Calcium Signaling Proteins in Human Diseases and their Potential as Drug Targets

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Abstract

The calcium (Ca\(^{2+}\)) signaling proteins are activated by a transient increase in free resting intracellular free Ca\(^{2+}\) concentration and regulate numerous cell processes including disease conditions. The neuronal Ca\(^{2+}\)-sensor-1, calmodulin, Ca\(^{2+}\)/calmodulin dependent protein kinases, and calcineurin are some of the important Ca\(^{2+}\) signaling proteins known to play an important role in various organisms and in human diseases, and have the potential as drug targets.

Introduction

Cell signaling is essential for all living organisms to communicate with both intracellular and extracellular environments. Cell signaling is mediated by several pathways including G-protein coupled receptors (GPCRs), and calcium (Ca\(^{2+}\)) signaling pathway that affects almost all cell process ranging from fertilization to death, and therefore, Ca\(^{2+}\) is also called as molecule of “life and death”[1]. A typical human cell maintains about 2 mM of Ca\(^{2+}\) in blood and extracellular fluid, whereas, the resting intracellular free Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]\(_i\)) is about 100 nM that transiently increases to about 100 M during the Ca\(^{2+}\) signaling process [2-3]. In the signaling process, many Ca\(^{2+}\) binding proteins binds to the increased [Ca\(^{2+}\)]\(_i\) to regulated downstream effectors and also act as buffers to maintain the Ca\(^{2+}\) homeostasis in the cell [3-5]. The Ca\(^{2+}\) signaling proteins have emerged as potential biomarkers for several disorders and also as drug targets for the treatment of infectious diseases in human. In this mini-review, cell functions of Ca\(^{2+}\)-signaling proteins neuronal calcium sensor-1, calmodulin, Ca\(^{2+}\)/calmodulin dependent protein kinases, and calcineurin, their roles in human diseases and potential as drug targets have been discussed.

Neuronal Calcium Sensor-1

One of the Ca\(^{2+}\)-binding proteins, neuronal calcium sensor-1 (NCS-1) is highly conserved from fungi to human containing four-EF hand Ca\(^{2+}\) binding domains, although, only three of the EF binds to Ca\(^{2+}\)[6-9]. NCS-1 has a critical physiological role in various organisms[7-10], such as neuronal growth, secretion, and regulation of Ca\(^{2+}\) channels in Lymnaea stagnalis, Xenopus, Drosophila, and mammals [11], memory and learning in Caenorhabditis elegans[12] and mice [13], neurotransmitter release in Drosophila[14], activity dependent synaptic facilitation of voltage-gated Ca\(^{2+}\) channels in rat calyceal nerve terminal [15], and in short-term synaptic plasticity in rat hippocampal neurons[16], long-term depression (LTD) via activation of metabotropic glutamate receptors (mGlRs) in rat cortical neurons[17], exploratory behavior and in the acquisition of spatial memory in mouse [18], and in neurite sprouting and spinal cord regeneration in rat [19]. In human, NCS-1 level was found up regulated in the prefrontal cortex of schizophrenic and bipolar patients [20], but, its level was decreased in leukocytes of schizophrenia and bipolar disorder patients [21], suggesting that NCS-1 may be associated with these abnormalities. In addition, NCS-1 is also a novel binding partner of paclitaxel (taxol), one of the most effective anticancer drugs, and protection of NCS-1 from paclitaxel-induced degradation by inhibiting calpain, a Ca\(^{2+}\)-dependent enzyme, might be useful for protection from peripheral neuropathy, a major side effect caused by paclitaxel treatment [22-24].

