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Review

FK506 binding proteins: Cellular regulators of intracellular Ca^{2+} signalling

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ABSTRACT

In many cell types the intracellular Ca^{2+} store performs a central role in the regulation of the cytosolic Ca^{2+} concentration ($[Ca^{2+}]_c$), the elevation of which triggers diverse and fundamental activities from reproduction to apoptosis, as well as being the major trigger for contraction. Two distinct classes of Ca^{2+} release channels, which mobilize Ca^{2+} from the store, exist; the inositol 1,4,5-trisphosphate (IP_3) receptor and the ryanodine receptor. Considerable attention has been directed towards the importance of modulatory proteins that interact with these channels including, FK506 binding proteins (FKBPs), FKBP12 and its isoform, FKBP12.6. Although FKBP12 was first identified as the principal intracellular target for the immunosuppressive drugs, FK506 and rapamycin, new insights into the role of FKBPs have since emerged. These regulatory proteins are reportedly important modulators of intracellular Ca^{2+} release. FKBPs may regulate ryanodine and IP_3 receptors either directly, by binding to the cytoplasmic aspect of the channel, or indirectly via modulation of two targets, the phosphatase, calcineurin or the kinase, mammalian target of rapamycin (mTOR). Dissociation of FKBP12 or FKBP12.6 from either Ca^{2+} release channel may increase, decrease or have no effect on ryanodine receptor- or IP_3 receptor-mediated Ca^{2+} release. These important controversies may be attributed to FKBPs' ability to regulate the receptor indirectly via the kinase and phosphatase pathways modulated by the accessory proteins. This brief review discusses the regulation of intracellular ryanodine and IP_3 receptor Ca^{2+} release channels by accessory FKBPs, with important implications for the role of FKBPs in the pathophysiology of a number of diseases.

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1. Introduction

In a variety of cell types the cytosolic Ca^{2+} concentration ($[Ca^{2+}]_c$) controls fundamental and diverse cellular events including hormone and neurotransmitter release, enzyme regulation, cell division and cell death, and is the major trigger for smooth muscle contraction, and is thus, an important regulator of Ca^{2+} signalling (Berridge et al., 2003; Bootman et al., 2006; Horowitz et al., 1996). The intracellular Ca^{2+} store contributes to the regulation of $[Ca^{2+}]_c$ by controlling Ca^{2+} release (Berridge et al., 2003; Bootman et al., 2001; McCarron et al., 2004; McCarron et al., 2006) and store-operated Ca^{2+} influx following

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release (Berna-Erro et al., 2012; Salido et al., 2009), to replenish the depleted store and maintain long-term cytosolic Ca^{2+} signals. Release of Ca^{2+} from the sarcoplasmic reticulum (SR) store occurs through activation of two distinct ligand-gated channel/receptor complexes; the inositol 1,4,5-trisphosphate (IP_3) receptor (Bolton et al., 1999; Bootman et al., 2001; MacMillan et al., 2012; MacMillan and McCarron, 2010; McCarron et al., 2004) and the ryanodine receptor (Bootman et al., 2001; Guo et al., 2012; McCarron et al., 2004; Zalk et al., 2007), to generate local and global Ca^{2+} signals. These channels play crucial roles in Ca^{2+}-mediated signalling that trigger many major physiological processes.

Ryanodine receptors exist as three mammalian isoforms (Fill and Copello, 2002; McPherson and Campbell, 1993; Meissner, 1994; Mironneau et al., 2001; Zorzato et al., 1990). All isoforms have a large cytoplasmic region (~4/5 of the molecule) and a short hydrophobic membrane-spanning region (~1/5 of the molecule) (Samso and Wagenknecht, 1998; Serysheva et al., 1999). The ion channel-forming, membrane spanning regions are highly conserved between different receptor isoforms and are localized to the COOH terminus (Lai et al., 1988). Ryanodine RyR1 receptor is primarily expressed in skeletal muscle (Zorzato et al., 1990), ryanodine RyR2 receptor is predominant in cardiac muscle (Otsu et al., 1990; Rossi and Sorrentino, 2002), while the type 3 isoform appears to be expressed in a variety of tissues including the brain (Giannini et al., 1995; Hakamata et al., 1992; Ledbetter et al., 1994). Unlike cardiac and skeletal muscle, which each express only one ryanodine receptor isoform, all three isoforms can be expressed in smooth muscle (Coussin et al., 2000; Fill and Copello, 2002; Mironneau et al., 2001; Neylon et al., 1995; Yang et al., 2005; Zheng et al., 2005). Ryanodine receptors are tetrameric Ca^{2+} release channels (Lai et al., 1989) composed of four subunits, each with a molecular mass of ~565 kDa surrounding a central Ca^{2+} pore (Inui et al., 1987; Lai et al., 1988; Otsu et al., 1990; Takeshima et al., 1989). The subunits act in a coordinated way to gate the Ca^{2+} release channel. The Ca^{2+} conductance of the ryanodine receptor is approximately 100 pS and Ca^{2+} is the principal endogenous effector of the channel. The receptors may be activated when the Ca^{2+} content of the store exceeds normal physiological values, as in store overload or pharmacologically (e.g., by caffeine or ryanodine) (Burdyga and Wray, 2005; MacMillan et al., 2005a; McCarron et al., 2006).

