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Review

STRIPAK complexes: Structure, biological function, and involvement in human diseases

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ABSTRACT

The mammalian striatin family consists of three proteins, striatin, S/G_2 nuclear autoantigen, and zinedin. Striatin family members have no intrinsic catalytic activity, but rather function as scaffolding proteins. Remarkably, they organize multiple diverse, large signaling complexes that participate in a variety of cellular processes. Moreover, they appear to be regulatory/targeting subunits for the major eukaryotic serine/threonine protein phosphatase 2A. In addition, striatin family members associate with germinal center kinase III kinases as well as other novel components, earning these assemblies the name striatin-interacting phosphatase and kinase (STRIPAK) complexes. Recently, there has been a great increase in functional and mechanistic studies aimed at identifying and understanding the roles of STRIPAK and STRIPAK-like complexes in cellular processes of multiple organisms. These studies have identified novel STRIPAK and STRIPAK-like complexes and have explored their roles in specific signaling pathways. Together, the results of these studies have sparked increased interest in striatin family complexes because they have revealed roles in signaling, cell cycle control, apoptosis, vesicular trafficking, Golgi assembly, cell polarity, cell migration, neural and vascular development, and cardiac function. Moreover, STRIPAK complexes have been connected to clinical conditions, including cardiac disease, diabetes, autism, and cerebral cavernous malformation. In this review, we discuss the expression, localization, and protein domain structure of striatin family members. Then we consider the diverse complexes these proteins and their homologs form in various organisms, emphasizing what is known regarding function and regulation. Finally, we explore possible roles of striatin family complexes in disease, especially cerebral cavernous malformation.

Abbreviations: AJ, adherens junction; APC, adenomatous polyposis coli; ARD, armadillo repeat domain; ARVC, arrhythmogenic right ventricular cardiomyopathy; Bsk, Basket; CaM, calmodulin; Cav-1, caveolin-1; CCM, cerebral cavernous malformations; Ccm3, cerebral cavernous malformation 3; CCM-ECs, CCM patient endothelial cells; CCT/TRiC, chaperonin containing TCP-1/TCP-1 ring complex; Cka, connector of kinase to AP-1; CTTNBP2/NL, cortactin-binding protein 2/cortactin-binding protein 2, N-terminal-like; DCM, dilated cardiomyopathy; dErk, *Drosophila* extracellular signal-regulated kinase; dJnk, *Drosophila* Jun N-terminal kinase; dMob4, *Drosophila* Mob3 functional homolog; dRassf, *Drosophila* Ras association domain family protein; DUB, deubiquitinase; EGFR, epidermal growth factor receptor; EMS, 8p11 myeloproliferative syndrome; eNOS, endothelial nitric oxide synthase; Eps15, epidermal growth factor receptor substrate 15; ERα, estrogen receptor alpha; Erk, extracellular signal-regulated kinase; ERM, ezrin/radixin/moesin; ERMES, endoplasmic reticulum–mitochondria encounter structure; FAR, factor arrest; FAT, focal adhesion targeting; FGFR1OP2, fibroblast growth factor receptor 1 oncogene partner 2; GAP, GTPase activating protein; GCKIII, germinal center kinase III; GH, glycine–histidine; GIPC, GAIP-interacting protein, C terminus; HBMECs, human brain microvascular endothelial cells; HEG1, heart of glass 1; Hep, Hemipterous; HGNC, HUGO Gene Nomenclature Committee; HMVECs, human dermal microvascular endothelial cells; Hpo, Hippo; HUVECs, human umbilical vein endothelial cells; ICAP-1, integrin cytoplasmic associated protein-1; IRF-3, interferon regulatory factor 3; Jra, Jun-related antigen; Kay, kayak; Krit1, K-Rev interaction trapped 1; Map4k4, mitogen-activated protein kinase kinase kinase kinase 4; MASK, Mst3 and Sok1-related kinase; mDia, mammalian homolog of *Drosophila* diaphanous; MEKK3, mitogen-activated protein kinase kinase kinase 3; Mink1, Msn-like kinase 1; MLC, myosin light chain; Mob3, monopolar spindle-one-binder family 3; MR, mineralocorticoid receptor; Msn, Misshapen; Mst, mammalian sterile 20-like; NDPK, nucleoside-diphosphate kinase; NLS, nuclear localization signal; NMDA, N-methyl-D-aspartate; NMDARs, N-methyl-D-aspartate receptors; OSM, osmosensing scaffold for MEKK3; PDCD10, programmed cell death 10; PDGFRA, platelet derived growth factor receptor alpha; PPARγ, peroxisome proliferator-activated receptor γ; PP2A, protein phosphatase 2A; PTB, phosphotyrosine-binding; PTP, protein-tyrosine phosphatase; RhoA, ras homolog gene family member A; ROCK, Rho-associated coiled coil-forming kinase; RTKs, receptor tyrosine kinases; SG2NA, S/G_2 nuclear autoantigen; SIKE, suppressor of IKKε; SIN, septation initiation network; SIP, SIN-inhibitory PP2A complex; SLMAP, sarcolemmal membrane-associated protein; Sok1, sterile 20/oxidant stress-response kinase 1; SPB, spindle pole body; SR, sarcoplasmic reticulum; STRIPAK, striatin-interacting phosphatase and kinase; STRIP1/2, striatin interacting proteins 1 and 2; TFAR15, TF-1 cell apoptosis related gene-15; TJ, tight junction; TLR3, Toll-like receptor 3; Tnf-α, tumor necrosis factor alpha; Tnik, TRAF2- and NCK-interacting kinase; TORC1, target of rapamycin complex 1; WD, tryptophan–aspartate; Ysk1, yeast Sps1/sterile-20-related kinase 1.

