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Calcium/calmodulin-dependent protein kinase IV: A multifunctional enzyme and potential therapeutic target

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ABSTRACT

The calcium/calmodulin-dependent protein kinase IV (CAMKIV) belongs to the serine/threonine protein kinase family, and is primarily involved in transcriptional regulation in lymphocytes, neurons and male germ cells. CAMKIV operates the signaling cascade and regulates activity of several transcription activators by phosphorylation, which in turn plays pivotal roles in immune response, inflammation and memory consolidation. In this review, we tried to focus on different aspects of CAMKIV to understand the significance of this protein in the biological system. This enzyme is associated with varieties of disorders such as cerebral hypoxia, azoospermia, endometrial and ovarian cancer, systemic lupus, etc., and hence it is considered as a potential therapeutic target. Structure of CAMKIV is comprised of five distinct domains in which kinase domain is responsible for enzyme activity. CAMKIV is involved in varieties of cellular functions such as regulation of gene expression, T-cell maturation, regulation of survival phase of dendritic cells, bone growth and metabolism, memory consolidation, sperm motility, regulation of microtubule dynamics, cell-cycle progression and apoptosis. In this review, we performed an extensive analysis on structure, function and regulation of CAMKIV and associated diseases.

Contents

Abbreviation: CaMKIV, calcium/calmodulin-dependent protein kinase IV; MAP2, microtubule-associated protein 2; CREB, cAMP response element-binding protein; CaM, calmodulin; CNS, central nervous system; SLE, systemic lupus erythematosus; EBV, Epstein-Barr virus; MAP, mitogen-activated protein.

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1. Introduction

Calcium/calmodulin-dependent protein kinase (CAMK) is a large family of protein kinases that act as an effector of calcium/calmodulin. These kinases are involved in many cellular processes such as neurotransmitter release, muscle contraction, gene expression, cellular metabolism and cell proliferation (Karcher et al., 2001; Mosialos and Gilmore, 1993; Ozcan and Tabas, 2010). These functions are regulated by calcium via forming a stable complex with calmodulin (CaM). The binding of Ca^{2+} with CaM increases its affinity for its targets, the Ca^{2+}/CaM dependent Ser–Thr kinases (Hook and Means, 2001; Soderling, 1999). It has been well documented that changes in the intracellular calcium signal perturbs functions of the nucleus such as gene expression, cell cycle regulation, apoptosis and cell proliferation (Bachs et al., 1992; Bito et al., 1997; Lu and Hunter, 1995; Nicotera et al., 1994). Calcium signaling is also involved in the regulation of central processes such as neurotransmitter release and muscle contraction (Anderson and Kane, 1998; Ghosh and Greenberg, 1995).

The main aspect of protein kinase action is the tight coupling of catalytic activity to various extracellular and intracellular signals to control several biological processes. CaM kinases regulate diverse cellular processes, including neurotransmitter release, muscle contraction, gene expression and cell proliferation (Hanson and Schulman, 1992). The action of Ca^{2+} is frequently mediated through interaction with calmodulin (CaM), often achieved through the regulation of protein phosphorylation. CaM-dependent protein kinases have been classified into myosin light chain kinase, phosphorylase kinase, CaM kinase I, CaM kinase II, EF-2 kinase (CaM kinase III) and CaM kinase IV (Nairn and Picciotto, 1994). CaMKI is a monomeric enzyme that phosphorylates numerous substrates *in vitro*, including the synaptic vesicle–associated proteins synapsin 1 and 2, and it regulates transcription activators activity, cell cycle, hormone production, cell differentiation, actin filament organization and neurite outgrowth (Goldberg et al., 1996). CaM-kinase II is a prominent kinase in the central nervous system that may function in long-term potentiation and neurotransmitter release (Hanley et al., 1987). CaM Kinase III phosphorylates eEF-2 in the presence of Ca^{2+}. CaMKIII kinase has been cloned as an enzyme of apparent molecular mass of 95 kDa, and it shows low homology to other known kinases (Riis and Nygard, 1997).

