore function.

2. Ions and Ion Channels—Basic Fundamental of Life

2.1. Ion Channels and Life in Single Cells

Life as researchers know it is contingent upon the ability to isolate, organize, coordinate and maintain a conducive environment for chemical reactions to occur that transform or conserve energy to support growth, reproduction and survival of cellular units in an ever-changing and often hostile external environment. The types and relative amounts of charged elements present at a given time that can vary widely in the external environment, but are tightly controlled within the confines of individual cells by semi-permeable membranes that are responsible for maintaining cellular shape and the internal compartmentalization that is necessary for ensuring the proper and efficient conduction of biochemical reactions [34][35][36].

Neutral relationships in living systems fluctuate due to the semi-permeable nature of the plasma membrane and the ionic concentration gradients that provide a form of stored energy for driving many of life's essential biologic reactions [37], e.g., neuronal action potential, muscular contraction, oxidative phosphorylation, in an effort to reach molecular equilibrium. The charged nature of the lipid bilayer also retains large, impermeable, negatively-charged, and osmotically active molecules within the cell that create a charge imbalance with the extracellular space. The charge imbalance must be reconciled in order to achieve osmotic equilibrium, homeostasis, and environmental support for biologic function and must be present to establish and maintain the voltage gradient across the membrane of active cells. Because the passage of each of the charged species differs, resolution of the charge imbalance must be achieved by coordinating the concentrations of charged species, typically Na^+ ions with limited access to the intracellular space and less impeded, positively charged K^+ ions. Based on the level of cellular activity and the composition of the extracellular space, the membrane potential can shift above or below the resting level, thus affecting conformational change in a variety of transmembrane proteins that selectively allow voltage-gated facilitated diffusion of specific charged species, e.g., K^+, Ca^{2+}, Na^+, Mg^{2+}, H^+, Cl^-, PO_4^{2-} and HCO_3^- ions, into and out of the intracellular space down their concentration gradients [38]. The gradients are created and maintained by the active transport of charge elements across cell membranes against their concentration gradient that derive energy from the breakdown of adenosine triphosphate (ATP) or by coupling the transport of charged particles against their concentration gradients in conjunction with the transfer of another charged element that flows down its concentration gradient [39][40]. The linked transport provides the requisite energy for the exchange, e.g., Na^+/Ca^{2+} exchanger, Na^+/H^+ exchanger, Cl^-/HCO_3^- exchanger. Sodium-potassium-ATPase (Na^+, K^+-ATPase; the sodium pump), serves as the primary energy-dependent transporter in most cells for establishing and maintaining the electrochemical gradient that is created by the differences in the intra- and extracellular Na^+ and K^+ ion concentrations across the cell membrane [40]. Channel opening and closing and the ability to subsequently restore the membrane's electrochemical gradient provides the basis for the cell's ability to monitor the extracellular environment to embrace favorable and avoid injurious conditions and for maintaining proper cellular homeostasis

for growth, cell motility and reproduction. Alterations in the voltage gradient that occur across plasma membranes in the process of living and in response to challenges from the extracellular environment result in a choreographed ebb and flow of charged elements that is necessary to adjust to changes that occur during the performance of biological functions. As long as individual cells are able to acquire oxygen and sufficient nutrients and to eliminate waste, they will grow and survive.

2.2. Ion Considerations in Multicellular Organisms

Ion concentrations and gradients and the modulation of the channels and transporters responsible for establishing and maintaining osmotic balance are also essential for survival at the level of multicellular organisms. The regulation of charge provides energy and establishes the basis for performing and maintaining many essential functions including the control of cellular replication, relative growth and cell death during embryonic development, the initiation of gene expression, organ function and plastic changes needed for organ repair and maintenance, the coordination of neuronal function, the development and modulation of neuronal circuitry controlling behavior and even the development of pathologic change associated with degenerative and proliferative disease that contributes to organismal demise [41].

Despite the significant specialization of function that is required to ensure the survival of multicellular organisms, the maintenance of cellular homeostasis and the elements of intercellular communication are conserved and are absolutely fundamental. They rely on the expression and coordinated functioning of ion channels to communicate and coordinate the benefits of cellular specialization to enable the organism to successfully compete for, and effectively occupy osmotically supportive niches for the good of the organism. In so doing, a conceptual shift in priority from ensuring survival of individual cells to survival of the whole is adopted. This requisite shift involves autophagy, a process for breaking down, eliminating or recycling damaged cellular components and the programmed elimination of certain cells to ensure optimum functioning of individual parts for the benefit of the whole, a process known as apoptosis or apoptotic cell death [42][43][44][45][46]. Autophagy serves to repair and replace dysfunctional cells and apoptosis plays an essential role in shaping an organism during embryonic development, in the maintenance of cellular volume and turnover and in the control of organ size.