Calmodulin

The Ca\(^{2+}\) binding protein calmodulin (CaM) interacts with various target kinases, and phosphatases including calcineurin [4, 25, 26]. The increased CaM level in peripheral blood cells is a distinct feature Alzheimer’s disease (AD), although, the changes in CaM level was not correlated with the severity of AD, suggesting that the increased CaM level may be an early manifestation of AD [27]. Moreover, the increased level of CaM level in peripheral blood cells was not detected...
in case of other types of dementia and neurodegenerative disorders such as dementia with Lewy bodies, frontotemporal dementia, amytrophic lateral sclerosis, Parkinson’s disease, and progressive supranuclear palsy [27]. Therefore, CaM is a potential biomarker for early diagnosis of AD and differentiating it with other dementia and neurodegenerative disorders [27]. In addition, the anticancer drug CBP501, which is in clinical trials for patients with non-small cell lung cancer and malignant pleural mesothelioma, inhibits CaM and causes sensitization of cancer cells to cisplatin or bleomycin that might provide the basis for the codrug effect CBP501 [28].

**Ca**\(^{2+}\)/calmodulin dependent protein kinases

Ca**\(^{2+}\)/calmodulin dependent protein kinases (CaMKs) are Ser/Thr class of kinases such as CaMKK, CaMKI, CaMKII, CaMKIII, and CaMKIV, which are activated by increased [Ca**\(^{2+}\)] and CaM[29-30]. The CaMKII inhibition might be effective for the treatment of heart disease [31]. Moreover, CaMKIV is essential for mesangial cell proliferation and a treatment target for lupus nephritis [32].

**Calcineurin**

The Ca**\(^{2+}\)** signaling proteins also play a critical role in infections mediated by viruses, bacteria, and fungi [3, 33-37]. Several Ca**\(^{2+}\)** signaling proteins, including calcineurin, has been identified as the major virulence factor in fungal infection of plant and human [38]. Calcineurin comprises of two subunits including a catalytic subunit A, and a regulatory subunit B [39, 40]. The function of the calcineurin is inhibited by the immunosuppressive drugs FK506 and Cyclosporin A (CsA) [41-43]. In recent studies, the calcineurin mediated signaling is found to play a critical role in fungal virulence that might help in understanding the evolution of antifungal resistance and the development of novel antifungal drug [38, 44]. One of the well-known targets of calcineurin is the transcription factor the calcineurin responsive zinc finger-1 (Crz1) in fungi and the nuclear factor of activated T-cells (NFAT) in mammals [45]. The Crz1 modulates various cell functions ranging from homeostasis, stress response, virulence, and hyphal growth in many fungi, including Aspergillus, Candida, Cryptococcus, and Fusarium [38]. In mammals, the NFAT transcription factors play critical roles in numerous cell processes, including organogenesis of immune, nervous, respiratory, and vascular systems [46, 47]. Inhibition of calcineurin might have a significant role in survival of a recipient [48, 49]. In addition, inhibition of the calcineurin B homologous protein 1 (CHP1), results in suppression of angiogenesis in cancer cells [50]. Moreover, in transgenic mice, expression of the activated forms of calcineurin or its target transcription factor NF-AT3, which is dephosphorylated by calcineurin and activates cardiac zinc finger transcription factor GAT4 in the nucleus, in the heart develops cardiac hypertrophy and heart failure like in the case of human heart disease [51]. Therefore, cardiac specific inhibition of calcineurin might be beneficial in the treatment of cardiac hypertrophy in humans [51, 52].

**Conclusion**

The Ca**\(^{2+}\)** signaling proteins NCS-1, CaM, CaMKs, and calcineurin play a critical role in human diseases. The NCS-1 has a putative role in schizophrenia and bipolar disorder, and might be useful protection form side effect from the anticancer drug. CaM plays a role in Alzheimer’s disease and a potential biomarker for early diagnosis of Alzheimer’s disease, and might be a target for anticancer drug therapy. In addition, CaMKs play roles in several diseases, including autoimmune, cancer, and cardiac. Another Ca**\(^{2+}\)** signaling protein calcineurin has been implicated in cardiac hypertrophy, and calcineurin in pathogenic fungi plays a key role in infection. Thus, some of these Ca**\(^{2+}\)** signaling proteins are expected to be developed as biomarkers for several human diseases and potent drug targets for fungal infection in future.

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**References**