CAMKIV is a multifunctional Ser/Thr kinase encoded by the *CAMKIV* gene in the human. It occurs abundantly in the brain and thymus, and it requires Ca^{2+}/CaM for its activity (Heist and Schulman, 1998; Hook and Means, 2001). CAMKIV regulates various cellular events through phosphorylation of transcription factors which play pivotal roles in immune response, inflammation and memory consolidation (Fukushima et al., 2008; Hanissian et al., 1993). Recently, CAMKIV was found to be primarily involved in the osteoclast differentiation via up-regulation of Notch1 protein stability (Choi et al., 2013). CaM-kinase phosphorylates and activates CAMKIV (Fujisawa, 2001; Hook and Means, 2001; Soderling, 1999). The phosphorylated CAMKIV further phosphorylates numerous proteins such as microtubule-associated protein 2 (MAP2), tau protein, synapsin I, tyrosine hydroxylase, cAMP response element-binding protein (CREB) and myosin light chain (Matthews et al., 1994; Miyano et al., 1992). Phosphorylation of CREB significantly mediates calcium-induced dendritic growth in cortical neurons (Redmond et al., 2002).

Despite of many available information on CAMKIV, an extensive analysis is still needed to clarify the physiological significance of CAMKIV. Hence, in this review our aim is to provide a detailed analysis of structure, function and mechanism of biological actions of CAMKIV.

2. Site of expression

Expression of CAMKIV in brain (Bland et al., 1994), thymus, CD4 T-cells, testis, and many other organs are described in Fig. 1. Due to high concentration in these organs, CAMKIV is considered as a necessary element for function of calcium in the central nervous system (CNS) and immune regulation. Sikela and Hahn (Sikela et al., 1989) demonstrated the presence of CAMKIV in the mouse brain. Moreover, immunohistochemical localization studies showed the presence of CAMKIV in several neuronal subpopulations. Expression level of CAMKIV is significantly high in the granule cells of the cerebellum (Ohmstede et al., 1989). Another studies, using CAMKIV enzyme activity, by Miyano et al. (Miyano et al., 1992) showed the presence of CAMKIV in the brain stem, cerebral cortex and cerebellum of various rat tissues. On the other hand, a very low level of CAMKIV was observed in skeletal muscle, liver, heart, spleen, lung, kidney and adrenal gland (Fig. 1). Wei et al. (Wei et al., 2002) performed immunostaining of adult mouse brain sections and showed the expression of CAMKIV in hippocampus, amygdala, insular cortex, anterior cingulate cortex, and somatosensory cortex.

Rat thymus and thymocytes express a relatively high level of CAMKIV (Chatila et al., 1996). This enzyme is selectively expressed in T lymphocytes in a tightly regulated manner. However, it is not detected in the B lymphocytes or monocytes (Hanissian et al., 1993). Recently, Koga et al. (Koga et al., 2012) proved that a knockdown of CAMKIV gene in T cells of systemic lupus erythematosus (SLE) patients resulted an increase in the percentage of CD25. Rat spleen and testis produce CAMKIV at lower level in comparison to thymus or brain (Chatila et al., 1996). Furthermore, presence of CAMKIV was also confirmed in the hippocampal neuron nuclei where it phosphorylates CREB to regulate the hippocampal gene expression (Bito et al., 1996).

It was experimentally proved that CAMKIV is expressed in Epstein–Barr virus (EBV) transformed B-lymphoblastoid cell lines (Hanissian et al., 1993; Mosialos et al., 1994). This observation raises the possibilities that this kinase is important for EBV-mediated B lymphocyte growth transformation. Hence, CAMKIV is the first cam-dependent enzyme thought to be regulated by a viral gene product. However, the mechanism of transformation of EBV transformed B-lymphocytes is still unclear. An elevated level of CAMKIV has been reported in the small cell lung carcinoma, hepatocellular carcinoma and epithelial ovarian cancer (Takai et al., 2002), indicating that changes in intracellular calcium concentration affect progression through the mitotic cell cycle. It is reported that CAMKIV regulates β-cell proliferation and apoptosis (Liu et al., 2012), and that CAMKIV transcript levels in pancreatic β-cells are influenced by melatonin (Bazwinsky-Wutschke et al., 2014, 2009).