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Editorial

Membrane Proteins: New Insights into Structure, Metabolic Functions and Disease-Relevant Mutations

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All cells require membrane proteins to perform a wide range of dynamic processes essential for cellular homeostasis and survival. This includes the transport of proteins, ions and electrons, signal transduction, enzymatic reactions, and inter-cellular communication. There are many important classes of membrane proteins, including active and passive transport proteins, ion channels, cell receptors, enzymes, and many others. To determine the structures of membrane proteins, it is first necessary to extract and purify them from cellular membranes, in which they closely interact with lipids and other membrane components. These procedures make it difficult to subsequently renature membrane proteins into their native conformation. It is for this reason that although, over a period of decades, the structures of many membrane proteins have been determined, the structures of many others remain unknown. ***Note,*** *although several sentences are dedicated in this opening paragraph to "structure determination", none of the examples discussed below include structure determination.* Importantly, the expression of mutant forms of membrane proteins with altered structure can cause a variety of serious diseases, which manifest in a plethora of patho-physiological processes of major clinical and scientific interest.

This Special Issue presents a collection of articles focused on the specific functions of proteins and ion channels in the contexts of the cell nucleus, modulation of disease-related signaling pathways, regulation of cell proliferation, migration and differentiation, and electrophysiological phenomena underlying hypokalemia-induced cardiac arrhythmia. Some of these contributions are briefly outlined below.

Ping Liu and colleagues [1] carried out a study of the depolarization of human cardiomyocytes induced by low extracellular potassium concentrations, a feature of hypokalemia-induced fatal cardiac arrhythmia. The authors examined the role in this system of the two-pore potassium channel family (K2P) two-pore K^+ channels, which belong to a class of K^+ channels that maintain the membrane potential in many cell types. Two-pore domain potassium channel (TWIK-1) is a subtype of K2P channels first identified in human kidney tissues. K2P channels form a dimer in which the K^+ selectivity is associated with a specific threonine residue (Thr118) present in a conserved sequence (TTGYG) responsible for the altered ion selectivity leading to depolarization of cardiomyocyte membrane potential at low extracellular potassium concentrations [2,3]. This study had two aims. The first was to determine if TWIK-1 channels are responsible for depolarization of the membrane potential at low [K^+], and secondly, the role of Thr118 in ion selectivity. The results clearly demonstrated that Chinese hamster ovary (CHO) cells expressing TWIK-1 depolarized in response to low [K^+] and this was accompanied by inward Na^+ currents. The specific role played by Thr118 in this phenomenon was also confirmed. By establishing that in response to low [K^+], TWIK-1 channels conduct inward leak Na^+ currents to induce depolarization of the human cardiomyocyte membrane potential, this study makes a valuable contribution to understanding of the role of these channel proteins in hypokalemia-induced fatal cardiac arrhythmia.

The manuscript from Dongchuan Zuo *et al*. [4] deals with the role of the transient receptor potential melastatin 7 (TRPM7) on the proliferation, migration and osteogenic differentiation of dental follicular cells (DFCs) which are responsible of the regeneration of tissues. Over many years, DFCs have attracted much attention, particularly in relation to molecular processes occurring during *in vitro* differentiation. Despite this attention, the mechanisms involved are not yet fully understood [5]. Structurally, TRPM7 is a bi-functional protein-receptor containing a kinase domain fused to an ion channel. TRPM7 regulates Mg^{2+} homeostasis, which is essential for cell survival, proliferation, migration and the differentiation of various cell types [6]. Furthermore, TRPM7 mediates Ca^{2+} influx in response to various stimuli, which induces osteogenesis in human bone marrow mesenchymal stem cells (MSCs) [7]. The report clearly shows that DFCs express TRPM7 transcript and protein, and used electrophysiological analysis to identify the corresponding functional activity. The study went on to demonstrate for the first time that suppression of TRPM7 expression inhibited the proliferation and migration of DFCs, suggesting an important role for TRPM7 in osteogenic differentiation and in the regulation of biological effects exerted by DFCs.

Batha and coworkers [8] provide new insights into the effects exerted by five known transcript variants of lamin

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A/C. These proteins polymerize to form a network which confers structural and mechanical integrity to the nucleus [9]. In addition, lamins play a pivotal role in DNA repair, replication, and transcription, with consequent effects on cellular differentiation, apoptosis, and cell aging. Mutations in the sequences of the five transcripts are correlated with more than 300 diseases and also with changes in expression patterns found in many types of cancers [10]. Furthermore, laminopathies affect various tissues by inducing changes in proliferation, expression and structural alterations that can culminate in malignant cancers. This report highlights the roles of different lamin A/C transcripts in the development of different types of cancer and many other diseases.

In summary, this Special Issue is a curated collection of examples of research focused on membrane protein function, especially as it relates to molecular mechanisms underlying the development of cancer and other important diseases. The collection presented in this Special Issue provides valuable insights into the challenges and rewards of applying varied and combined experimental and methodological approaches to study these important biological systems.

Abbreviations

TWIK-1, two-pore domain potassium channel; K2P, two-pore potassium channel family; CHO, Chinese hamster ovary; TRPM7, transient receptor potential melastatin 7; DFCs, dental follicular cells; MSCs, mesenchymal stem cells.

Author Contributions

DVM: Conceptualization, Writing–original draft, Writing–review and editing. DVM read and approved the final manuscript. DVM has participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

Given her role as the Guest Editor, Daniela Valeria Miniero had no involvement in the peer-review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Graham Pawelec.

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