As in life, the death of a cell depends on maintaining the proper water content within a space-limiting membrane. The free passage of water across the plasma membrane occurs by osmosis when differences in osmotic pressure exist between the cell's external and internal environs [41][47][48][49]. In the presence of low osmotic pressure, water diffuses through the cell membrane resulting in an increase in cellular volume. Although water generally follows the flux of Na^+, the restoration of cell volume in normal cells in response to small isovolumetric fluctuations in osmotic pressure, typically involves a large influx of Ca^{2+} and the extrusion of K^+, Cl^-, and organic osmolytes through activation of a wide variety of transmembrane protein channels in the cell membrane, e.g., Ca^{2+}-activated K^+ (K_{Ca}) channels (predominantly the large-conductance (BK_{Ca}) and intermediate-conductance (IK_{Ca}) Ca^{2+}-activated K^+ channels), voltage-gated K^+ (Kv) channels, inwardly rectifying K^+ (K_{IR}) channels, two-pore-domain K^+ (K_{2P}) channels and the extrusion of organic osmolytes, e.g., amino acids, polyalcohols, and amines, through volume-regulated anion channels (VRAC) associated with the production of free radicals [41][47][50][51]. In the presence of

high osmotic pressure, water leaves the cell thereby reducing cell volume and initiating a regulatory volume increase (RVI) mechanism associated with increased levels of intracellular Na^+, Cl^-, and organic osmolytes through the activation of Na^+/Cl^- and $Na^+/K^+/2Cl$ cotransporters and Na^+/H^+ exchangers [52][53][54][55][56]; **Figure 1**. The maintenance of intracellular and extracellular ionic balance, osmotic pressure and cell volume, is essential for the support of life sustaining biochemical reactions and survival [42][43][47][55][57][58][59]. The mechanisms and elements enabling ionic exchange are conserved and extraordinarily redundant in cells throughout the animal kingdom [60][61]. When working well, the multiplicity of pathways effectively guarantees continued conduction of essential functions and provides a means to escape elimination when exposure to harmful or lethal stresses occurs.

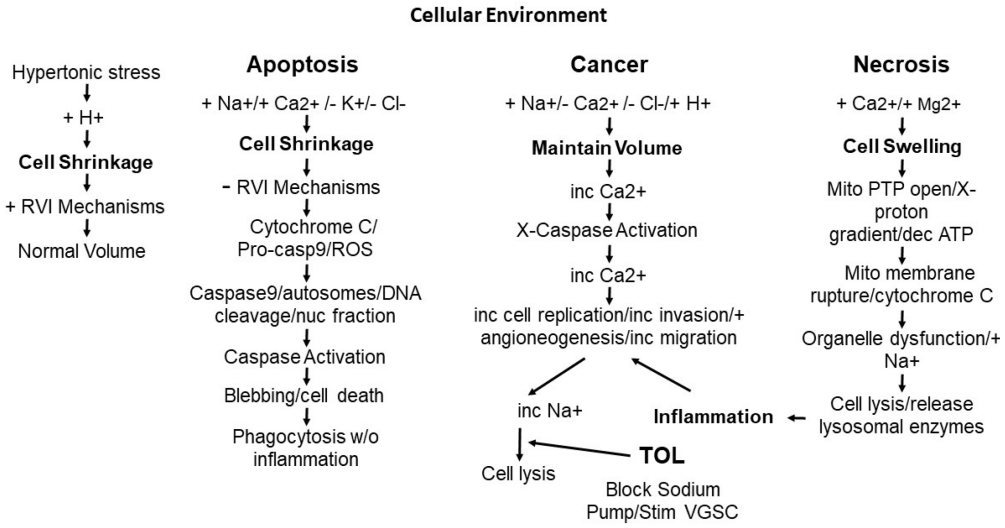

Figure 1. The diagram presents major steps in the metabolic pathways occur in cells in response to extrinsic environmental challenges (hypertonicity, hypoxia, toxins, immune response, and trauma) and intrinsic signaling that trigger influx (+) or efflux (−) of ions orchestrated through numerous channels between the extracellular matrix and the intracellular space resulting in shifts in cell volume, downstream activation, increase (inc), decrease (dec), or inhibition (X) of processes affecting cellular function and survival. The numbers and types of channels expressed and the resulting number of ions exchanged determines cellular functioning and provides targets for developing treatments to modulate pathologic change and provides the means for cells to develop resistance and avoid elimination with intervention affecting steps closer to cellular elimination having less opportunity for resistance.

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