Similarly, three distinct IP_3 receptor isoforms have been identified (Furuichi et al., 1994; Furuichi and Mikoshiba, 1995; Iino, 2000; Mikoshiba, 2007; Patel et al., 1999). Most cells express IP_3 receptors (De Smedt et al., 1994; Taylor et al., 1999; Vermassen et al., 2004; Wojcikiewicz, 1995), but the patterns of expression are varied. Unlike ryanodine receptors, IP_3 receptors are poorly expressed in skeletal, but extensively expressed in brain and other tissues including smooth muscle (Michikawa et al., 1996; Patel et al., 1999; Taylor, 1998). For example, the type 1 IP_3 receptor is particularly prominent in the cerebellum (De Smedt et al., 1997; Wojcikiewicz, 1995), the type 2 isoform is predominantly expressed in the brain, kidney, cardiac and skeletal muscle (De Smedt et al., 1997) whereas the type 3 isoform is extensively expressed in the gastrointestinal tract, pancreas and thymus (Blondel et al., 1993; Rosker et al., 2009; Tasker et al., 1999). IP_3 receptors also exist as tetramers, composed of four closely-related subunits with a monomeric molecular mass of ~300 kDa (Foskett et al., 2007; Joseph et al., 2000; Maeda et al., 1991; Monkawa et al., 1995; Patel et al., 1999). Structurally, each receptor contains a cytoplasmic NH_2 terminus comprising ~85% of the protein mass, a hydrophobic region predicted to contain six membrane-spanning helices that contribute to the ion-conducting pore of the channel, and a relatively short cytoplasmic COOH terminus (Joseph et al., 1995; Michikawa et al., 1994; Ross et al., 1992; Wojcikiewicz, 1995). In several cell types, such as smooth muscle and non-excitable cells, the IP_3 receptor is the predominant Ca^{2+} release mechanism and responds to elevated levels of the ubiquitous second messenger, IP_3, generated from phosphatidylinositol-specific phospholipase C-mediated hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) in response to diverse stimuli including G-protein-coupled receptor (GPCR)- or tyrosine kinase- linked receptor agonists (Berridge and Irvine, 1984; Bootman et al., 2001; MacMillan et al., 2012). The IP_3 receptor is a Ca^{2+}-selective cation channel, the gating of which is regulated by many intracellular modulators in addition to IP_3, including its permeating ion, Ca^{2+} (Bezprozvanny et al., 1991; Foskett et al., 2007; Iino, 1990; Mak et al., 1998; Missiaen et al., 1999), phosphatases (MacMillan et al., 2005b; Mikoshiba, 2007), and kinases (Adkins et al., 2000; Foskett et al., 2007; Mikoshiba, 2007; Wojcikiewicz and Luo, 1998). To add to the complexity, channel activity of both IP_3 and ryanodine receptors may importantly also be regulated by cytosolic associated regulatory proteins including, calmodulin (Adkins et al., 2000; Cornea et al., 2009; Fill and Copello, 2002; McCarron et al., 2006; Yamaguchi et al., 2005), FK506 binding proteins (FKBPs) (Bielefeldt et al., 1997; Cameron et al., 1995b; Fill and Copello, 2002; MacMillan et al., 2005b; MacMillan and McCarron, 2009; McCarron et al., 2006; Taylor, 1998) and IRBIT (IP_3 receptor binding protein released with IP_3) (Ando et al., 2003; Mikoshiba, 2012; Yang et al., 2011), as well as luminal regulatory proteins such as the Ca^{2+} binding protein calsequestrin (Beard et al., 2005, 2002; Fill and Copello, 2002; Gyorke et al., 2004; McCarron et al., 2006) and the integral proteins triadin and junctin (Groh et al., 1999; Hong et al., 2002; Kirchhefer et al., 2006, 2001; McCarron et al., 2006; Ohkura et al., 1998), which can trigger a vast array of physiological processes (Table 1).

Of the host of accessory proteins which modulate the activity of the receptors, FKBPs, initially identified as cellular targets for the clinical immunosuppressive drug, FK506 (tacrolimus) (Galat, 2003; Harding et al., 1989), are of particular importance. FKBPs may regulate ryanodine receptors and IP_3 receptors either directly, by binding to the cytosolic aspect of the channel, or indirectly via the kinase and phosphatase pathways modulated by these accessory proteins (MacMillan et al., 2005b, 2008; MacMillan and McCarron, 2009). Accordingly, FK506 and its analogue, rapamycin (sirolimus), exert multiple effects on intracellular signalling by disrupting the binding of FKBPs to the receptor, and by regulating either phosphatase or kinase activity, respectively. The multiple effects of the drugs, may account, at least in part, for the apparently disparate findings which exist in the literature on the role of FKBPs in Ca^{2+} signalling.

For the purposes of this brief review, attention will focus on the role of accessory FKBPs as cytosolic regulators of the two classes of intracellular Ca^{2+} release channel, the ryanodine receptor and IP_3 receptor.

2. FK506 binding proteins

FKBPs are named according to their molecular mass, which range from 12 to 135 kDa, and belong to the immunophilins, a family of highly conserved proteins that are the principal intracellular targets for immunosuppressive drugs such as FK506 and rapamycin. The FKBP family has more than 20 members, of which at least 8 are mammalian (Kang et al., 2008). These proteins have been identified as accessory proteins of ryanodine and IP_3 receptor Ca^{2+} release channels. Two major FKBP isoforms to be recognised as regulators of these channels are the 12 kDa protein, FKBP12 (Cameron et al., 1995b; MacMillan et al., 2005b, 2008;