Editorial

Calcium Regulatory Proteins as Therapeutic Targets

Calcium is a ubiquitous signal molecule and critical to cell function. Maintaining calcium homeostasis is essential to life. Calcium homeostasis is mediated by a number of plasma membrane and intracellular calcium channels and transporters that are driven by stimuli that allow rapid alterations in release and uptake [1]. A large electrochemical gradient is created across the plasma membrane as a result of the differential in calcium concentration between the extracellular and cytosolic domains. Therefore changes in intracellular calcium can occur rapidly as a result of calcium influx into cells through calcium channels or transporters in the plasma membrane. Internal stores can also contribute to oscillations in intracellular calcium through receptor mediated release and uptake. Changes in intracellular calcium mediate alterations in cell function through activation of calcium-dependent kinases and regulatory proteins.

The manipulation of genes encoding calcium channels and transporters has provided insight into the critical role ion transport plays in physiology. Mutations in calcium channels cause a variety of disorders. Mice that are deficient in calcium channel pore forming subunits are often not viable as calcium channels are critical for muscle function. In skeletal and cardiac muscle the ryanodine receptor contributes to elevation of intracellular calcium that is required for calcium binding to contractile regulatory proteins and muscle contraction. Mice lacking the skeletal muscle ryanodine receptor (RyR1) are lethal at birth due to respiratory failure and mutations in the RyR1 protein can cause severe disorders such as malignant hyperthermia and central core disease in skeletal muscle [2]. Mutations in the cardiac RyR2 are associated with stress-induced catecholaminergic polymorphic ventricular tachycardia in the heart [3]. In the heart contraction is initiated by calcium influx through the L-type Ca^{2+} channel. The L-type Ca^{2+} channel is also critical to cardiac excitation as it is responsible for the plateau phase (phase 2) of the action potential [4]. The pore forming and ion conducting α subunit ($Ca_v1.2$) plays a critical role in development as $Ca_v1.2^{-/-}$ transgenic mice are lethal before 14.5 days postcoitum [5]. Conversely over-expression of the $Ca_v1.2$ subunit leads to hypertrophy [6] and increased expression of the auxiliary β subunit leads to alterations in channel activity reminiscent of heart failure [7]. Ca^{2+} influx into cells is also regulated by the Na^+/Ca^{2+} exchanger that exchanges Na^+ ions for Ca^{2+} ions across the plasma membrane. Several isoforms of the exchanger have been identified including a mitochondrial isoform that is responsible for the regulation of calcium release from the mitochondria [8]. Recent evidence suggests the exchanger contributes to ischemic damage in the heart [9].

A recently discovered group of non-selective plasma membrane cation channels that conduct calcium and are activated by temperature, osmolarity, mechanical stress and noxious stimuli are the transient receptor potential (TRP) channels. A number of families of the channels have been identified but the main subfamilies are canonical (TRPC), vanilloid (TRPV) and melastatin-related (TRPM) channels [10]. They are expressed in a number of cell types and have been linked to chronic inflammatory diseases in humans [10].

The importance of calcium is highlighted by the fact that many naturally occurring mutations in calcium transporting proteins are known to underlie human disorders including childhood absence epilepsy, familial hemiplegic migraine, spinocerebellar ataxia type 6 (a severe movement disorder), hypokalemic periodic paralysis and X-linked congenital stationary night blindness [11].

In this Hot Topic the importance of the RyR in regulating intracellular calcium in skeletal and cardiac muscle is discussed using insights from biophysical studies performed in lipid bilayers [12]. The calcium-permeable Canonical, Melastatin and Ankyrin type TRP channels are reviewed including their roles in asthma and stroke [13] and recent studies implicating the Na^+/Ca^{2+} exchanger in myocardial injury are presented [9]. Finally the role of calcium transporting proteins including the L-type Ca^{2+} channel in regulation of mitochondrial function during oxidative stress is examined [14]. Understanding how calcium regulatory proteins contribute to the development of pathology has facilitated the development of therapy aimed at preventing disease. The most recent developments in therapy are discussed in each review article.

Keywords: Calcium, ion channels, ryanodine receptor, transient receptor potential, Na^+/Ca^{2+} exchange, disease.

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