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Contents

1. Introduction

The mammalian striatin family consists of three proteins, striatin (HUGO Gene Nomenclature Committee (HGNC) approved symbol, STRN), S/G_2 nuclear autoantigen (SG2NA; HGNC approved symbol, STRN3), and zinedin (HGNC approved symbol, STRN4) (Benoist et al., 2006). Of note, there is not a STRN2 member of the striatin family because, confusingly, STRN2 is an alias for an unrelated protein, striamin. While the striatin family of proteins are highly expressed in the central and peripheral nervous systems and are probably important for brain function, they are also expressed in many other tissues. Thus, while they may have specialized functions, they likely also carry out one or more functions common to many different cell types. Striatin family members have no intrinsic catalytic activity, but rather function as scaffolding proteins harboring a variety of protein–protein interaction domains. Strikingly, they are capable of organizing multiple diverse, large signaling complexes, which participate in a variety of cellular processes.

To date, the only striatin family-associated proteins found in nearly all striatin family complexes are the structural A and catalytic C subunits of protein phosphatase 2A (PP2A) (Moreno et al., 2000), a major eukaryotic serine/threonine phosphatase that exists primarily as heterotrimers made of an A subunit, a C subunit, and one of many "B-type" regulatory/targeting subunits. Based on the altered substrate specificity of striatin family-associated PP2A and the lack of other B-type subunits in these complexes, striatin family members were postulated to comprise a novel B‴ family of PP2A B-type regulatory subunits (Moreno et al., 2000).

Recent proteomic analysis of striatin family-associated proteins revealed the additional presence of germinal center kinase III (GCKIII) kinases together with PP2A and other components, earning these striatin family complexes the name striatin-interacting phosphatase and kinase (STRIPAK) complexes (Goudreault et al., 2009). In addition, separate STRIPAK-like complexes have been found that are not yet known to contain both PP2A and a kinase.

In the last few years, members of striatin family complexes have been connected to clinical conditions. These include cerebral cavernous malformation (CCM), a common type of angioma that can cause symptoms ranging from headaches to stroke, cardiac dysfunction, cancer, diabetes, and autism. While striatin family complexes have been linked to these conditions, specific mechanistic roles for STRIPAK complexes in disease remain to be delineated.

Recently, there has been a great increase in the number of functional and mechanistic studies aimed at identifying and understanding the roles of STRIPAK and STRIPAK-like complexes in cellular processes of multiple organisms. Novel complexes have been identified, and their roles in specific signaling pathways have been explored, often by mutating or depleting the striatin family member or associated proteins. Together, the results of these studies have sparked increased interest in striatin family complexes because they have revealed roles in signaling, cell cycle control, apoptosis, vesicular trafficking, Golgi assembly, cell polarity, cell adhesion, cell migration, neural and vascular development, and disease.

In this review, we will first introduce striatin, SG2NA, and zinedin and briefly discuss their expression, localization, and protein domain structure. Next, we will consider the diverse complexes these proteins and their homologs form from yeast to man, including what is known regarding function and regulation. Finally, we will explore possible roles of STRIPAK complexes in disease.